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REVIEW ARTICLE

Refractive surgery beyond 2020

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Abstract

Refractive surgery refers to any procedure that corrects or minimizes refractive errors. Today, refractive surgery has evolved beyond the traditional laser refractive surgery, embodied by the popular laser in situ keratomileusis or 'LASIK'. New keratorefractive techniques such as small incision lenticule extraction (SMILE) avoids corneal flap creation and uses a single laser device, while advances in surface ablation techniques have seen a resurgence in its popularity. Presbyopic treatment options have also expanded to include new ablation profiles, intracorneal implants, and phakic intraocular implants. With the improved safety and efficacy of refractive lens exchange, a wider variety of intraocular lens implants with advanced optics provide more options for refractive correction in carefully selected patients. In this review, we also discuss possible developments in refractive surgery beyond 2020, such as preoperative evaluation of refractive patients using machine learning and artificial intelligence, potential use of stromal lenticules harvested from SMILE for presbyopic treatments, and various advances in intraocular lens implants that may provide a closer to 'physiological correction' of refractive errors.

Introduction

'Refractive surgery' encompasses any procedure that corrects refractive error, one of the leading causes of reversible visual impairment in the world [1]. It is now recognized that refractive surgery has signficant impact on quality of life and daily work, with benefits extending beyond spectacle independence [2]. Laser refractive surgery is recognized as an extremely effective and safe procedure for low to moderate levels of refractive error [3], with more than 99.5% achieving spectacle independence [4]. The US FDA run Patient-Reported Outcomes with laser in situ keratomileusis showed that, on average, 95% of patients were satisfied with their treatment [5].

Today, refractive surgery has evolved beyond the stereotypical 'laser eye surgery'. Developments in femtosecond laser technology has led to the improvement of laser in situ keratomileusis (LASIK) and the birth of refractive lenticule extraction [6]. Novel refractive surgical implants have also been introduced, ranging from intracorneal to intraocular implants. However, with laser refractive surgery already achieving excellent clinical outcomes, it is often difficult to demonstrate that these newer procedures are superior to the established techniques [7].

Thus, the next frontier of refractive surgery challenges clinicians and scientists to achieve outcomes superior to the 'traditional 20/20', often used to depict 'perfect' uncorrected distance visual acuity (UDVA). Technologies have been developed to enhance preoperative assessments and imaging for better patient selection, there are now improved customized treatments to specifically correct ocular aberrations, and novel techniques to adapt to dynamic refractive

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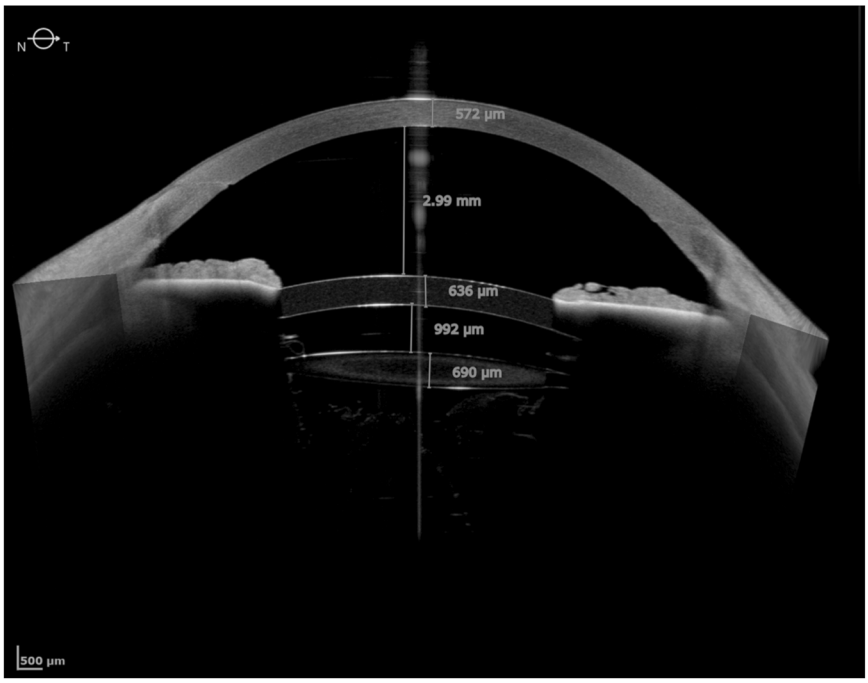

Fig. 1 High-resolution swept-source optical coherence tomography imaging of the anterior segment of a pseudophakic eye. High-resolution swept-source OCT imaging of the anterior segment of a pseudophakic eye in which after piggy-back implantation of a sulcus lens to fix a refractive surprise after uneventful cataract surgery (ANTERION, Heidelberg Engineering GmbH, Heidelberg, Germany).

changes in the eye such as presbyopia. In this review, we summarize the evolution of refractive surgery, which now ranges from keratorefractive procedures to refractive lens exchange. Each section will discuss historical development, recent advancements, and possible progress into the future beyond 2020.

Preoperative evaluation for refractive surgery

Traditionally, refractive surgery may be considered as two major sub-disciplines, which can be applied jointly in some cases to correct complex refractive errors: keratorefractive or intraocular lens (IOL)-based surgery. Keratorefractive surgery involves altering the corneal surface shape; while with IOL-based surgery, an IOL implant is added to the optical elements. Corneal topography provides an assessment of corneal surface shape, while wavefront analysis provides an assessment of image formation by the entire eye's optical system. Conventionally, these investigations have been routinely used in preoperative evaluation for refractive surgery.

Placido-based curvature topographic systems are valuable tools in gauging the corneal curvature and refractive status, but do not directly portray the actual shape of the cornea [8]. Scheimpflug corneal tomography is a 3-D imaging technique that characterizes the anterior/posterior corneal surfaces, along with corneal thickness distribution. Preoperative assessment is important to exclude any contraindicated corneal conditions, while detection of subclinical keratoconus suspects is crucial to prevent iatrogenic postsurgical ectasia [9]. Integrating data derived from corneal topography, biometry, and wavefront analysis can also help clinicians validate decisions about customized refractive surgery treatments and IOL power selection.

Beyond corneal topography: biomechanics and high-resolution imaging

Recently, the addition of corneal biomechanics to corneal topography has been studied as a potential adjunct to preoperative evaluation for keratorefractive procedures. The corneal visualization tonometer (Corvis ST, Oculus Optikgeräte GmbH; Wetzlar, Germany) uses an ultra-high speed Scheimpflug camera that visualizes corneal changes during deformation to produce various parameters [10]. The Pentacam HR topography and Corvis ST biomechanical parameters were then analysed together using different artificial intelligence methods [11]. A tomographic and biomechanical index may provide greater accuracy for detecting subclinical keratoconus among eyes clinically deemed to have 'normal topography' [11].

High-resolution swept-source optical coherence tomography (SS-OCT) provides anterior segment imaging and measurements in a single platform [12]. Newer OCT platforms capture corneal topography and tomography, anterior segment metrics, axial length measurement, and IOL calculation—Fig. 1 [13]. With OCT biometry, the ocular measurement can be combined with high-resolution macular scans for simultaneous screening for macular pathology [14]. In addition, corneal epithelial thickness measurements

