Medical Coverage Policy

Corneal Remodeling for Refractive Errors

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as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses procedures used specifically for the correction of refractive errors (i.e., myopia [nearsightedness], hyperopia [farsightedness], presbyopia [loss of near vision with age], and astigmatism).

This policy is not intended to address corneal procedures, including corneal transplantation, performed for the treatment of eye diseases.

Coverage Policy

Coverage for services for or related to routine refraction and the surgical treatment of refractive errors varies across plans. Please refer to the customer's benefit plan document for coverage details.

If coverage is available for services for or related to routine refraction and the surgical treatment of refractive errors, the following conditions of coverage apply.

Corneal Crosslinking

Conventional, epithelium-off, corneal collagen crosslinking (C-CXL) using a U.S. Food and Drug Administration (FDA) approved drug/device system (e.g., Photrexa® Viscous or Photrexa® with the KXL® System) (CPT Code® 0402T; HCPCS Code J2787) is considered medically necessary for the treatment of EITHER of the following:

- progressive keratoconus
- corneal ectasia following refractive surgery

when ALL of the following criteria are met:

- age 14–65 years
- progressive deterioration in vision
- absence of visual disturbance from a significant central corneal opacity or other eye disease (e.g., herpetic keratitis, neurotrophic keratopathy)

C-CXL is considered experimental, investigational or unproven for any other indication including when combined with a second refractive procedure.

All other corneal collagen crosslinking procedures (e.g., epithelium-on/trans-epithelial) are considered experimental, investigational or unproven.

Corneal Relaxing/Corneal Wedge Resection

Correction of surgically-induced astigmatism 3.00 diopters (D) or greater with a corneal relaxing incision (CPT® code 65772) or corneal wedge resection (CPT® code 65775) (i.e., astigmatic keratotomy [AK]), post-cataract or post-corneal transplant surgery is considered medically necessary in an individual who is intolerant of glasses or contact lenses.

Corneal relaxing incision (CPT® code 65772) or corneal wedge resection (CPT® code 65775) (i.e., astigmatic keratotomy [AK]) is considered not medically necessary for any other indication.

<u>**Intrastromal Corneal Ring Segments**</u>

The insertion of intrastromal corneal ring segments (CPT® code 65785) (e.g., INTACS® prescription inserts) is considered medically necessary when provided in accordance with the Humanitarian Device Exemption (HDE) specifications of the U.S. Food and Drug Administration (FDA) for the treatment of myopia and astigmatism in patients with keratoconus who meet ALL of the following criteria:

- progressive deterioration in vision, such that adequate functional vision on a daily basis with contact lenses or spectacles can no longer be achieved
- age 21 years of age or older
- clear central corneas
- corneal thickness of 450 microns or greater at the proposed incision site
- corneal transplantation is the only other remaining option for improving functional vision

Intrastromal corneal ring segments (CPT® code 65785) (e.g., INTACS® prescription inserts) are considered experimental, investigational or unproven for any other indication.

<u>**Other Procedures**</u>

Each of the following refractive procedures is considered not medically necessary:

- conductive keratoplasty (CPT® code 66999)
- lamellar keratoplasty (non-penetrating keratoplasty) (CPT® codes 65710; 66999)
- laser thermokeratoplasty (LTK) (CPT® code 66999)
- limbal relaxing incisions for non-surgically induced astigmatism (CPT® code 66999)
- penetrating keratoplasty (PK) (corneal transplantation, perforating keratoplasty) (CPT® codes 65730; 65750; 65755; 66999)

Each of the following refractive procedures is considered experimental, investigational or unproven:

- automated lamellar keratomileusis (ALK) (i.e. standard keratomileusis) for the treatment of all refractive errors (CPT® code 65760)
- corneal inlay (CPT® code 66999)
- hexagonal keratotomy in all cases (CPT® code 66999)
- keratophakia for the correction of all refractive errors (CPT® code 65765)
- laser epithelial keratomileusis (LASEK) (CPT® code 66999)
- minimally-invasive radial keratotomy (mini-RK) in all cases (CPT® code 66999)
- orthokeratology in all cases (HCPCS code V2599)
- scleral expansion surgery (CPT® code 66999)

General Background

In the normal eye, both the cornea and lens function to refract or bend light rays and focus them on the retina to produce clear images. Refractive error (ametropia) is present when parallel rays

of light entering the non-accommodating eye do not focus on the retina. The errors are defects in the functioning power of the eye due to an imperfectly shaped eyeball, cornea or lens, so that viewed objects are focused either in front of or behind the retina, resulting in blurred vision. Refractive errors include myopia, or nearsightedness; hyperopia, or farsightedness; astigmatism, in which an uneven curvature of the cornea blurs vision for both near and far objects; and presbyopia, which is associated with aging and loss of flexibility of the lens, limiting the ability of the eye to change its point of focus from far to near.

Keratoconus is a non-inflammatory degenerative condition in which collagen fibers within the cornea weaken and progressively thin. As a result the thinning the fibers can no longer maintain the normal round shape of the cornea. Consequently, the cornea bulges outward, steepens and develops a progressive conical shape. This abnormality prevents light that is entering the eye from focusing directly on the retina, resulting in irregular astigmatism and progressive myopia or visual loss. Corneal ectasia, also known as keratectasia or iatrogenic keratoconus, is caused by irregularities in the cornea that lead to disturbances of vision as a result of astigmatism. The term corneal ectasia can refer to a group of conditions, most notably keratoconus, but can also be related to irregular astigmatism that can develop after a patient undergoes refractive surgery (laser in situ keratomileusis [LASIK] or photorefractive keratectomy [PRK]). Corneal ectasia after laser refractive surgery is a keratoconus-like focal biomechanical disorder characterized by progressive distortion of the corneal shape and optical quality. The cornea can continue to bulge, leading to a worsening of vision (American Academy of Ophthalmology [AAO], 2018).

In a 2016 study, Woodward et al. found that Black and Latino Americans had significantly higher odds of being diagnosed with keratoconus than white Americans (57% and 43%, respectively), while Asian Americans were 39% less likely to develop the condition than white individuals. Other factors which have been found to increase the risk of development of keratoconus include asthma, sleep apnea, Down syndrome, connective tissue disorders, allergic eye disease, a family history of keratoconus, and Leber congenital amaurosis (Oyeniran and Tauqeer, 2021; Woodward, et al., 2016; Gomes, et al., 2015).

Refractive surgery refers to surgical procedures designed to correct refractive errors by reshaping the corneal surface, and to improve the focusing power of the eye, thus reducing or eliminating the need for corrective lenses. According to the AAO, refractive surgery is an elective procedure which may be considered by those who wish to become less dependent on spectacles or contact lenses or when there is an occupational or cosmetic reason to not wear spectacles (AAO, 2022a).

The need to correct refractive errors depends on the patient's symptoms and visual needs. Those with low refractive errors may not need correction. Small changes in refractive corrections in asymptomatic patients are usually not recommended. The major reasons for treating refractive errors are to improve visual acuity, function and comfort. Other reasons for treatment include enhancing binocular vision and decreasing strabismus. Patients with high refractive errors generally require correction to achieve satisfactory vision. Options for correcting refractive errors include spectacles, contact lenses or surgery. Spectacles should be considered before contact lenses or refractive surgery. The majority of adults can tolerate up to 3.0 D of difference in eyeglass refractive correction. Occasionally, individuals may tolerate more than 3.0 D of difference (AAO, 2018).