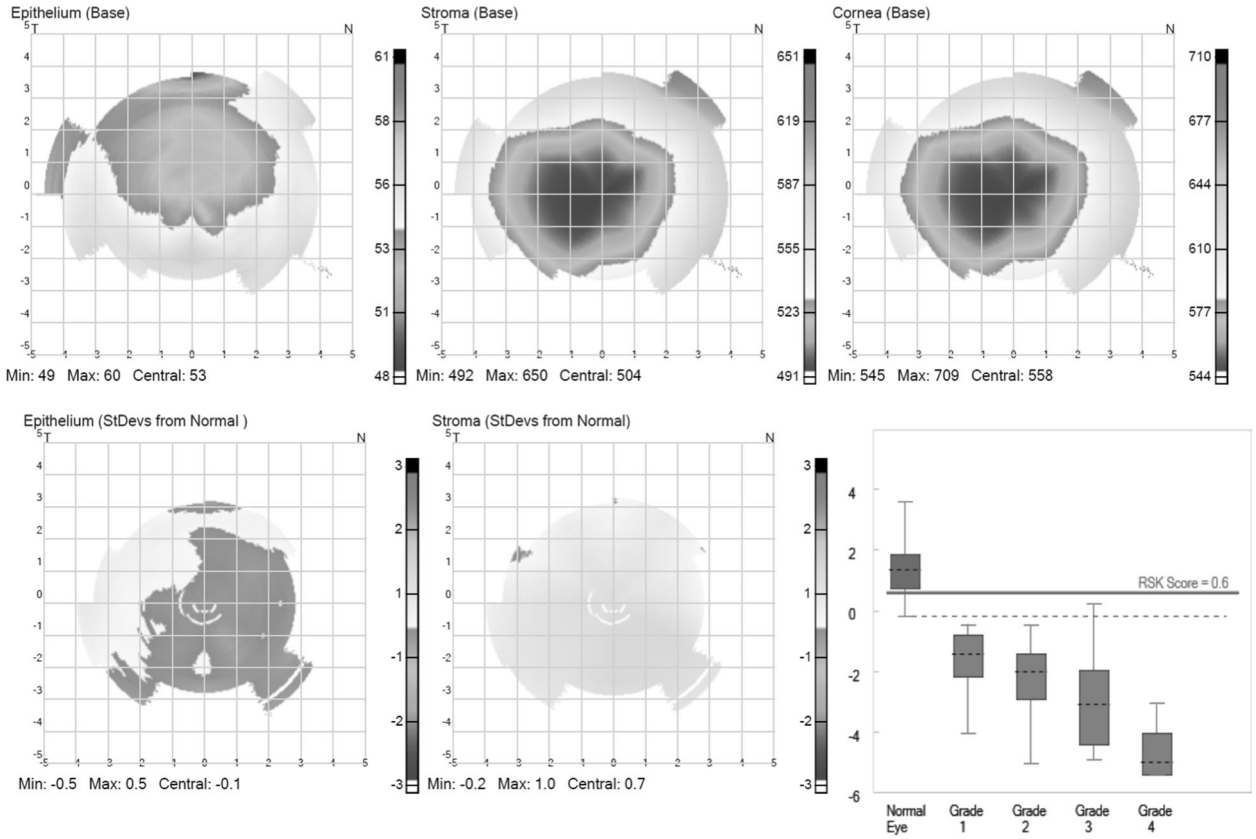

Fig. 2 Precision high-frequency ultrasound device (50 MHz) imaging of the cornea. Ultrasound imaging can accurately image behind the iris allowing for improved ICL sizing. In addition to measurements of the anatomic structures comprising the anterior of the eye such as anterior chamber, the instrument can delineate the corneal epithelial layer thickness (ArcScan Insight 100, ArcScan Inc, Golden, USA).

may have a role in planning for refractive surgery; or identification of early keratoconus through identification of focal epithelial thinning usually associated with areas of corneal steepening [15]. Very high-frequency ultrasound corneal analysis and high-resolution OCT can also generate epithelium thickness maps (Fig. 2) [16].

Aberrometry and wavefront sensing

The development of new instrumentation to measure human optical aberrations and the recent refinements in the excimer laser delivery systems have opened a new era in vision correction: patient-customized, wavefront-guided treatment. Modern aberrometers are equipped with a corneal topographer system to compute the effect of the anterior and posterior corneal contribution to the ocular wavefront, and by subtraction, the effect of internal optics (the crystalline lens, or an IOL in pseudophakia). As described later, aberrometry data can be used to generate custom wavefront-guided ablation profiles procedures that aim to correct both the spherocylindrical refraction and higher-order aberrations (HOAs). Wavefront aberrometers measure only monochromatic aberrations whereas our eyes can see a polychromatic world. In the future, the discrepancy between the measured monochromatic wavefront and the actual polychromatic wavefront may help to find the precise amount of HOAs to correct. The ideal flat wavefront for high fidelity may be optimal for young patients with intact accommodative abilities, whereas adjusted-shape designed to increase the depth of focus may be preferable for some presbyopic patients [17]. The functional needs of the patient will have to be taken into consideration to truly optimize wavefront refractive surgical strategies, and adaptative optic capabilities will certainly have to be accessible to achieve these tasks [18]. A new aberration series has been proposed to better fit the low- and higher-order components of the wavefront. This new basis may quantify the aberrations more accurately and provide clinicians with coefficient magnitudes which better underline the impact of clinically significant aberration modes [19].

Cataract assessment using lens densitometry

Objective assessments to quantify cataract are becoming indispensable for modern cataract surgeons, especially to reliably assess early- to moderate-stage cataracts, and

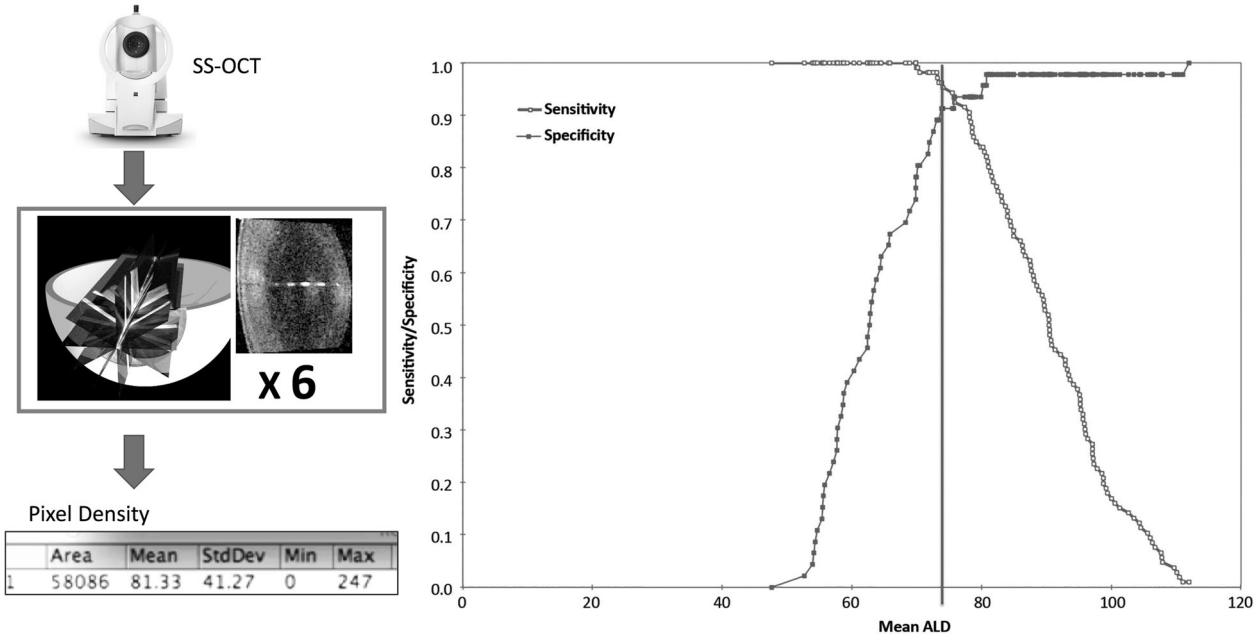

Fig. 3 Average lens density (ALD) quantification with swept-source optical coherence tomography (SS-OCT). Six radial B-scans including the lens were acquired three times at each meridian (0, 30, 60, 90, 120, and 150 degrees). An algorithm measured the density of the region of interest on a scale of 0–255 pixel intensity units. In a recent study, an SS-OCT ALD measurement of 73.8 pixel units or greater strongly suggested the presence of cataract, with a sensitivity of 96.2% and a specificity of 91.3%.

documenting cataract progression. Various clinical classifications, such as the subjective Lens Opacification Classification System (LOCS III), have limited use in assessing cataract density. Objective methods such as Scheimpflug imaging (Pentacam, Oculus Optikgeräte GmbH) and double-pass aberrometry (Optical Quality Analysis System, Visiometrics SL) have been shown to be repeatable and reliable methods to grade lens density [20]. Artal et al. have shown that an OSI of 1 or greater corresponds to lens opacification in the absence of ocular surface, corneal disease, or retinal disease [21]. Another device that can assess lens density is the IOLMaster 700 (Carl Zeiss Meditec AG), which is based on SS-OCT. Assessing cataract density using this SS-OCT technology has been reported to be reliable, using either a 2-dimensional (2-D) analysis based on a single B-scan centered on the vertex, or an automated global 3-D analysis (Fig. 3) [22].

Beyond 2020: preoperative assessment for refractive surgery: machine learning

Machine learning is a general technique to find appropriate parameters or functions to classify input data from large amounts of training data. Many methodologies to implement machine learning, such as support vector machines, decision trees, or neural networks, have so far been advocated. Deep learning is one of the machine learning techniques dealing with the training of multilayer artificial neural networks. In recent years, multilayered neural networks, especially convolutional neural networks, have achieved impressive results in many types of image classifications in many scientific fields. Several studies have reported on the sensitivity and the specificity of keratoconus detection using machine learning [23–27]. In order to discriminate keratoconus from normal corneas these studies used either topographic numeric indices measured with a Placido disk-based corneal topographer, or tomographic numeric indices measured with a scanning slit tomographer and a rotating Scheimpflug camera, for machine learning. Deep learning using the whole image of six corneal color-coded maps (anterior elevation, anterior curvature, posterior elevation, posterior curvature, total refractive power, and pachymetry map) with the anterior segment OCT has also been performed to determine the diagnostic accuracy or the grade of keratoconus.

Cataract surgery is one of the most frequently performed surgeries in the world, and is increasingly a refractive as well as a rehabilitative procedure. IOL power calculations are undergoing continual improvements, with the latest generations' formulas have shown promising precision and less refractive surprises compared with second and third generations' formulas [28]. Accurate estimation of the effective lens position (ELP) is widely considered the main limiting factor in refractive predictability, and classical IOL power calculation formulas rely on a thin-lens model to calculate the IOL power with the use of 2–7 biometric parameters to predict ELP [29]. Most available formulas are based on optics, regression calculations or ray tracing.