Refractive Procedures

Corneal Collagen Crosslinking
Corneal collagen crosslinking (CXL) is proposed to minimize or stop the keratoconus disease process by strengthening and stabilizing the collagen lamellae by mimicking the age-related crosslinking that occurs in the cornea over time. Ideally, the treatment results in mechanical

stiffening of the cornea, decreasing the disease progression (e.g., decreasing keratometry readings, increasing corneal thickness) (Hersh, et al., 2017).

The original procedure, conventional CXL (C-CXL), also referred to as epithelium-off (Dresden protocol), involves total removal of the epithelium prior to the administration of riboflavin and ultraviolet. C-CXL uses a combination of riboflavin (vitamin B2) eye drops, absorbed throughout the cornea stroma, with ultraviolet A (UVA) radiation to trigger a photochemical reaction that changes the crosslinks between and within collagen fibers in the corneal stroma. After the riboflavin drops are applied to the cornea, the UVA irradiation is performed for 30 minutes at an intensity of 3 milliwatts per square centimeter (mW/cm^2). Common side effects of epithelium-off CXL include pain, corneal edema and mild stromal haze which typically resolve within a few days. Major long-term complications such as corneal ulceration, perforation, or scarring have been reported to be rare events (Hayes, 2020; Craig, et al., 2014).

C-CXL has evolved into a standard treatment option for a defined subgroup of patients. The procedure is FDA approved for individuals age 14–65 years, with progressive keratoconus or for the treatment of corneal ectasia following refractive surgery. Individuals with progressive deterioration in vision are considered appropriate candidates. Serial eye exams may demonstrate a reduction in uncorrected or best corrected visual acuity, a change in refraction, increasing prescription strength for spectacles or contact lenses, and/or change in corneal shape (AAO, 2021b).

Visual disturbance from a significant central corneal opacity or other eye disease such as herpetic keratitis, neurotrophic keratopathy, severe dry eye, or autoimmune disorders are not candidates for C-CXL. Corneal opacity occurs when the cornea becomes scarred and light cannot pass through the cornea to the retina. The cornea may appear white or clouded over. Corneal opacity can be the result of infection, trauma, herpes simplex virus and other diseases. These individuals are more likely to need a corneal transplant, and are unlikely to be helped by C-CXL (Choi and Donnenfeld, 2022; Hayes, 2020; Galvis, et al., 2017; U.S. Food and Drug Administration [FDA], 2016).

One proposed modification of C-CXL is the epithelium-on procedure in which the epithelium remains intact (also called transepithelial crosslinking [T-CXL]). This method requires more time for the riboflavin to penetrate into the cornea but the potential advantage is decreasing the risk for adverse effects such as infection and scarring. Accelerated CXL (A-CXL) involves a similar UVA dose achieved in a shorter amount of time by increasing the fluence rate or irradiance and decreasing the total exposure time. The shorter exposure time is intended to decrease the intra-procedure time. Topography-guided CXL (TG-CXL) is performed using a customized, patient-specific UVA irradiation pattern that superimposes concentric circular zones over the keratoconic cone region of the cornea. The proposed benefit of TG-CXL is to deliver varying amounts of energy depending on the severity of the curvature, with higher levels of energy being delivered to the innermost zones compared with outmost zones. Finally, partial epithelium-removal CXL (P-CXL) is performed by partially removing the epithelium in an effort to reduce corneal damage and promote faster re-epithelialization. Few studies have investigated the safety and effectiveness of these modified corneal crosslinking procedures (Choi and Donnenfeld, 2022; Oyeniran and Tauqeer, 2021; Hayes, 2020; Sadoughi, et al., 2018; Aixinjueluo, et al., 2017; Craig, et al., 2014).

Corneal collagen crosslinking has been investigated for use in the earlier stages of keratoconus and other corneal ectatic diseases including pellucid marginal degeneration (PMD), degenerative corneal diseases like Terrien Marginal Degeneration, and infectious keratitis. C-CXL has been studied in the pediatric population, however there is no consensus on treatment timing or technique, and long-term data are still needed. C-CXL has been proposed as an adjunct procedure

with other refractive procedures including laser in-situ keratomileusis (LASIK), corneal ring implantation, radial keratotomy, phototherapeutic keratectomy (PTK) and photorefractive keratectomy (PRK). There is insufficient evidence to support C-CXL for the treatment of these other conditions or in combination with other refractive procedures (Oyeniran and Tauqeer, 2021; Davis, et al., 2020; Hayes, 2020; Wei, et al., 2019; Zhu, et al., 2018; Chan, et al., 2017; Galvis, et al., 2017; Randleman, et al., 2015; Craig, et al., 2014).

U.S. Food and Drug Administration (FDA)
On April 15, 2016, the FDA issued a new drug application (NDA) approval for Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%, and Photrexa (riboflavin 5'-phosphate ophthalmic solution) 0.146%, to be used with the KXL System (Avedro, Inc., Waltham, MA), a UV light source, for the treatment of progressive keratoconus. On July 15, 2016, the FDA supplemented the NDA approval for the treatment of corneal ectasia following refractive surgery. The NDA noted that the safety and effectiveness of corneal collagen crosslinking has not been established in patients aged < 14 years and the clinical trials did not include patients who were age 65 years or older (FDA, 2016).

Literature Review
Conventional Corneal Crosslinking (C-CXL) Epithelium-Off for Keratoconus: Studies in the form of systematic reviews, meta-analysis and/or randomized controlled trials (RCTs) support the safety and effectiveness of conventional CXL epithelium off for the treatment of progressive keratoconus. Outcomes have reported a significant improvement in keratometry values (mean, maximum and minimum) and corrected distance visual acuity. Adverse events, such as corneal hazing, have been minimal and transient. CXL has also evolved into an accepted treatment for the management of progressive keratoconus (Hersh, et al., 2017; Seyedian, et al., 2015; Lang, et al., 2015; Li, et al., 2015; Sykakis, et al., 2015; Chunyu, et al., 2014; Craig, et al., 2014; Wittig-Silva, et al., 2014; Hersh, et al., 2011; Wittig-Silva, et al., 2008).

Conventional Corneal Crosslinking (C-CXL) for Corneal Ectasia Following Laser Refractive Surgery: Hersh et al. (2017) conducted a randomized controlled trial (n=179) to evaluate the safety and efficacy of corneal collagen crosslinking (CXL) for the treatment of corneal ectasia following laser refractive surgery. Patients were randomized to CXL with epithelium-off (n=91) or to the sham group that received riboflavin alone with epithelium left intact. Criteria for study participation included: age ≥ 14 years; axial topography pattern consistent with corneal ectasia (including relative inferior steepening with inferior:superior difference >1.5 diopters [D]); corrected distance visual acuity [CDVA] worse than 20/20, and corneal thickness as measured on Pentacam (Oculus GmbH, Wetzlar, Germany) of > 300 µm at the thinnest area. The primary outcome measure was the change of topography-derived maximum keratometry (K) over one year. Secondary outcomes included: corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), manifest refraction spherical equivalent, endothelial cell count, and adverse events. In the CXL treatment group, there was a significant decrease in the mean maximum K value (0.7 ± 2.1 D) at 12 months postoperatively compared to preoperative value (p<0.05). In the control group, there was a significant increase in the mean maximum K value (0.6 ± 2.1 D) between baseline and 12 months postoperatively (p<0.05). The difference between maximum K change between treatment and control was statistically significant (p<0.0001). In the crosslinking treatment group, there was a significant improvement of 5.0 letters of visual acuity between preoperatively and 12 months postoperatively. In the control group, there was a loss of 0.3 letters. The difference in CDVA was 5.3 letters which was statistically significant (p<0.0001) at one year in favor of the CXL group. In the CXL group, there was a significant improvement of 4.5 letters of visual acuity between at the preoperative baseline and 12 months follow-up. In the control group, there was a loss of 0.1 letter. The difference in UDVA change at year one between CXL and control was 4.6 letters, a statistically significant finding (p<0.001). There was no significant difference in manifest refraction spherical equivalent (MRSE) or endothelial cell density

analyses between the groups. The only significant improvement in the CXL group from the patient questionnaire was improvement in vision night driving (p<0.05). There was one serious adverse event involving epithelial ingrowth beneath the LASIK flap on postoperative day 35. The ingrown cells were removed with resolution of the event. At the final 12-month visit, there were five eyes with persistent corneal haze and one corneal scar. Author-noted limitations of the study included the fact that most eye crossed over to CXL at three months. Two control eyes were available at the one year follow-up. A second limitation of the control group is that the epithelium was not removed in the control eyes. Additional limitations include the small patient populations, number of patients lost to follow-up (n=29; 16%) and short-term follow-up.

Corneal Crosslinking – Variations and Other Populations: Burcel et al. (2022) conducted a randomized trial (n=79 eyes) to compare treatment outcomes of epithelium-off corneal collagen crosslinking (CXL) for progressive keratoconus, using a standard versus an accelerated protocol. The study included patients ≥ age 18 years with progressive keratoconus, and no prior history of eye surgery. Excluded from the study were patients with herpetic keratitis or recurrent infections; corneal endothelial pathology; immune disorders; or pregnant or breastfeeding. All patients underwent epithelial debridement and administration of a riboflavin solution. Forty two eyes (32 patients) were treated with a standard CXL procedure (UVA 365 nm wavelength for 30 minutes at 3.0 mW/cm2), and 37 eyes (30 patients) were treated with an accelerated CXL protocol (370 nm UVA light for 10 minutes at 9.0 mW/cm2). Outcome measures included best corrected visual acuity (BCVA); manifest refraction spherical equivalent (MRSE); cylindrical values; corneal dioptric powers on steepest meridian (Kmax); central corneal thickness (CCT); and demarcation line depth (DLD). Follow ups were completed at one, six, 12, and 24 months post-procedure. Both groups demonstrated statistically significant improvements in BCVA, MRSE, cylindrical values, Kmax, and CCT, with no significant between-group differences in these measures. The DLD to CCT ratio was significantly greater in the standard CXL group (66% vs. 62%, p=0.02), possibly due to the limited riboflavin diffusion in the accelerated protocol. The authors noted the lack of confocal microscopy and topographic morphological indices analysis as limitations of the study. Additional limitations included the small patient population and underrepresentation of women.

Larkin et al. (2021) conducted a randomized controlled trial of pediatric patients (n=60) to compare corneal crosslinking (CXL) plus standard care to stabilize progressive keratoconus, versus standard care alone. All subjects underwent corneal tomography, visual acuity testing (logarithm of the minimum angle of resolution [logMAR]), refraction assessment, and apical corneal thickness measurement. The eye with the more advanced keratoconus was deemed the study eye. The CXL group underwent epithelium-off corneal crosslinking, and spectacle or contact lens correction in the study eye, as needed. The control group received refraction testing with provision of glasses and/or contact lens fitting for one or both eyes, as needed. The study included pediatric subjects aged 10-16 years with a diagnosis of progressive keratoconus. Excluded from the study were patients with corneal opacification, corneal apex thickness of less than 400 μm, mean corneal power in the steepest meridian (K2) of more than 62 diopters (D), Down syndrome, or an inability to refrain from contact lens wear for seven days before follow-up tomography. The CXL group included a higher proportion of male participants (83% vs 63% in the control group) and a higher proportion of white individuals (40% vs 17%). Forty five percent of all subjects were of South Asian or Asian British ancestry. The mean age was 15 years. Outcome measures included: K2 in the study eye; progression of keratoconus; corneal thickness; refraction; best-corrected visual acuity; and vision-related quality of life (QoL). Follow ups occurred every three months for 18 months. Of those randomized to the CXL group, one subject did not undergo treatment, and another did not meet trial eligibility but underwent CXL and was included in the analysis. In the control group, four subjects withdrew or were lost to follow up, and five crossed over to the study arm and underwent CXL. A total of 23 control subjects completed the 18-month follow up. At 18 months, the mean K2 in the study eye was 49.7 D (standard deviation [SD], 3.8 D) in the CXL group and 53.4 D (SD, 5.8 D) in the standard care group. The adjusted mean difference in K2 in

the study eye was −3.0 D (95% confidence interval [CI], −4.9 to −1.1 D; p=0.002), favoring CXL. On average, patients in the CXL group showed significantly lower logMAR values for uncorrected and best-corrected visual acuity compared with those receiving standard care (p=0.002 and p=0.002, respectively). Keratoconus progression in the study eye occurred in two patients in the CXL group, versus 12 patients in the control group. There were no statistically significant difference between the groups in apical corneal thickness, refraction measures as spherical equivalent, and quality of life scores. No adverse events were reported. Author-noted limitations of the study included the exclusion of some data due to unreliable tomography measurements, and a very significant overrepresentation of subjects of South Asian ethnicity, which is strongly associated with keratoconus in the UK, and which may limit the applicability of study findings to other populations. The authors also noted that only 43% of control subjects subsequently showed clinical progression, indicating there may be a higher proportion of keratoconus patients in this age group who achieve spontaneous stabilization than previously expected. Additional limitations include short length of follow up, and high loss to follow up in the control group. Of note, the VibeX Rapid and Avedro KXL system used in this study are not currently approved for use in the United States.

Nath et al. (2021) conducted a systematic review and meta-analysis of 12 randomized controlled trials (RCTs) (n=966 eyes) to evaluate the safety and efficacy of transepithelial corneal crosslinking compared to established epithelium-off corneal crosslinking for corneal ectasia. The majority of the studies were conducted in Europe. The authors included RCTs comparing transepithelial and epithelium-off crosslinking, and for any corneal ectasia. Excluded were observational studies; narrative and systematic reviews; commentaries; case reports; in vitro studies; studies with treatment for an indication other than ectasia; and studies comparing T-CXL to no treatment. Outcomes included the change in maximal keratometry (K_{max}) in diopters (D) at 12 months after crosslinking; K_{max} at longest follow up; uncorrected and corrected distance visual acuity; rate of disease progression; and complications. Length of follow up was one to three years. The change in K_{max} differed significantly between the transepithelial and epithelium-off groups, with a larger decrease observed in the epithelium-off group at 12 months (p=0.004) and at longest follow up (p<0.001). No significant difference was found between the two groups in corrected or uncorrected distance visual acuity. Transepithelial crosslinking was associated with significantly fewer complications than the epithelium-off method (p=0.020; rate of 2% versus 4%), although it was associated with an increased rate of disease progression at 12 months (p=0.022). On average, 2% of subjects treated with the epithelium-off approach showed disease progression at the 12-month follow up, whereas 7% progressed in the transepithelial cohort. Author-noted limitations included inability to complete subgroup analyses due to lack of detailed data, and some studies were noted to have a high risk of bias. Additional limitations were small patient populations and heterogeneity of the intervention technique.