Supervised machine learning can create classification or regression models using algorithms trained from data without relying on prior assumptions. The Hill-Radial Basis Function and the Kane Formula belongs to this category. Currently, the results of these methods do not routinely exceed that of classic formulas [30], but a recent article showed that the combination of theoretical optics, regression, and artificial intelligence components could achieve better results [31].

Keratorefractive surgery

Keratorefractive essentially involves treating refractive errors by reshaping the cornea—traditionally with an excimer laser, but now possible using only a femtosecond laser via refractive lenticule extraction [32]. The evolution of keratorefractive surgery began with surface ablation techniques such as photorefractive keratectomy (PRK) that involves epithelial removal [33], or laser epithelial keratomileusis (LASEK) where 20% alcohol is used to displace the corneal epithelium [34]. The detached epithelial sheet was initially preserved to reduce inflammation and pain, but later techniques involved removal as the alcohol was found to affect its vitality [35]. More recently, excimer laser ablation has been used to remove the corneal epithelium directly i.e. transepithelial PRK [36]. One advantage of transepithelial PRK is that the epithelial layer removal and excimer is performed at the same time—although most reports suggest that healing time and visual outcomes results do not vary greatly amongst various techniques of epithelium removal [37, 38]. Surface ablation has regained popularity over the past few years due to the safety of the surgery and better biomechanics [39], especially in patients with high myopia and thin corneas [40, 41]. While the refractive predictability of surface ablation is comparable with LASIK, myopic regression may be more common after surface ablation [42]. Moreover, scarring and haze can occur from the healing response in the Bowman's layer and anterior corneal stroma [43]. Low-dose topical mitomycin-C (0.02–0.04%) is usually applied after excimer laser to reduce haze formation [44, 45]. Nonetheless, patients may still experience more discomfort after surface ablation compared with LASIK, due to the healing of the epithelium [46].

Laser in situ keratomileusis (LASIK)

While LASIK corneal flaps were previously created using an oscillating microkeratome [47], the addition of femtosecond lasers greatly reduced the risk of some of the more significant flap complications such as buttonhole, free cap, and irregular cuts [48]. One of the other main benefits of

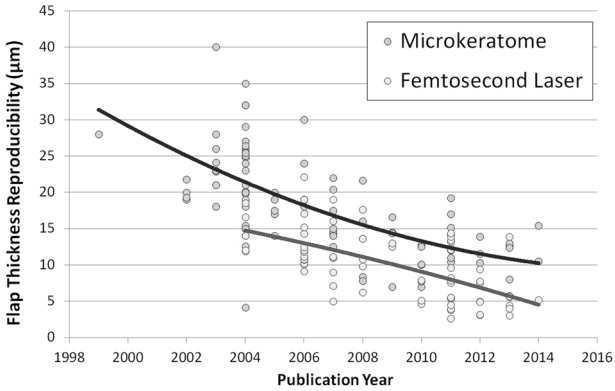

Fig. 4 Central flap thickness reproducibility comparing microkeratome and femtosecond laser. Graph showing the central flap thickness reproducibility for all studies published between 1998 and 2014, grouped by mechanical microkeratome (blue) and femtosecond laser (red).

femtosecond lasers was the improved reproducibility of flap thickness, which enabled the use of thinner flaps with increased safety. Flap thickness reproducibility is an important factor for residual stromal thickness (RST) safety planning as a thicker than intended flap can lead to a lower than predicted RST and risk of ectasia—Fig. 4. The standard deviation of central flap thickness from older microkeratomes was reported to be in the range of 20–40 µm [47, 49], compared with current femtosecond flap thickness reproducibility of less than 5 µm [50, 51].

A review of LASIK outcomes was reported on by Sandoval et al. [4] in 2016. The authors reviewed articles published between 2008 and 2015 representing more than 67,000 eyes. They found UDVA was 20/40 or better in 99.5% of eyes, spherical equivalent refraction was within ±1 diopter (D) of target in 98.6% of eyes, and loss of 2 or more lines of corrected distance visual acuity (CDVA) was 0.61%. Subjectively, patients were very satisfied with only 1.2% of patients reporting to be dissatisfied with the procedure. Within this analysis were treatments that were performed as far back as 2008. Therefore, some of the lasers that contributed to these outcomes would no longer fall into the "modern laser" category in 2020, so we can only expect future reviews to show even better outcomes.

Despite these excellent outcomes, it is still important to counsel patients on the occasional suboptimal effects, such as increased glare and haloes, residual refractive error or irregular astigmatism [52]. Dry eye is one of the most common side effects, which is usually temporary and may be managed with topical lubricants in most cases [53]. Postoperative flap-related complications include flap displacement, diffuse lamellar keratitis (DLK) [54], or epithelial ingrowth [55], all of which may be treated with topical eye drops or in some cases may require laser treatment or flap-lift [56]. Rarely, corneal ectasia can still occur, which has greatly reduced with

the advent of more accurate preoperative imaging and assessments as already described [57].

Advances in excimer laser and wavefront-guided treatments

Both LASIK and surface ablation techniques rely on the excimer laser to reshape the cornea, which were initially based on a spherical shape as in the Munnerlyn formula. Aspheric profiles were first tested by Seiler et al. [58] who demonstrated significantly less induction of spherical aberration and glare. The introduction of flying spot lasers and a Gaussian beam profile further improved outcomes. Laser frequency has also been increasing over the years, which has reduced ablation time and the impact of corneal dehydration. O'Brart et al. [59] showed that increasing optical zone diameter decreased the impact of night vision disturbances, so modern lasers use large optical zones and improved transition zones [60].

As described above, another advance was the use of aberrometry measurements to treat naturally occurring HOAs [61–63]. However, wavefront-guided treatments did not eliminate residual HOAs, but did slightly reduce the induction of spherical aberration [64]. Wavefront-optimized treatments shifted the aim of the treatment to the control of spherical aberration, but can have variable effects on other HOAs [65, 66]. An alternative method for custom treatments is corneal topography-guided laser ablation [67], most useful where the refractive error of the eye matches its corneal topography i.e. most of the aberration is produced by the cornea [68]. Currently, excimer lasers with active eye tracking systems to compensate for cyclotorsion and microsaccadic eye movements are already considered common standards of care for such treatments [69].

Beyond 2020: keratorefractive surgery for presbyopia correction

Traditionally, the principles used for monovision have been applied to keratorefractive surgery [70, 71], to provide patients with good distance and reading vision with high patient satisfaction [70, 72]. However, careful patient selection is required, with the loss of fusion and stereoacuity leading to poor acceptance as a potential outcome [73, 74].

Another option of keratorefractive surgery for presbyopia correction is to create a 'multifocal cornea'. The majority of corneal multifocal treatments essentially creates a "central island" to provide near vision, while a hybrid combination of multifocality with some induced anisometropia may have improved safety [75, 76]. However, some studies using this hybrid protocol report an unacceptable rate of loss of two lines of CDVA [77]. Therefore, caution must be used when treating the cornea with any multifocal laser ablation profile because the change in optical quality can increase the risk of losing lines of CDVA in poorly selected candidates. Suggested selection criteria include low hyperopia (up to +3 D) or myopia (up to −4 D), low astigmatism, a maximum requirement of +2 near vision add and photopic pupillometry of less than 3.5 mm [78].

Recently, the application of extended depth of field in keratorefractive surgery has come from the research on the use of spherical aberration to increase the depth of field [79, 80]. Laser blended vision (LBV) is based on nonlinear changes in asphericity. LBV is tolerated by more than 95% of patients [81–83], compared with monovision which is tolerated by only between 59 and 67% of patients [84]. Because it is not a multifocal treatment, LBV has also been shown to provide good distance, intermediate, and near vision without the increased risk for losing lines of corrected visual acuity [81, 82, 85].

Small incision lenticule extraction (SMILE)

Following the introduction of the VisuMax femtosecond laser (Carl Zeiss Meditec, Jena, Germany), an all femtosecond laser, keyhole, flapless procedure was developed, referred to as SMILE. The SMILE procedure involves using a femtosecond laser to delineate a refractive lenticule within the stroma connected to the surface by a small incision—Figs. 5 and 6. The femtosecond interfaces are surgically separated and the refractive lenticule is removed through the small incision. SMILE brings two main advantages over LASIK: faster dry eye symptom recovery and better spherical aberration control [86–88]. Both of these advantages stem from the minimally invasive pocket incision that results in maximal retention of anterior corneal innervation as well as structural integrity. The evidence for reduced dry eye is supported by studies on corneal nerve regeneration [89], and recovery of corneal sensitivity [90].