Shajari et al. (2019) conducted a systematic review and meta-analysis to compare the results of conventional corneal crosslinking (C-CXL) and accelerated corneal crosslinking (A-CXL) for the treatment of keratoconus. Twenty two studies (n=1158 eyes; n=577 C-CXL eyes, n=581 A-CXL eyes) including fourteen prospective randomized controlled trials, four prospective non-randomized comparative studies and four retrospective reviews met the inclusion criteria. Complete and published studies comparing C-CXL and A-CXL with at least one predetermined outcome were included. Ex vivo, pediatric studies and studies that combined corneal crosslinking and photorefractive keratotomy were excluded. The primary outcomes were measured changes in uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), spherical equivalent (SE), spherical and cylindrical error, central and minimum corneal resistance factor (CRF), anterior stromal keratocyte density, sub-basal nerve density, endothelial cell density (ECD), percentage of hexagonal endothelial cells, as well as average, maximal and minimal keratometry values. Secondary outcomes included absolute demarcation line and time of re-epithelialization. C-CXL compared to A-CXL was statistically significant regarding minimum

keratometry (p<0.00001) and demarcation line depth (p<0.00001), and A-CXL was statistically significant regarding corneal thickness (p=0.0005). There was no statistically significant difference in uncorrected distance visual acuity(p=0.09), corrected distance visual acuity (p=0.98), spherical equivalent (p=0.11), spherical error (p=0.29), cylindrical error (p=0.32), maximal keratometry (p=0.05), average keratometry (p=0.65), central corneal thickness (p=0.15), corneal biomechanical properties (p≥0.21), time of re-epithelialization (p=0.76), sub-basal nerve density (p=0.69), endothelial cell density (p=0.30) and morphology (p≥0.40). Out of the studies reviewed, only two reported adverse events post procedure which included delayed epithelial healing in two cases of C-CXL and four cases of A-CXL. One study reported transient mild haze in ten eyes of C-CXL and ten eyes of A-CXL. Only one case of severe central haze was reported in the C-CXL population after the one month follow-up period. Post procedure follow-ups were recorded at one, three and six month intervals as well as at one year. Author noted limitations included: use of heterogeneous A-CXL protocols (e.g., various duration, composition and frequency of riboflavin exposure) and all trials were weighed similarly regardless of study type. Larger studies with long term follow-ups are necessary to evaluate the effectiveness of A-CXL versus C-CXL.

In a 2018 Directory Report, Hayes reviewed nine randomized controlled trials (RCTs), two prospective trials, six prospective comparative cohort studies, and six retrospective comparative cohort studies. Sample sizes ranged from 50–205 eyes and follow-ups ranged from 1–3 years. Interventions included: C-CXL; accelerated CXL (A-CXL); trans-epithelial CXL (T-CXL); topography-guided CXL (TG-CXL); and partial epithelium-off CXL (P-CXL). Comparators included: no treatment versus C-CXL (n=5 studies); sham treatment versus C-CXL (n=1 study); A-CXL versus C-CXL (n=8 studies); T-CXL versus C-CXL (n=6 studies); TG-CXL versus C-CXL (n=2 studies); and P-CXL versus C-CXL (n=1 study). Alternative CXL approaches varied, with the key differences in approach being the removal/non-removal of the corneal epithelium, and alteration in the fluence rate (irradiance) and exposure time to UVA radiation. The overall quality of the body of evidence was rated as low. There was some evidence that CXL may slow or stop progression of keratoconus by altering the corneal topography (i.e., flattening of the cornea), but results were conflicting. In addition, it is unclear how visual acuity and corneal thickness outcomes are affected by CXL. Most adverse events were transient and consisted primarily of delayed or impaired epithelial healing and corneal haze. Less common events included sterile infiltrates, stromal scarring or edema, herpes simplex keratitis, and peripheral corneal vascularization. Studies included small patient populations and short-term follow-ups. There was a lack of evidence reporting on the quality-of-life following conventional C-CXL. The report made the following conclusions:

- Conventional corneal crosslinking (C-CXL): There was a moderately sized body of low-quality evidence that suggested some positive but inconsistent results regarding the benefits of C-CXL for the treatment of progressive keratoconus in adolescent and adult patients compared with no treatment or sham treatment. Data for long-term safety and efficacy are lacking.
- Accelerated corneal crosslinking (A-CXL) compared with C-CXL for the treatment of progressive keratoconus in adolescent and adult patients: There was a moderately sized body of low-quality evidence that suggested A-CXL is similar to C-CXL for halting keratoconus progression. Data concerning long-term safety and efficacy of A-CXL compared with C-CXL is lacking. In A-CXL, a similar UVA dose (fluence) as used in C-CXL is achieved in a shorter amount of time by increasing the fluence rate or irradiance and decreasing the total exposure time.
- Trans-epithelial corneal crosslinking (T-CXL) compared with C-CXL for the treatment of progressive keratoconus in adolescent and adult patients: There was a limited and low-quality body of evidence that C-CXL is superior to T-CXL for halting keratoconus progression. Long-term safety and efficacy data are lacking.

- Topography-guided corneal crosslinking (TG-CXL) or partial epithelium-off corneal crosslinking (P-CXL) compared with C-CXL for the treatment of progressive keratoconus in adolescent and adult patients. There was a paucity of evidence comparing these alternative CXL treatments with C-CXL. TG-CXL is performed using a customized, patient-specific UVA irradiation pattern that superimposes concentric circular zones over the keratoconic cone region of the cornea. In P-CXL, CXL is performed by partially removing the epithelium in an effort to reduce corneal damage and promote faster re-epithelialization.

In the 2020 annual review of this report twelve new abstracts were identified and did not change the 2018 Hayes conclusion. The abstracts included one randomized comparison study, three prospective nonrandomized studies, four cohort studies, and four systematic review and meta-analysis.

Wen et al. (2018a) conducted a systematic review and meta-analysis to compare standard epithelium-off corneal cross-linking (SCXL) and trans-epithelial corneal collage cross-linking (TECXL) for the treatment of keratoconus. Eight studies (n=455 eyes) including five randomized control trials, one prospective comparative study and one retrospective review met the inclusion criteria. Studies were included when the following criteria were met: 1) patients with keratoconus; 2) compared SCXL versus TECXL; and 3) contained at least one primary or secondary outcome measure. Studies were excluded that had fewer than ten patients. The primary outcomes were measured by change in uncorrected distance visual acuity (UDVA), maximum keratometry (Kmax), and mean keratometry (mean K) at one year following each intervention. The secondary outcomes were measured by changes in corrected distance visual acuity (CDVA), mean refractive spherical equivalent (MRSE), central corneal thickness (CCT), endothelial cell density (ECD), and the occurrence of adverse events at the one-year follow-up post CXL. At the one year follow-up, there was a significant reduction of mean K in the SCXL patient population compared with TECXL (p=0.03). There were no statistically significant differences in UDVA and Kmax. There were no significant differences between the two groups in CDVA, MRSE, CCT and ECD at the one year follow-up. There were few adverse events reported for both procedures. The major complications following SCXL were transient corneal edema and stromal haze. Isolated events such as herpes simplex keratitis and sterile infiltrates were reported. No significant complications were observed or reported following TECXL. Author-noted limitations included: use of heterogeneous TECXL protocol, different UVA illumination time, UVA irradiation intensity and riboflavin concentration; short term follow-up; and the limited number of included studies. Additional randomized controlled trials with long term follow-up are needed to validate the effectiveness of TECXL.

Wen et al. (2018b) conducted a systematic review and meta-analysis to compare standard corneal cross-linking (SCXL) to accelerated corneal cross-linking (ACXL) for the treatment of keratoconus. Thirteen studies, seven randomized controlled trials and six non-randomized comparative studies (prospective and retrospective), were included in the meta-analysis (n=713 eyes; n=352 SCXL eyes, n=361 ACXL eyes). Studies were included when the following criteria were met: diagnosis of keratoconus, comparison of SCXL versus ACXL, primary and secondary outcomes were reported and a minimum of six months follow-up. Studies not containing the above criteria were excluded. The primary outcomes measured changes in uncorrected distance visual acuity (UDVA), mean keratometry and maximum keratometry. Secondary outcomes included corrected distance visual acuity (CDVA), mean refractive spherical equivalent, central corneal thickness and endothelial cell density. Post procedural follow-ups were noted after six months but varied among studies with the longest term at 15 months. SCXL "appeared" to flatten the Kmax (n=12 studies) and reduce CCT (n=4 studies) greater than ACXL. ECD was reduced less following ACXL compared to SCXL (n=7 studies). There were no statistically significant differences in the change of UDVA (n=7 studies), mean K (n=8 studies), CDVA (n=10 studies) and MRSE (n=9 studies). Only one trial reported an adverse event which was mild transient corneal haze after both procedures. Author noted limitations included: heterogeneous ACXL protocols; variation in surgical procedures, operational techniques, and outcome measures; and short term follow-ups. Larger studies with long term

follow-ups are necessary to evaluate the effectiveness of SCXL versus ACXL and to establish a consistent protocol for ACXL.

Rush and Rush (2017) conducted a randomized controlled trial (RCT) (n=144) to compare conventional corneal collagen crosslinking (C-CXL) (control group) to trans-epithelial collagen crosslinking (T-CXL) with enhanced riboflavin solution (study group) for the treatment of corneal ectasia. Subjects, ages 10–70 years, had a Snellen BSCVA of 20/25–20/400 and a progressive corneal ectasia disorder (e.g., keratoconus, pellucid marginal degeneration or post–refractive surgery ectasia) with a preoperative minimum thinnest corneal pachymetry measurement of at least 400 microns thick. Follow-ups occurred for up to 24 months. The primary outcome measure was change in the maximum simulated keratometry value (K_{steep}). The secondary outcome was the change in the best spectacle-corrected visual acuity (BSCVA). At 24 months the C-CXL group had significant improvement in K_{steep} (p=0.0381) and in BSCVA (p=0.0032) compared to baseline. The T-CXL group had no significant change in K_{steep} (p=0.4565) and a significant improvement in BSCVA (p=0.0164). The C-CXL group demonstrated a greater change in K_{steep} compared with the T-CXL group at 12 and 24 months of follow-up (p=0.0409 and p=0.0320, respectively). There was no significant difference between the groups in the BSCVA at 12 (p=0.4978) and 24 months (p=0.4947). There was no statistically significant difference in the number of adverse events or in the rate of keratoplasty between the C-CXL control group and the T-CXL study groups (p=0.0636 and p=0.1910, respectively). The authors noted that limitations of the study included: the use of logMAR visual acuity as well as, the use of change in refraction to define disease progression and not collecting variables such as depth of treatment as measured on optical coherence tomography, change in pachymetry measurements and change in endothelial cell counts during the study interval. The T-CXL medical device and medication used in this procedure were not FDA approved.

Soeters et al. (2015) conducted an RCT (n=61 patients/61 eyes) comparing the effectiveness and safety of trans-epithelial CXL (n=35 eyes) to epithelium-off (epi-off) CXL (n=26) in progressive keratoconus. Inclusion criteria were age >18 years, clear central cornea, documented progression defined by an increase in Kmax, K_{steep}, mean keratometry, and/or topographic cylinder value by >0.5 D over the previous 6–12 months. Patients were excluded who had a minimal pachymetry of < 400 mm prior to UVA irradiation, or a history of previous ocular infection. The primary outcome measure was clinical stabilization of keratoconus after one year, defined as Kmax increase <1 diopter (D). Secondary outcomes included corrected distance visual acuity (CDVA), corneal thickness, IOP and endothelial cell count. Transepithelial CXL showed less potent effects on keratoconus stabilization and regression compared to epi-off CXL. The trend over time in Kmax flattening was significantly different between the groups (p<0.022). There was a significant different trend in CDVA, with a more favorable outcome in the transepithelial group (p<0.023). Corneal thickness remained stable in the trans-epithelial CXL group. The epi-off group showed an expected lowered optical pachymetry after treatment, which normalized at the 12-month time point. No difference in intraocular pressure over time was measured between the groups; the endothelial cell counts were unremarkable. Adverse events occurred in 4 of 26 eyes (15%) in the epi-off group and included herpes simplex keratitis, stromal scar, and central haze. No complications were reported in the trans-epithelial group. Study limitations include the un-blinded design and unequal sample size in groups.

An RCT published by Al Fayez et al. (2015) (n=70 eyes) compared the safety and efficacy of epithelium-on (n=34 eyes) versus epithelium-off (n=36 eyes) CXL for progressive keratoconus. Inclusion criteria were progressive (i.e., increase in the maximum K value or manifest astigmatism ≥ 1 D within the previous year) mild and moderate keratoconus (stages I and II on the Amsler–Krumeich scale), corneal thickness ≥ 400 mm, mean K ≤ 53 D, and clear cornea with no Vogt striae. Patients were excluded if they had central corneal scarring, previous ocular surgery, ocular surface pathology or infection, or collagen vascular disease. The mean follow-up was 40 months with a primary outcome of change in the maximum K reading (Kmax). Secondary outcomes were

refraction, corneal pachymetry, endothelial cell count, intraocular pressure (IOP), and adverse events. Keratoconus stabilized or improved in all patients in the epithelium-off group, whereas only 15 patients (45%) in the trans-epithelial group stabilized or improved, and 19 patients (55%) progressed (p<0.0001). Compared to baseline, Kmax decreased significantly in the epithelium-off group and increased significantly in the trans-epithelial group after three years of follow-up. The difference between both groups was statistically significant (i.e., p=0.0007, p=0.0001, and p=0.0001 at one, two, and three years, respectively). The difference in UDVA was statistically significant in favor of the epithelium-off group at all follow-up points after one year. No statistically significant difference was found between groups in refraction, endothelial cell count, corneal thickness, or IOP at three years. These study results indicated that epithelium-off was significantly more effective than trans-epithelial corneal crosslinking in slowing the progression of keratoconus.

Professional Societies/Organizations
The 2018 American Academy of Ophthalmology (AAO) Summary Benchmark for Preferred Practice Pattern® Guidelines on corneal ectasia includes a discussion of the initial and follow-up evaluation of the condition. The guideline listed collagen crosslinking as a treatment option that can improve corneal rigidity by increasing bonds between fibers.

In the 2022 Refractive Surgery Preferred Practice Pattern, the AAO stated that options for the treatment of corneal ectasia after LASIK include corneal crosslinking. Studies have shown that CXL induced by topical riboflavin and ultraviolet irradiation may arrest keratectasia, as demonstrated by preoperative and postoperative corneal topography/tomography and a reduction in maximum keratometric readings. Long-term stability after CXL therapy for treatment of post-refractive corneal ectasia has been reported and has received FDA approval.