Biomechanically, SMILE offers a theoretical advantage over LASIK by preservation of the stronger anterior stromal lamellae. Randleman et al. [91] and Scarcelli et al. [92] demonstrated that the strength of the stroma decreases from anterior to posterior within the central corneal region. Petsche et al. [93] found a similar result for transverse shear strength to decrease with stromal depth. Applying this knowledge to SMILE, since the anterior stroma remains uncut, the strongest part of the stroma continues to contribute to the strength of the cornea postoperatively. This has been evaluated using a theoretical [94], finite element modeling [95, 96], and laboratory experiments [97]. The clinical effect is less induction of spherical aberration compared with LASIK [98]. Therefore, it is possible to increase the optical zone diameter with SMILE, further reducing the spherical aberration induction, without

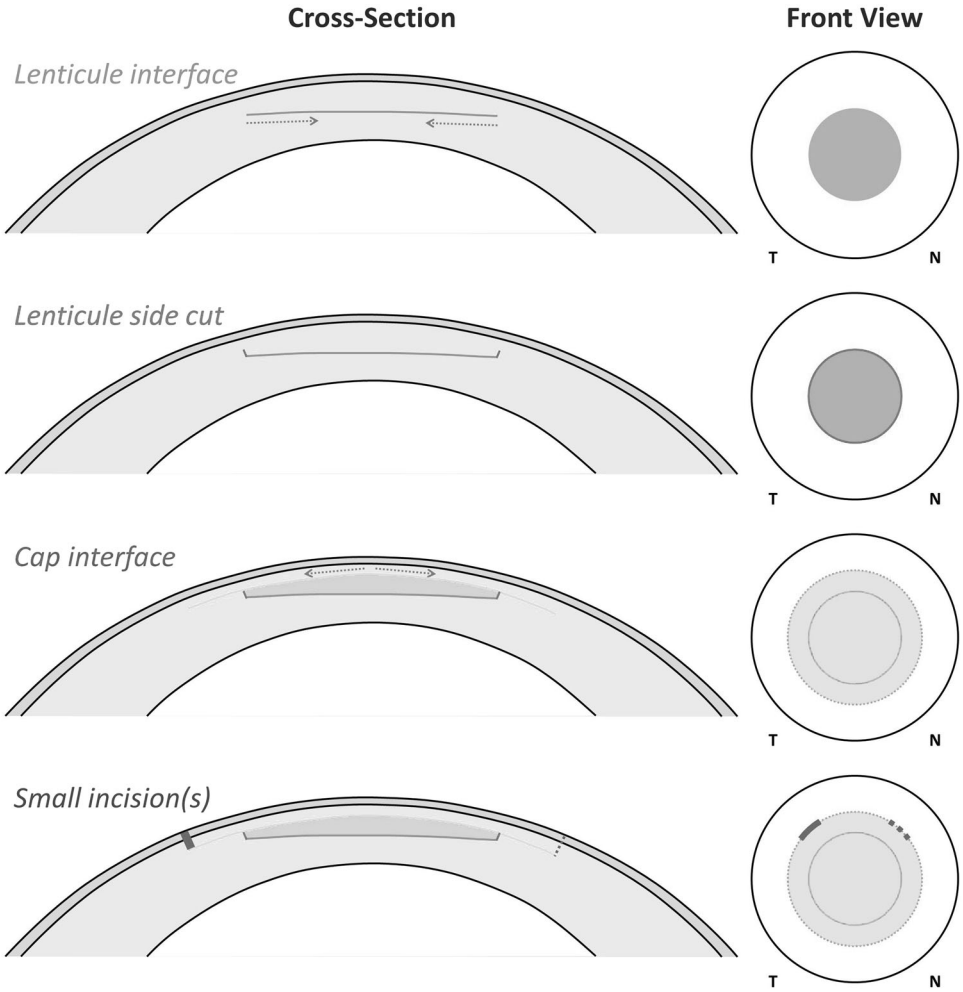

Fig. 5 Series of diagrams showing the femtosecond cutting sequence for a SMILE procedure. (1) lenticule interface from out-to-in, (2) lenticule side cut, (3) cap interface from in-to-out, and (4) the small incision(s). Reprinted with permission from Reinstein et al. [117].

compromising the corneal biomechanics compared with the equivalent LASIK treatment [99].

Refinements to SMILE

As SMILE has gained popularity, nearly every aspect of the treatment has been optimized. Initially, the main weakness was the slightly delayed visual recovery relative to the overnight 'wow' effect associated with LASIK. However, detailed research into the energy level and spot/track spacing has significantly improved visual recovery, without compromising the ease of lenticule separation [100–104]. Most published results suggest that SMILE is safe, effective, and predictable for treating moderate myopia and modest levels of astigmatism [105], with postoperative visual outcomes comparable with femtosecond LASIK [106, 107]. Vision-related quality of life has also been found to be comparable between SMILE and LASIK [108–110].

Suction loss is the most common complication for SMILE, with an incidence of about 0.50% [111–113]. However, there is a clear management protocol for this, further guided by a decision tree by Reinstein et al. [111, 112]. Thus, it is possible to complete the treatment on the same day (continuing with SMILE or converting to LASIK) without affecting the visual or refractive outcome [111, 112]. Postoperative complications of SMILE are essentially the same as LASIK, however there are two areas where some small differences have been identified. The first is with DLK where a unique appearing sterile multifocal inflammatory keratitis can present after SMILE, which needs to be aggressively treated [114]. The second area is epithelial ingrowth, which can be more common due to the instrument implanting epithelial cells within the interface by the instruments through the small 2-mm incision. This can be successfully treated by using a Nd:YAG laser or washing out the interface. Finally, a number of options for retreatment or enhancement after SMILE have been developed, including surface ablation, converting the cap in to a flap via side cut or Circle [115], and thin flap LASIK [116]. SMILE is now a mature and established procedure [117] that provides patients with a safe and effective outcome

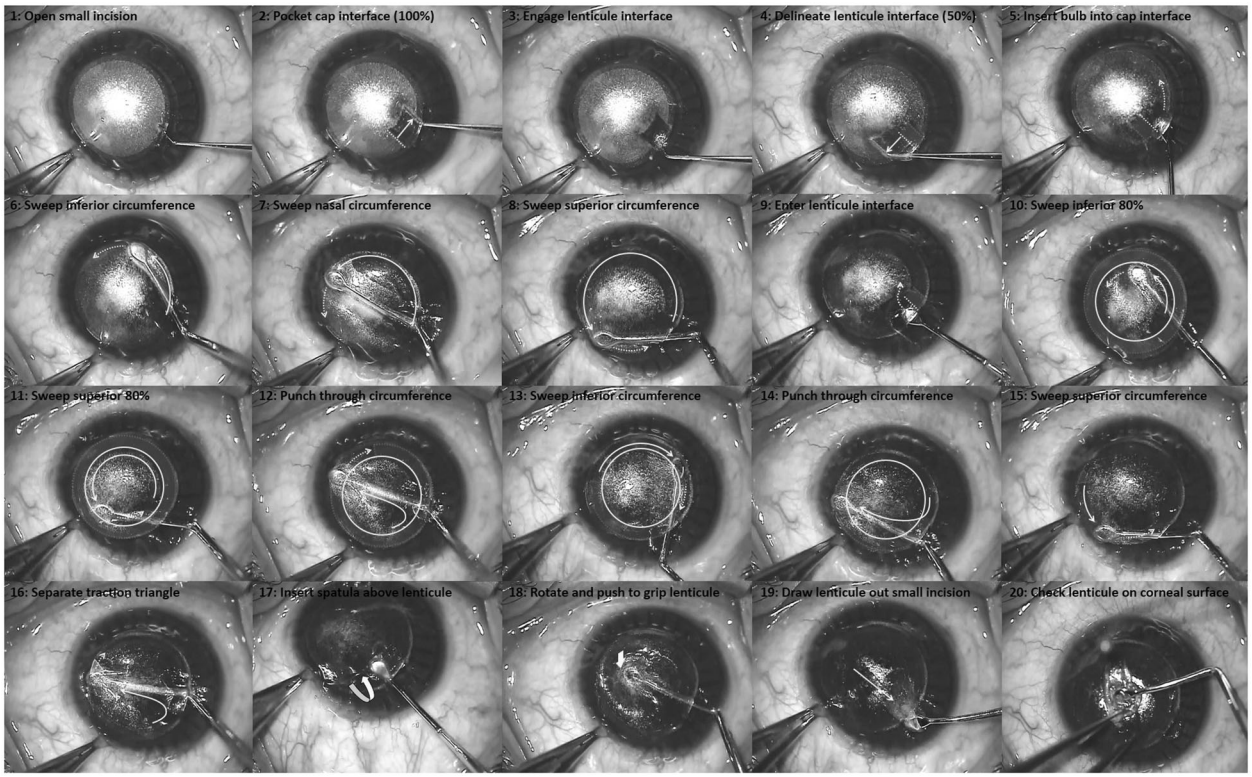

Fig. 6 Series of images showing the standard surgical technique for SMILE. Reprinted with permission from Reinstein et al. [117].