Corneal Relaxing Incisions/Corneal Wedge Resection (Astigmatic Keratotomy [AK])
Corneal relaxing incisions are a type of incisional treatment used in the management of astigmatism, and include astigmatic keratotomy (AK) and limbal relaxing incisions (LRIs). In AK, either transverse or arcuate incisions are made in the paracentral cornea to change its curvature in order to reduce or eliminate corneal astigmatism by allowing the cornea to become more rounded when it heals. AK is often performed for the correction of surgically-induced astigmatism and following medically-indicated cataract removal or corneal transplant surgery. Variations of AK include the Ruiz Procedure and the Troutman Wedge Resection also referred to as a corneal wedge resection. The wedge resection, often used with corneal relaxing incisions, effectively decreases astigmatism. However, clinical results have been reported to be unpredictable, therefore, the technique is typically reserved for the correction of post-keratoplasty astigmatism of high degree.

Limbal relaxing incisions (LRIs) or peripheral corneal relaxing incisions are also a variant of AK in which incisions are placed just on the far peripheral aspect of the cornea. The incisions are created with blades designed to achieve a consistent depth. Femtosecond lasers may also be used to create arcuate incisions. LRIs may be used to treat low to moderate degrees of astigmatism and have been performed alone or combined with cataract extraction and intraocular lens implantation to reduce preoperative corneal astigmatism (AAO, 2022a). The correction of iatrogenic astigmatism is generally supported, while the use of LRIs to treat astigmatism not resulting from a prior surgery (e.g., correction of pre-existing, non-surgically induced astigmatism during cataract surgery) is considered not medically necessary.

Intrastromal Corneal Ring Segments (INTACS)
This procedure involves inserting a flexible ring beneath the surface of the cornea to elevate the edge of the cornea to flatten the front of the eye, decreasing nearsightedness. Different size rings are used to correct different degrees of nearsightedness. Intrastromal corneal ring segments have

been investigated for two indications—as a refractive procedure to correct mild myopia and as a treatment of keratoconus.

U.S. Food and Drug Administration (FDA): On April 9, 1999, INTACS™ (Keravision Inc., Fremont, CA) received premarket application (PMA) approval from the FDA for the treatment of adults with mild myopia (from -1.0 to -3.0 D) who have ≤ 1.0 D of astigmatism. Intrastromal corneal ring segments are considered not medically necessary for patients with mild myopia. They are considered investigational for children, for patients with moderate to severe myopia (greater than -3.0 D), for patients with more than 1.0 D of astigmatism, and for hyperopia.

On July 26, 2004, INTACS® prescription inserts for keratoconus (Addition Technology, Sunnyvale, CA) received humanitarian device exempt (HDE) approval from the FDA. A humanitarian use device (HUD) is exempt from the effectiveness requirements of a PMA. According to the FDA, INTACS prescription inserts are indicated for the reduction or elimination of myopia and astigmatism in a specific subset of patients with keratoconus who meet all of the following criteria:
- progressive deterioration in vision, such that adequate functional vision on a daily basis with contact lenses or spectacles can no longer be achieved
- 21 years of age or older
- clear central corneas
- corneal thickness of 450 microns or greater at the proposed incision site
- corneal transplantation is the only remaining option to improve functional vision

Literature Review: Case series and comparative trials have evaluated the safety and effectiveness of intrastromal corneal implants for keratoconus (Torquetti, et al., 2009; Kymionos, et al., 2007; Colin and Malet, 2007; Ertan and Bahadir, 2006; Colin, 2006; Kanellopoulos, et al., 2006; Siganos, et al., 2003; Boxer, et al., 2003; Colin, et al., 2001). Some studies have had limitations including retrospective design, small sample size, and short-term follow-up. However, results of the available evidence indicate that the use of intrastromal corneal implants for individuals with keratoconus is associated with improved functional vision and can defer or possibly eliminate the need for corneal transplantation.

Intrastromal corneal ring segments have been investigated as a treatment for corneal ectasia after LASIK. According to the AAO, reported techniques vary in the size, number, and symmetry of the implants as well as the location of the incision. Although early results show potential, long-term efficacy for this procedure remains to be determined (AAO, 2022a). Treatment for post- LASIK ectasia is not an FDA-approved indication for intrastromal corneal ring segments.

Laser in Situ Keratomileusis (LASIK)
LASIK is a type of laser surgery of the cornea performed to correct refractive errors. A slice of the patient's cornea is removed, shaped to the desired curvature with an excimer laser, and then sewn back to the remaining cornea. In recent years, LASIK surgery has become the procedure of choice for treating moderate to high levels of myopia, with or without astigmatism. In 1995, the first refractive laser systems approved by the U.S. Food and Drug Administration (FDA) were the excimer lasers for use in photorefractive keratectomy (PRK) to treat myopia and, later, to treat astigmatism. Physicians then began using these lasers for LASIK surgery and to treat refractive disorders other than myopia. The laser emits an ultraviolet beam that is able to reshape the cornea. Refractive errors are minimized with the aid of a programmed computer that, using a patient's refraction and corneal topography, controls the laser beam to precisely remove corneal tissue.

Residual refractive errors after penetrating keratoplasty are usually responsible for decreased visual acuity despite a clear graft. The mean amount of astigmatism that has been reported after penetrating keratoplasty for keratoconus is usually between 2 and 6 D. Correction with spectacles

or contact lenses should be considered initially, followed by the possibility of incisional refractive surgery if the patient is intolerant to either of these alternatives. The goals of LASIK after penetrating keratoplasty are to decrease the degree of anisometropia and ametropia to levels at which correction with glasses or contact lenses can be tolerated (Sierra and Hardten, 2019). Anisometropia means that the two eyes have a different refractive power, so there is unequal focus between the two eyes. This is often due to one eye having a slightly different shape or size from the other causing asymmetric curvature (astigmatism), asymmetric far-sightedness (hyperopia), or asymmetric near-sightedness (myopia).

Photorefractive Keratectomy (PRK)
PRK involves the reshaping of the surface of the cornea with an excimer laser to correct mild-to-moderate myopia. The laser alters the anterior curvature to modify a particular refractive error by varying the ablation pattern. Photoastigmatic keratectomy (PARK or PRK-A) is a refractive surgical procedure used to correct myopia with astigmatism. Both procedures are considered not medically necessary for patients with hyperopia of up to 6.0 D, and myopia of up to -10.0 D, with or without astigmatism up to 4.0 D, because the refractive corrections achieved with PRK and PARK are less precise than that achieved by eyeglasses or contact lenses. PRK and PARK are considered investigational for patients with hyperopia greater than 6.0 D, myopia greater than -10.0 D, astigmatism greater than 4.0 D, and for all other refractive errors. This is based on the FDA-approved indications for PRK and PARK.

Other Procedures

Conductive Keratoplasty (CK): CK is the application of radiofrequency thermal energy to increase the curvature of the cornea and thereby reduce hyperopia. On April 11, 2002, ViewPoint CK System® (Refractec Inc., Irvine, CA) received premarket approval (PMA) from the FDA. Based on data submitted with the PMA application, the ViewPoint CK System® is approved for the treatment of patients who are at least 40 years of age, who have mild to moderate hyperopia (0.75 D to 3.25 D), 0.75 D or less astigmatism, and whose eyesight has changed very little over the previous 12 months, as demonstrated by a change of less than 0.50 D in refraction. According to the FDA, CK improves distance vision in farsighted people, but the amount of farsightedness correction is not always permanent. Those who require very acute vision for work-related activities may still need glasses, and glasses will also be needed for reading.

Currently, there is insufficient evidence in the peer-reviewed literature to support the effectiveness of CK for the treatment of presbyopia. Studies are primarily in the form of case series with small sample sizes (n=10-27) and follow-ups of 1-3 years (Ye, et al., 2011; Stahl, 2007). A larger series by McDonald and colleagues (2004) reported preliminary results of a multicenter clinical trial supported by the FDA to evaluate the effectiveness of CK for the treatment of presbyopic symptoms of emmetropic and hyperopic eyes. A total of 143 patients with presbyopic symptoms were enrolled in this one-year study and treated to improve near vision in one eye (unilateral treatment). In addition, 33 fellow eyes were treated to improve distance vision (bilateral treatment). At six months follow-up, 77% of examined eyes had J3 or better monocular UCVA, and 85% of patients had binocular UCVA of 20/25 or better distance along with J3 or better near, a combination that represents functional acuity for a presbyopic individual. Of eyes treated with CK, 92% had an uncorrected binocular vision of 20/32 and J5, which also allows a high degree of uncorrected visual function. It was noted that follow-up was too short for meaningful determination of refractive stability; follow-up to three years and beyond is needed for accurate evaluation of stability.

According to the AAO (2022a) disadvantages of CK include early overcorrection, regression and induced astigmatism. The procedure is not frequently used today.

Lamellar Keratoplasty (Non-Penetrating Keratoplasty): This is a corneal transplant procedure in which a partial thickness of the cornea is removed. The diseased tissue is replaced with a partial-thickness donor cornea. There are two types of lamellar keratoplasty: anterior lamellar keratoplasty (including the subtype deep anterior lamellar keratoplasty [DALK]) and posterior lamellar keratoplasty (also referred to as endothelial keratoplasty). Lamellar keratoplasty may be indicated for a number of corneal diseases, including scarring, edema, thinning, distortion, dystrophies, degenerations and keratoconus. However, it is considered not medically necessary when performed solely to correct astigmatism and other refractive errors.

Laser Thermokeratoplasty (LTK) (Other Than Conductive Keratoplasty): LTK utilizes the following methods: superficial treatment of Gassett and Kaufman for keratoconus, holmium, YAG laser thermokeratoplasty, or the hot needle of Fyodorov. Based on review of the literature, all of these methods of thermokeratoplasty have been abandoned in current refractive surgery because the corneal wound-healing response produces postoperative scarring and instability.

Limbal Relaxing Incisions (LRIs): LRIs, or peripheral corneal relaxing incisions, are a variant of astigmatic keratotomy (AK) (see above) in which incisions are placed just on the far peripheral aspect of the cornea. LRIs may be used to treat low to moderate degrees of astigmatism and have been performed alone or combined with cataract extraction and intraocular lens implantation to reduce preoperative corneal astigmatism (AAO, 2022a). As such, the use of LRIs to treat astigmatism that is not surgically induced is considered not medically necessary.

Penetrating Keratoplasty (PK) (Corneal Transplantation, Perforating Keratoplasty): PK involves replacement of the full-thickness of the cornea with a donor cornea, but retains the peripheral cornea. As with lamellar keratoplasty, this procedure may be indicated for a number of corneal diseases. Most PKs are performed to improve poor visual acuity caused by an opaque cornea. PK has also been used to remove active corneal disease, such as persistent severe bacterial, fungal, or amebic inflammation of the cornea (keratitis) after appropriate antibiotic therapy. The most common indications for PK are: bullous keratopathy, keratoconus, corneal scar with opacity, keratitis, corneal transplant rejection, Fuch's dystrophy, corneal degeneration, other corneal dystrophies, corneal edema, and herpes simplex keratitis. PK is considered not medically necessary when performed solely to correct astigmatism or other refractive errors. Surgically induced astigmatism is a potential complication of PK that may require refractive surgery.

Automated Lamellar Keratoplasty (ALK): ALK, also referred to as standard keratomileusis, is a technique that shapes the cornea with a microkeratome, an oscillating sharp blade used to incise the corneal stroma beneath the Bowman membrane, rather than with a laser. It is considered investigational for treatment of all refractive errors. The AAO Refractive Surgery Preferred Practice Pattern assessment stated that ALK had only fair predictability. Complications of ALK include irregular astigmatism, thin flaps, free or displaced caps, anterior chamber perforation, interface opacities, infectious keratitis, and epithelial ingrowth. The AAO has further stated that ALK has been largely abandoned due to the advent of laser-in-situ keratomileusis (LASIK) (AAO, 2022a).

Corneal Inlay: Corneal inlays have been proposed as a treatment for presbyopia. The device is a thin disc shaped lens with micro-perforations proposed to help focus images clearly within the eye like glasses or contact lenses. Although the inlay has no refractive power, the goal of the device is to have the central opening function as a pinhole to increase depth of focus and improve near vision without changing distance vision. The inlay is implanted through a pocket-shaped laser incision of the cornea. Variations of corneal inlays described in the literature include the KAMRA® (AcuFocus™, Irvine, CA); the Raindrop® (ReVision Optics, Laguna Hills, CA), and the Flexivue Microlens™ (Presbia, Amsterdam).

On April 17, 2015, the KAMRA® inlay (AcuFocus™ Inc., Irvine, CA) received premarket application (PMA) approval from the FDA for the treatment of presbyopia. According to the FDA, the KAMRA inlay is indicated for intrastromal corneal implantation to improve near vision in patients between the ages of 45 and 60 years with presbyopia who have not had cataract surgery. Contraindications to device implantation include severe dry eye syndrome, eye infection or inflammation, and keratoconus. The pivotal study was a prospective, single-armed, multicenter clinical trial (n=508). The non-dominant eye of subjects was implanted with the AcuFocus corneal inlay. Patient selection criteria included uncorrected near visual acuity worse than 20/40 and better than 20/100 in the eye to be implanted, as well as distance visual acuity correctable to at least 20/20 in both eyes. Exclusion criteria included cataracts, corneal abnormalities, uncontrolled eyelid disease and keratoconus. At 12 months of follow-up, 80.8% of subjects achieved the primary effectiveness endpoint of uncorrected near visual acuity of 20/40 or better. Post-approval evaluation of the device required by the FDA includes a prospective multi-center observational study designed to monitor the safety of patients who participated in the pivotal trial and are still implanted with the KAMRA Inlay. Patients will be followed for an additional two years for a total of five years post-implantation. The KAMRA inlay has been marketed outside the US since 2009 and is available in 50 countries, including Australia, Austria, Canada, Chile, Hungary, Japan, Jordan, South Korea, Lebanon, Malaysia, Netherlands, New Zealand, Oman, Saudi Arabia, Singapore, Turkey, and the United Arab Emirates (FDA, 2015).

On June 16, 2016, the Raindrop® Near Vision Inlay® (ReVision Optics, Inc., Lake Forest, CA) received premarket application (PMA) approval from the FDA for the treatment of presbyopia. According to the FDA, the Raindrop Near Vision Inlay was indicated for intrastromal implantation to improve near vision in the non-dominant eye of phakic, presbyopic patients with the following characteristics:

- 41 to 65 years of age
- manifest refractive spherical equivalent of +1.00 diopters (D) to -0.50 D with ≤ 0.75 D of refractive cylinder
- do not require correction for clear distance vision,
- require near correction of +1.50 D to +2.50 D of reading add

The pivotal study for FDA approval was a multicenter prospective, single-armed, non-randomized clinical trial (n=373 patients). Selection criteria for subjects included presbyopic adults, needing from +1.50 D to +2.50 D of reading add with uncorrected near visual acuity worse than 20/40 and better than 20/200 in the non-dominant eye. Two years after implantation, the primary effectiveness endpoint was met, with 92% of patients (336/364) able to see with ≥ 20/40 vision at near distances with the inlay-implanted eye. The adverse event (AE) safety endpoints were that the total number of AEs should occur in < 5% of eyes and any single AE should occur in < 1% of eyes. Of the 22 AE categories, seven AE categories (e.g., secondary surgical intervention: 44/373 [12%]) exceeded the target rate of 1% (FDA, 2016). In March 2019, the FDA issued a Class 1 Device Recall of the Raindrop Near Vision Inlay, due to an increased risk of corneal haze. The inlay is not currently commercially available.