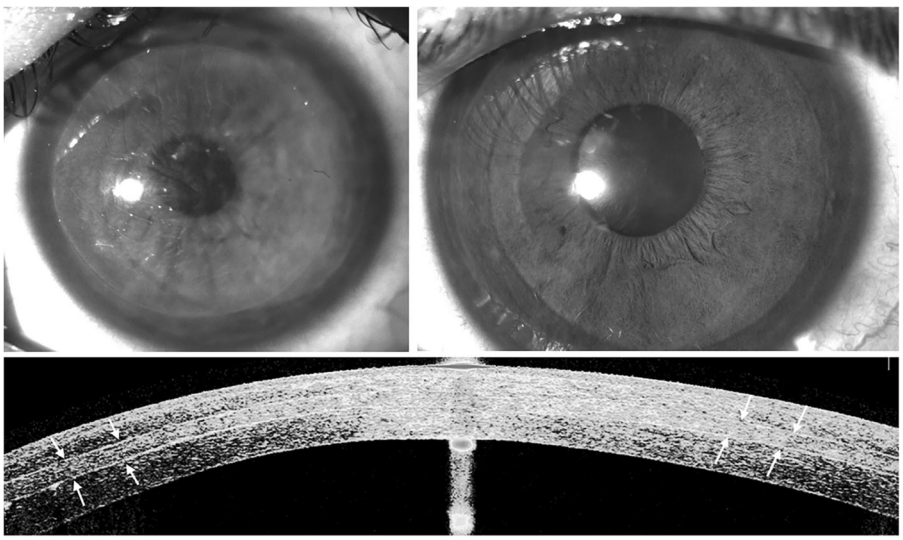

Fig. 7 Corneal stroma enhancement with a decellularized corneal stroma lenticule in a patient with advanced keratoconus. Slit-lamp pictures 1 week (top-left) and 3 months after surgery (top-right; note the complete transparency recovery). Corneal OCT image (down): the implanted lenticule is easily identified 6 months after surgery (white arrows).

with current reports demonstrating that the visual and refractive outcomes are similar to LASIK [87, 118–120].

Beyond 2020: stromal lenticule implantation

The increasing popularity of SMILE is providing surgeons with thousands of human donor stromal lenticules that could potentially be used for the treatment of presbyopia [7, 121], hyperopia [9, 122, 123], and corneal ectatic diseases, such as keratoconus (Fig. 7) [124, 125]. The greater precision of the femtosecond laser allow for more accurate stromal lenticule creation, and may offer advantages over commercialized synthetic inlays in the aspect of biocompatibility, retaining nutrient flow within the stroma and reduced risk of extrusion. On the other hand, these biological inlays have a low but potential risk for rejection, while subject to eye banking and corneal transplantation regulations for donor quality and safety. The preoperative

decellularization of these donor lenticules may reduce the risk of rejection [4, 124, 126, 127].

Preliminary human clinical results suggest biocompatibility, safety and long-term transparency of these implants in vivo [121–125]. However, one of the main limitations is the unpredictability of the refractive outcome, which is dependent on the stromal remodeling of both the inlay and the recipient stroma, leading to significant undercorrections [6, 123, 128, 129]. Further studies with larger samples, longer follow-ups, technique refinements, and treatment nomograms are required. On the other hand, encouraging results are being reported for advanced keratoconus, where a precise refractive outcome is not the target, but refractive stability may delay the need for corneal transplantation (Fig. 7) [124, 125]. Stromal lenticules (either plano or negative meniscus shape) and allogenic stromal ring segments have been used in clinical trials for keratoconus showing a moderate improvement in all visual, refractive and keratometric parameters [31, 37, 38].

Intracorneal implants

In 1949, José Ignacio Barraquer, described the "thickness law", forming the basis for intracorneal implants leading to a hyperopic or myopic shift [130]. Keratophakia was described in 1964 as a lamellar refractive surgery procedure for the treatment of hyperopia and presbyopia, but abandoned due to interface scarring and unpredictable refractive results [131]. However, this led to the development of synthetic intracorneal implants known today as "inlays". Early corneal inlays (made of polymethyl-methacrylate-PMMA or polysulfone) were associated with loss of transparency, corneal thinning or melting, and implant extrusion due to interruption of nutrient flow within the stroma [132, 133]. This critical limitation was partially overcome with the development of intracorneal ring segments (ICRS), new synthetic inlays with perforated designs, and new hydrogel biomaterials permitting the exchange of nutrients, such as glucose and oxygen within the corneal stroma [132, 134, 135]. Today, intracorneal implants for the treatment of myopia and astigmatism have been superseded by keratorefractive surgery. Intracorneal rings are made of inert, biocompatible synthetic materials that are implanted deep into the stroma to modify the corneal curvature and regularize its shape to reduce the refractive error—Fig. 8 [136]. Their capability to flatten the central cornea, reduce keratometric values, and corneal astigmatism, have made ICRS an important therapeutic approach for the visual rehabilitation of keratoconic eyes. However, the low refractive predictability and significant risk of losing corrected vision have caused ICRS to be abandoned as a purely refractive option in non-pathologic eyes [137].

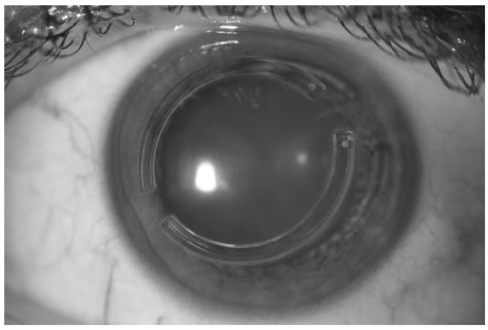

Fig. 8 Slit-lamp photograph of an eye with intracorneal implants. Intracorneal ring implanted in a patient with keratoconus.

Presbyopia corneal inlays

Corneal inlays have several theoretical advantages: there is no corneal tissue removal, it is minimally invasive, and can be explanted [138, 139]. There are three types of corneal inlays [138]: corneal reshaping inlays to reshape of the anterior corneal curvature, leaving a multifocal cornea; refractive inlays where there is a modification on the refractive index of the cornea with a bifocal optic; and small aperture inlay which improves the depth of focus. The technical specifications of these various inlays are summarized in Table 1. Presbyopia inlays are implanted in the nondominant eye, centered on the first Purkinje reflex within a corneal pocket or under a stromal flap [133]. The implantation depth depends on the inlay: those that alter the curvature of the cornea are implanted more superficially, while those with a small aperture or a different refraction index are implanted deeper to reduce anterior corneal curvature changes and to allow a proper diffusion of nutrients within the corneal stroma [133, 139]. Outcomes from various significant clinical trials of these corneal inlays are summarized in Table 2.

The Raindrop^{TM} (ReVision Optics Inc., Lake Forest, CA, USA) corneal reshaping inlay is made of a biocompatible hydrogel material with 80% water to allow the passage of nutrients within the corneal stroma (Fig. 9 left) [138–140]. It has no refractive power, formed by smoothly transitioning regions that provide near vision in the steepest central area, intermediate vision around this central area, and distance vision in the periphery that is marginally affected by the inlay [138–140]. Despite most patients being satisfied, 7.8% of eyes required inlay removal due to discontent with the visual outcome [141]. Other complications included marked glare (2.1%) or halos (4.1%) even one year after surgery; flap-related dry eye syndrome (4.7%), and inlay-related central corneal haze (14%)—Fig. 9 right. The Raindrop implant was discontinued from the market in January 2018 due to the evidence of late haze with loss of CDVA in clinical practice [132, 142].

Table 1 Technical specifications of commercially available presbyopia inlays.

Inlay	Material	Type of inlay	Measurements	Mechanism of action
Raindrop	Biocompatible hydrogel 80% water	Corneal reshaping inlay	Thickness of 10 µm at the periphery, and 32 µm at the center Diameter: 2 mm	Reshapes the anterior cornea, creating a hyperprolate region → multifocal cornea
Flexivue	Clear copolymer of hydroxyethyl methacrylate and methyl methacrylate with an ultraviolet blocker	Refractive inlay	Thickness 15–20 µm Diameter: 3 mm	The central 1.8-mm diameter of the disc is plano in power (for distance vision) and the peripheral zone has an add power which ranges from +1.25 D to 3.0 D in 0.25 D increments (for near vision)
Icolens	Copolymer of hydroxyethyl methacrylate and methyl methacrylate	Refractive inlay	Thickness: 15 µm Diameter: 3 mm	Central zone for distance and peripheral positive refractive zone for near
Kamra	Polyvinylidene fluoride, nanoparticles of carbon	Small aperture inlay	Thickness: 5 µm Diameter: 3.8 mm	Increases the depth of focus through the principle of small aperture optics

The Flexivue Microlens™ (Presbia Cooperatief U.A., Amsterdam, Netherlands) and Icolens™ (Neoptics AG, Huenenberg, Switzerland) are bifocal inlays with a central 0.15 mm opening to facilitate the transfer of nutrients and oxygen through the cornea, implanted into a corneal pocket at 280–300 µm depth in the nondominant eye [133, 143, 144]. Light rays passing through the central zone of the inlay that does not have refractive power will be sharply focused for distance vision, while the refractive peripheral zone focus light rays on the retina for near vision (Table 1) [133, 143]. Available scientific evidence with these inlays is far more limited, with monocular reduction of UDVA, loss of contrast sensitivity and a significant frequent loss of CDVA reported [4, 16–18].

The Kamra Vision™ (Acufocus Inc., Irvine, CA, USA) is the most widely used corneal inlay, with nearly 20,000 inlays implanted worldwide [139, 140]. It has a central 1.6 mm aperture, and 8400 microperforations (5–11 µm in diameter) in the peripheral opaque ring to allow nutritional flow through the cornea (Fig. 10 left) [138–140]. However, as it is an opaque inlay it may be vey obvious in light-colored eyes. It improves near vision by increasing the depth of focus through the principle of small aperture optics (blockage of the peripheral unfocused rays of light) [139, 140]. It is usually implanted into a 6 × 6 mm diameter stomal pocket and 200–270 µm depth in the nondominant eye. A prospective, multicenter clinical trial (507 eyes with emmetropic presbyopia and 3-year follow-up) reported an average 3.3-line improvement in UNVA, 1-line improvement in UIVA, and 0.4-line reduction in UDVA on the implanted eye, while no loss in binocular distance vision was observed [19]. Despite the opaque nature of this inlay, no scotomas in the visual field have been observed, with a mean reduction of ~1 dB in contrast sensitivity [138, 145]. 8.7% of eyes required inlay removal due to dissatisfaction with the visual outcome. Other complications included significant glare (19%), halos (25%) night vision problems (30%), and inlay-related central corneal haze (2.8%)—Fig. 10, middle.

Beyond 2020: future of intracorneal implants and corneal inlays

Corneal inlays have proven to be an effective alternative for presbyopia management. However, the future of inlays beyond 2020 looks uncertain. Despite clinical investigation for more than 15 years, they have still not gained full popularity among refractive surgeons due to the frequent problems of centration, biological intolerance, and optical performance, causing a relatively high explantation rate over time secondary to late complications such as corneal stromal opacities, late hyperopic shift or inadequate visual performance [26]. The most promising of inlays remain the Kamra implant where it was observed in that UNVA, refractive stability, patient satisfaction, haze risk, and explantation rate significantly improved when the Kamra was implanted inside a lamellar pocket (and not a flap). This stromal pocket was created with a femtosecond laser using tight spot-line separation settings and with a depth ≥40% of the total corneal thickness. This could be due to a reduction in wound-healing response due to the reduced keratocyte density of the posterior stroma [19]. Similar outcomes were previously reported by other authors (Table 2), including eyes with previous cataract surgery with a monofocal IOL [21–23]. Perhaps more importantly, it has been shown that the procedure is reversible—Alió et al. demonstrated that Kamra inlay removal can be safely performed without permanently affecting corneal topography and aberrometry, with more than 60% of patients recovered preoperative visual acuity [24]. Certainly, more improvements are needed in the future as careful slit-lamp examination showed in most cases a mild haze, and occasionally, prominent donut-like scarring (Fig. 10 right) [24]. Corneal confocal microscopy demonstrated that the Kamra inlay had good

Table 2 Studies evaluating the clinical outcomes of the different available presbyopia inlays for the correction of presbyopia in emmetropic patients (those studies performing a concomitant myopic or hyperopic ablation have not been included).

Author	Year	Inlay	Technique	Eyes	Follow-up (months)	Efficacy	Safety	Patient dissatisfaction	Explant rate	Financial interests
Garza et al. [132]	2013	Raindrop	Flap	20	12	100% UNVA ≥ 20/40	42% lost 1 line of CDVA 68% lost 1 line of CNVA	5%	5%	Yes
Yoo et al. [142]	2015	Raindrop	Flap	22	6	Mean UNVA of 20/35	32% showed a decreased postop UDVA	18%	Non reported	No
Whitman et al. [185]	2016	Raindrop	Flap	373	12	UNVA improved by 5.1 lines 93% UNVA ≥ 20/25	UDVA decreased by 1.2 lines CDVA decreased by half of 1 line	8%	3%	Yes
Malandrini et al. [133]	2015	Flexivue	Pocket	81	36	UNVA improved by 6 lines	8% lost >1 line of CDVA	9% still required reading glasses	7.4%	Yes
Beer et al. [186]	2019	Flexivue	Pocket	30	36	UNVA: 76.9% in J1 (from 87.1% at the 1-year postop)	16.1% lost >3 lines of CDVA at 1 year (stable thereafter)	26.7% (from 9.7% at the 1-year postop)	13.3%	Yes
Baily et al. [144]	2014	Icolens	Pocket	52	12	17% UNVA ≥ 20/40	77% lost ≥1 lines of CDVA	10%	21.1%	No
Seyeddain et al. [187]	2012	Kamra	Flap	32	36	97% UNVA ≥ 20/40[a]	31.4% lost ≥1 lines of CDVA	15.5%	0%	Yes
Vukich et al. [145]	2018	Kamra	Flap/Pocket	507	36	UNVA improved by 3.3 lines 72.4% UNVA ≥ 20/32	UDVA decreased by 0.4 lines CDVA was reduced by no more than 1 letter	5.5 (1–7 scale; 7 being "very satisfied")	8.7%	Yes

Efficacy is defined as mean postoperative monocular uncorrected near visual acuity (UNVA) in the implanted eye; safety is defined as percentage of eyes losing lines of monocular corrected distance visual acuity (CDVA) in the implanted eye.

UDVA uncorrected distance visual acuity, *UDVA* uncorrected distance visual acuity, *J* Jaeger.

[a]Binocular visual function, as monocular one was not available.

i- ntrastromal tolerance, although a low grade of keratocyte activation was found in all patients, and a stronger response was associated with a negative visual outcome [25].

Phakic IOL implantation

The first phakic IOLs (PIOLs) were angle-supported and placed in the anterior chamber as early as 1953 by Dr. Strampelli [146]. In 1977, Prof. Worst developed the 'iris-claw' lens made from PMMA, reducing complications such as glaucoma [147]. It was only until 1986 when posterior chamber PIOLs were developed by Dr. Fyodorov, who's designed was adapted to develop the implantable collamer lens (ICL)—made of a proprietary copolymer of hydroxyethyl methacrylate and porcine collagen. PIOL implants have the potential to confer better vision, achieve higher patient satisfaction compared with keratorefractive surgery in selected patients; and avoids the risk of corneal ectasia [148]. Another advantage is that the crystalline lens is retained, thus keeping natural accommodation in younger patients, with potentially less posterior segment complications such as retinal detachment [149]. However, careful patient selection is required for PIOL implantation as other complications such as glaucoma and cataract can occur [150]. Thus, such procedures are usually performed in patients who have contraindications to traditional laser refractive surgery or cannot achieve correction due to extremes of refractive error [149].

Current phakic IOLs

PIOLs come in two varieties: anterior chamber PIOLS and posterior chamber PIOLs. Anterior chamber can be further divided into angle-supported IOLs and iris-claw IOLs but only the iris-claw (Ophtec BV, the Netherlands and J&J, USA) is still available. The Artilens (as it is called now) is fixated in the eye to the iris. The lens is first centered in front of the pupil and then the iris tissue in the mid-periphery (which is immobile during pupillary movement) is enclosed between the claws to hold it in place. It comes in a rigid PMMA version (Fig. 11, left) and in a foldable version called artiflex (Fig. 11, right) and is made of polysiloxane. The Artilens can correct myopia, hyperopia, and astigmatism.

The archetypal posterior chamber PIOL is embodied by the Visian ICL (STAAR Surgical, USA) for the past two decades. The EVO ICL V4c (2011) is a single piece PIOL designed with a central port to eliminate the need for iridotomy or iridectomy that was required by earlier ICL models. The central port also allows aqueous flow from the posterior chamber to the anterior chamber to maintain normal physiology (Fig. 12) [151]. The main benefit of the

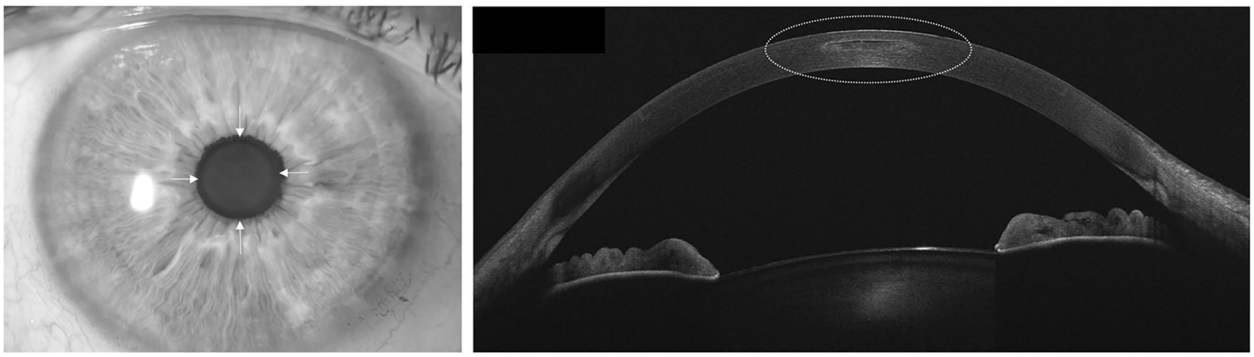

Fig. 9 Raindrop inlay. Slit lamp (left; white arrows point the edges of the inlay) and anterior segment optical coherence tomography (OCT) pictures (right). Observe how the thin inlay is seen in the OCT image and it appears surrounded by a mild stromal haze (yellow dashed line).

EVO+ ICL (2016), which is available in powers from −0.50 to −14.00 D, is its extended optical zone (Fig. 12). A prospective, fellow eye-controlled study reported no difference in the safety, efficacy, predictability, and stability comparing the V4c and EVO+ ICL [152]. Through 5 years of postoperative follow-up, only one eye had developed an asymptomatic cataract in the conventional ICL group. There was no incidence of pigment dispersion glaucoma or pupillary block in any eye of either group [152].

Beyond 2020: presbyopia-correcting PIOLs

The next potential frontier for PIOLs is to correct presbyopia using multifocal designs [153]. The Implantable Phakic Contact Lens (Presbyopia, Care Group) is made of hydrophilic acrylic material and has a trifocal diffractive optic (optical zone of 3.5 mm in diameter). It is available with additions between +1.5 and +3.5 D in steps of 0.5 D. Unfortunately no peer review article has been published. STAAR Surgical submitted their multi-site European clinical trial data for the EVO+ Visian ICL with an aspheric extended depth of focus (EDOF) optic, a lens that is designed to provide correction of myopia or hyperopia and presbyopia. Results from the clinical trial were submitted in July 2019 and if approved, this lens could be commercially available in the second quarter of 2020.

Refractive lens exchange

Refractive lens exchange or clear lens extraction is the removal of a clear crystalline lens and insertion of an IOL that replaces or augments the refractive ability of the eye [154]. This may be performed in selected patients where corneal laser surgery is not possible, or cannot achieve the desired refractive outcome [155]. Refractive lens exchange remains controversial in some clinical practices, as endophthalmitis can be more devastating compared with the risk of corneal infections that come with keratorefractive surgery [156]. Moreover, refractive lens exchange may have a higher risk of complications such as retinal detachment, compared with conventional cataract surgery if the patients are younger or more highly myopic [157]. Nonetheless, with the advances in surgical technology leading to better refractive outcomes, fast visual recovery and reduction in postoperative complications [158–160], the much improved risk-benefit ratio has led to this practice being performed more commonly in carefully selected patients [161]. The major advantage of refractive lens exchange is that all forms of refractive error can be treated based on the design of the IOL. Today, aspherical IOLs are widely used, as they match the optical quality of the eye's natural lens and compensate for the positive spherical aberration of the cornea to provide sharper vision in eyes with larger pupils, or in situations with low lighting. Astigmatism may also be corrected with toric IOLs, which have different powers in opposite meridians of the lens. However, the surgeon needs to meticulously adjust the orientation of the IOL inside the eye for optimal astigmatism correction, because for every 3 degrees of misalignment 10% of the astigmatic correction is lost.

Presbyopia-correcting IOL implants

In recent years, new presbyopia-correcting IOL designs have rapidly developed using different refractive principles. However, proper patient counseling and setting realistic expectations are of the utmost importance, especially with regards to loss in contrast sensitivity, as well as the occurrence of glare and haloes. Moreover, precise IOL power calculation, preoperative evaluation, and treatment of ocular co-morbidities such as ocular surface disease, are key steps to ensure a satisfactory outcome. Today there is such a wide range of prebyopbia-correcting IOLs that the surgeon needs to discuss the most appropriate option based on the risk-benefits, balanced with patients' expectations with visual requirements.

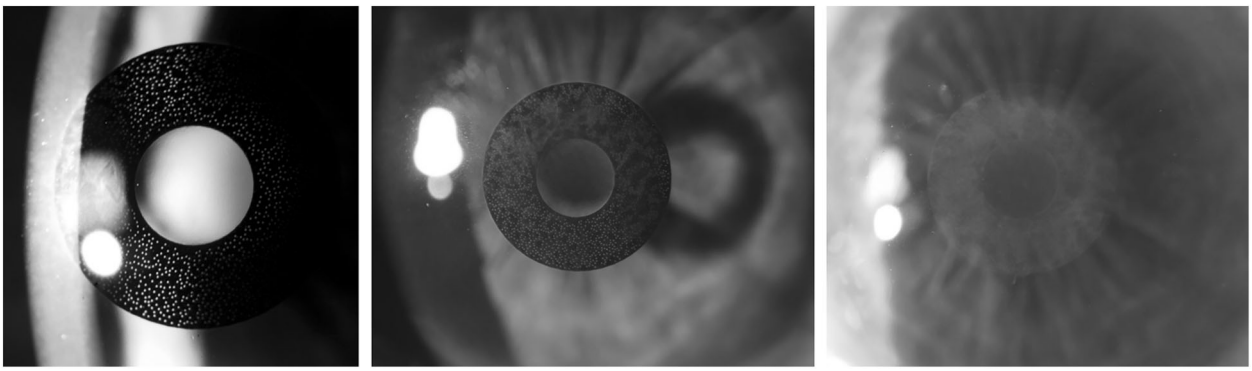

Fig. 10 Kamra inlay. Slit-lamp pictures 3 months (left; observe the peripheral microperforations to allow corneal nutrition) and 3 years after implantation (middle). Note the progressive moderate haze associated with visual loss that justified inlay explantation, remaining a donut-shape central corneal scar still visible 4 years after inlay removal (right).

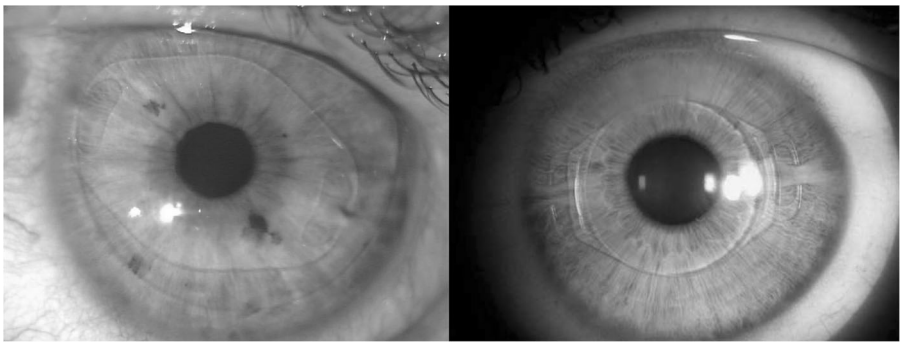

Fig. 11 Anterior chamber iris-claw intraocular lenses. Left: rigid polymethyl-methacrylate (PMMA) lens. Right: foldable lens made of polysiloxane. Both from Ophtec BV, the Netherlands and J&J, USA.

The first presbyopia-correcting IOLs were generally based on diffractive lens designs, either using apodization, in which a near-dominant central area is surrounded by concentric rings of decreasing height that result in diffraction of light at both distance and near [162]; or an aspheric anterior surface and a posterior surface with diffractive rings that focus both near and distance light regardless of pupil size [163]. Refractive segmented varifocal IOLs use an asymmetrical shape of the near-vision segment to transition between near- and far-vision zones [164]. Trifocal diffractive IOL attempts to improve intermediate vision by providing a third focus—Fig. 13, left [165]. The HOAs and visual quality have been reported to be similar to that of bifocal diffractive IOLs [166].

EDOF IOLs aim to give an elongated focus of vision by manipulating the induced spherical aberration of the IOL. However, the spherical aberration causes a degradation of visual quality and may affect distance visual acuity [167]. In order to negate this negative effect, some multifocal lenses incorporate limited amounts of negative spherical aberration. For example, the Tecnis Symfony IOL (J&J, USA) uses a biconvex anterior aspheric and posterior achromatic diffractive surface IOL with an echelette design [168]. Studies suggests that these IOLs mainly improve distance and intermediate vision with some loss in contrast sensitivity [169]. Other examples of hybrid multifocal IOLs that manipulate aberrations with multifocality is FineVision Triumf (Fig. 13, right). Another way to extend the depth of focus is to use the pinhole principle. The IC-8 (Acufocus, USA) utilizes a non-diffractive 3.23 mm opaque PVDF mask with a 1.36 mm central aperture that blocks unfocused paracentral light rays and permits paraxial light rays to enter (Fig. 14) [170]. This IOL may provide good distance, intermediate and near vision but decrease the peripheral visual field beyond 30 degrees of the fixation point. In particular this IOL may be effective in eyes with irregular corneal astigmatism.

Beyond 2020: accommodative IOL implants

The development of presbyopia-correcting IOL is challenging as accommodation is a dynamic process, and the above-mentioned designs do not directly address the mechanism of accommodation. Accomodative IOLs (AIOLs) attempt to imitate the mechanism of natural accommodation, with various theoretical assumptions. However, much more development is required to improve its clinical outcomes. AIOLs generally consist of either single-optic, dual-optic, or deformable surface designs [171]. They may be placed either in the sulcus or inside the capsular bag [172]. Single-optic AIOL have flexible supporting elements to transmit ciliary muscle contraction into

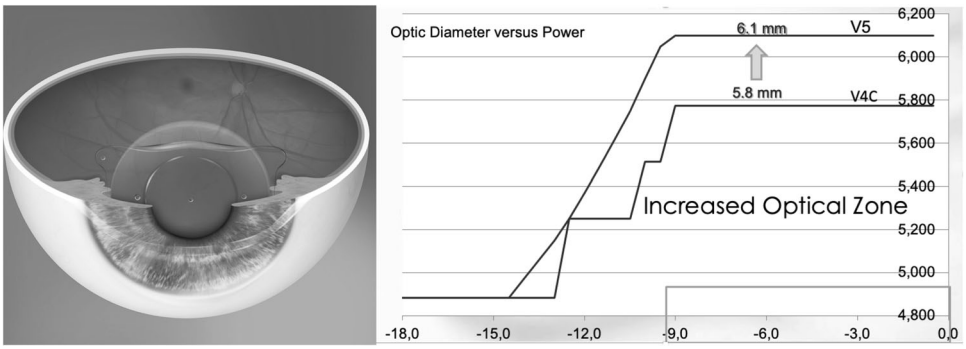

Fig. 12 Example of implantable collamer lens (ICL) in situ. The central port allows aqueous flow from the posterior chamber to the anterior chamber in order to maintain the normal physiology of the anterior segment of the eye. The EVO+ Visian ICL (STAAR Surgical, USA) introduced in 2016 now was an extended optical zone.

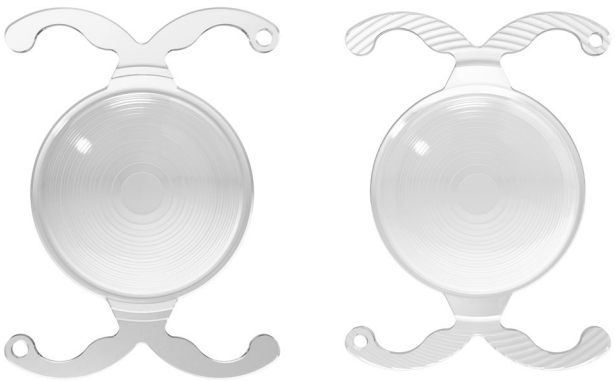

Fig. 13 Example of multifocal intraocular lens implants recently available. Left: trifocal intraocular lens implant. Right: hybrid design extended depth of focus (EDOF) intraocular lens implant.

an anterior displacement of the lens optic, resulting in increased dioptric power of the eye to improve near vision [173]. Experimental evidence suggests that beyond 6 months, the emptied capsular bag is unable to provide any significant dynamic force to an intracapsular located device [174], suggesting that sulcus placement of AIOLs may be needed [175–177]. A dual-optic lens design essentially consists of two separate optics: a high-powered 'plus' anterior optic of fixed dioptric power and a 'minus' posterior optic, coupled by spring haptics [178]. These lenses were designed to occupy the capsular bag completely, thus the capsular tension could theoretically change the distance between the anterior and posterior optic. Thus far, only the Lumina AIOL (AkkoLens International, Breda, The Netherlands) has published clinical evidence with positive clinical results. This acrylic hydrophilic polymer AIOL consisting of two mobile optical elements, which is implanted in the ciliary sulcus. The anterior element provides 5 D of correction, while the posterior provides 10–25 D of correction based on ocular biometry. Each optic has internal sinusoidal surfaces where its power increases linearly when one of the lenses slides onto the other due to ciliary body action. Therefore, when the eye accommodates and the ciliary muscle contracts, the two optics of the lens change their longitudinal position, passing one over the other thereby resulting in an increase of the dioptric power of the lens. Deformable surface AIOLs attempt to change the shape of its surface during accommodation, many of which are in the early research phase [175].

Summary and future developments in refractive surgery

The field of refractive surgery is rapidly evolving and cannot be comprehensively described in this review, with a wide variety of options to correct refractive error—Table 3. Rapid advances in technology and innovation has now increased the range of refractive surgical options available to patients. Preoperative assessments now allow for customized laser ablations to further achieve better visual quality. Developments in preoperative and intraoperative OCT imaging may also improve surgical planning and accuracy of incisions or placement of implants [12]. Keratorefractive surgery is now established as a safe and effective treatment option for refractive errors, with excellent visual outcomes, improvement in quality of life and achieves high patient satisfaction [179]. Keratorefractive surgery may also be combined with corneal collagen cross-linking, what may improve the safety profile in selected eyes with thinner corneas in the future [180–182]. Meanwhile, SMILE is a minimally invasive 'flapless' procedure that is still being optimized, and gradually found to be comparable with traditional LASIK. Moreover, obtained stromal lenticules from SMILE procedures introduce a new field of potential surgical applications for the treatment of presbyopia [121], hyperopia [122, 123], and keratoconus, among others [124, 125]. These corneal stroma lenticule inlays may also be decellularised to improve biocompatibility [124, 126, 127]. On the other hand, significant improvement in efficacy, speed, and safety profiles of intraocular surgery has disrupted the traditional risk-benefit considerations associated with intraocular phakic implants and refractive lens exchange. Future improvements in femtosecond laser technology could also allow for customized capsulotomies to support special PCIOL implants during refractive lens exchange [183], or even induce refractive correction within

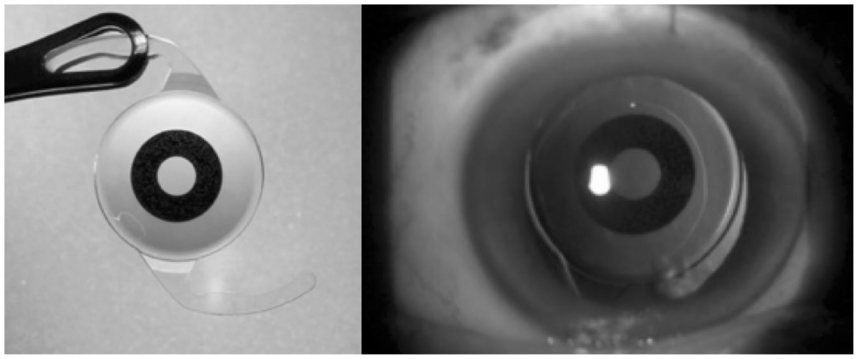

Fig. 14 Photographs of a small aperture intraocular lens implant before and after implantation in situ. Example of small aperture intraocular lens implant, which utilizes the pinhole principle to increase the depth of focus to about 3D.

Table 3 Summary of refractive surgery techniques.

	Myopia, hyperopia, and astigmatism	Presbyopia
Keratorefractive surgery	Laser in situ keratomileuses (LASIK) Surface ablation including photorefractive keratectomy (PRK), laser epithelial keratomileusis (LASEK)	Monovision treatment Multifocal treatment profiles EDOF treatment profiles e.g., 'laser blended vision'[b]
	Small incision lenticule extraction (SMILE)—myopia and astigmatism SMILE[a]—hyperopia treatment	SMILE—stromal lenticule implantation for presbyopia treatment[a]
Intracorneal implants	Intracorneal ring segments (currently not used for pure refractive correction)	Kamra inlay Flexivue microlens implant[b] Icolens[b]
Phakic intraocular lens implants	Implantable collamer lens (ICL) Iris-claw anterior chamber intraocular lens	Implantable phakic contact lens (IPCL)[b] EDOF EVO+ Visian ICL[a]
Refractive lens exchange	Aspheric and toric IOLs	Diffractive IOLs EDOF IOLs IC-8 IOL[b] Accommodative IOLs

IOL Intraocular lens implants, *EDOF* extended depth of focus.

[a]Early clinical data available, not yet approved for clinical use at time of publication.

[b]CE mark at time of publication.

the cornea or IOL without ablation using low energy levels [184]. With these emerging trends, it is important for ophthalmologists to be aware of the advantages and disadvantages of each refractive surgery option weighed against optical corrective options, while emphasizing on careful and appropriate patient selection.

Beyond 2020, refractive surgery may be guided by artificial intelligence (neural networks) in which multiple diagnostic tools will receive information about the eye and will guide the surgeon regarding the lens or the best corneal refractive surgery method to perform on a specific patient, to adequately correct the refractive error improving the quality of the retinal image to beyond normal levels. Most probably, pharmacology will have a role in the prevention of myopia, but not in the way we use it now but with the use of substances capable of stiffening the sclera and avoid further myopic progression. Presbyopia might be even prevented by eye drops capable of halting the hardening and thickening of the crystalline lens, and stimulating the ciliary body selectively. We might have a pharmacological prevention-treatment of cataracts, which would displace most cataract surgical procedures to be performed on patients at an older age than today. Moreover, therapeutic refractive surgery, emerging today, to restore pathological situations such as corneal irregular astigmatism secondary to medical or surgical causes (such as corneal graft surgery), might be managed not only with excimer laser ablations, but also with intracorneal ablations without excision of any type of tissue and no incisions, simply volatilizing tissue within the cornea (and old idea that has been pursued for long time). Moreover, intralenticular cataract surgery (by preserving the capsular bag and its subsequent "refill" with polymers with refractive properties) could provide an alternative to classical cataract surgery that preserves the elasticity of the lens (absent due to the unavoidable fibrosis after standard phaco techniques), and so enhance

postoperative near visual function by a preservation of accommodation capacities.

Author contributions All authors contributed to the overall concept, literature search, analysis, and interpretation of the literature and writing of the manuscript with designing of tables and figures.

Compliance with ethical standards

Conflict of interest MA has no financial conflicts of interests to declare. DZR is a consultant for Carl Zeiss Meditec AG (Jena, Germany) DZR acknowledges a financial interest in Artemis Insight 100 VHF digital ultrasound (ArcScan Inc., Golden, CO)

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