The Presbia Flexivue Microlens™ (PresbiBio, LLC., Sandyford Dublin) is a refractive optic corneal inlay that functions by altering the corneal index of refraction to improve near vision performance, by the means of a bifocal optic which separates distance and near focal points. The basic principle is corneal multifocality, providing distance vision through a plano central zone surrounded by one or more rings of varying additional power for intermediate and near vision. The Flexivue Microlens is a 3-mm-diameter, transparent hydrogel-based implant made from a hydrophilic acrylic material and contains an ultraviolet blocker. Depending on the add power, the thickness of the inlay varies from 15 μm to 20 μm. The Microlens received its CE Mark for the European Economic Area. It is not currently FDA-approved and is not commercially available in the U.S. (Beer, et al., 2020; Presbia, 2022; Moarefi, et al., 2017).

Additional options in corneal inlays are being studied with the Presbyopic Allogenic Refractive Lenticule (PEARL) techniques. PEARL is a procedure that places a small piece of tissue from one part of the cornea into another part. The inlay is proposed to change the shape of the cornea with the goal of improving near vision. The surgeon uses a laser to make a small cut in the cornea. A lenticule (a small disc of corneal tissue) is removed through the cut. The lenticule is sculpted and reshaped with a laser, then placed into a small pocket made in the patient's cornea. Because the inlay is made of the patient's own tissue, it is biologically compatible, making it less likely to cause complications of artificial corneal inlays. The procedure is still under investigation (Moarefi, et al., 2017; Boyd, 2016).

Evidence in the published peer-reviewed medical literature evaluating the safety and effectiveness of corneal inlays is primarily in the form of case reports and case series (Darian-Smith, et al., 2022; Linn, et al., 2017; Verdoorn, 2017; Whang, et al., 2017; Jalali, et al., 2016; Dexl, et al., 2015; Yoo, et al., 2015; Yilmaz, et al., 2011; Seyeddain, et al., 2010). These studies included small patient populations with follow-up periods ranging from six months to four years. Adverse events included cataract progression and device explantation.

Vukich et al. (2018) conducted a prospective nonrandomized multicenter open-label single-arm study (n=507) to evaluate the safety and efficacy of the KAMRA corneal inlay. Patients, aged 45–60 years, with presbyopia and corrected distance visual acuity (CDVA) to 20/20 in both eyes were included in the study. The eye to be implanted had uncorrected near visual acuity (UNVA) between 20/40 and 20/100 and cycloplegic refractive spherical equivalent of +0.50 diopters (D) to -0.75 D with 0.75 D or less of refractive cylinder, and required a near correction of +1.00 to +2.50 D of reading addition (add). The eyes also had a minimum central corneal thickness of ≥ 500 μm, corneal power ≥ 41.00 D and ≤ 47.00 D in all meridians and an endothelial cell count of more than 2000 cells/mm^2. The primary outcome was the percentage of eyes with a UNVA ≥ 20/40. Several subgroups were predetermined before study initiation to measure contrast sensitivity (n=335), defocus curve (n=114), and visual fields (n=224). The corneal inlay was implanted under a lamellar resection, either a corneal pocket created by a femtosecond laser (n=471) or under a corneal flap (n=37) created by a mechanical microkeratome. The mechanism of action of the KAMRA (increase in depth of focus by blocking peripheral unfocused rays of light) was reflected in the defocus curves. Reported outcomes at 36 months included the following:
- The implanted eyes exhibited 3.5 diopters of defocus range above 20/40, with 363/417 patients (87.1%) and 391/417 patients (93.8%) having 20/40 or better monocular and binocular uncorrected near visual acuity (UNVA). The mean visual acuities significantly improved for both positive and negative defocus after implantation.
- Patients implanted via a femtosecond laser pocket procedure demonstrated further improved near vision, with 131/145 patients (90.3%), 137/145 patients (94.5%) having 20/40 or better monocular and binocular UNVA, respectively.
- UDVA of 20/25 or better was maintained in 135/145 patients (93.1%) and 100% of implanted eyes.
- The results of a patient questionnaire showed that for those in the pocket group, near vision tasks were all graded as much easier to perform postoperatively than preoperatively (p<0.001). Minimal change was reported in ease of performing distance vision tasks. There was a significant reduction in the ease of watching television and driving at night (p<0.05).

Ocular adverse events included decreases in CDVA of ≥ 2 lines and secondary surgical interventions which included six inlay repositionings and 44 removals (8.7%). The removal rate was significantly less in the pocket group and further reduced with deeper implantation. There was also one event each of corneal edema, corneal haze, amorphous material around a fold in the inlay, and stromal thinning secondary to abnormal healing response to corneal trauma. Less than 1.0% of the patients reported severe glare or halos postoperatively. Author-noted limitations of the study included the fact that the questionnaire was not validated before the study; the deep implantation cohort was small relative to the whole cohort size; and the subgroups of lamellar

resection and implantation depth were created following the study, which limited the statistical power of the analyses on these variables. Another limitation was the number of patients lost to follow-up (n=49; 8.7%).

Hexagonal Keratotomy: This technique uses a computer-assisted microkeratome to reshape the cornea. It works similarly to a carpenter's plane, making a hexagonal pattern of cuts versus the radial cuts seen in radial keratotomy (RK). Hexagonal keratotomy has been used to treat hyperopia which occurs naturally and also to treat presbyopia after RK. Hexagonal keratotomy is now rarely used, due to complications like poor healing and irregular astigmatism, and as newer techniques in refractive surgery have been developed (Mercer, et al., 2023).

Keratophakia: This technique involves the insertion of a donor cornea lens into the corneal stroma to change the shape of the cornea and modify its refractive power. Keratophakia was not addressed in the 2022 AAO Preferred Practice Pattern on Refractive Surgery, and there is a paucity of studies evaluating keratophakia for refractive errors. The effectiveness of keratophakia for correction of refractive errors has not been proven in the peer-reviewed medical literature.

Laser Epithelial Keratomileusis (LASEK): LASEK, a modification of photorefractive keratectomy (PRK), is a surface ablation procedure that attempts to preserve the epithelium. The postoperative outcomes of LASEK have been reported to be similar to those of PRK. Proposed advantages of LASEK compared to LASIK are that more stromal tissue is reserved, and flap-related complications do not occur. However, patients undergoing LASEK experience more postoperative discomfort and slower recovery of vision than those who have had LASIK. The AAO Preferred Practice Pattern Refractive Surgery stated that the potential for the development of corneal haze remains a concern since LASEK is a modification of PRK (AAO, 2022a). There is a lack of evidence in the peer-reviewed literature to support the safety and efficacy of this procedure.

Kuryan et al. (2017) published results of a Cochrane review (n=3 RCTs/154 subjects) to assess the effects of LASEK versus LASIK for correcting myopia. RCTs were selected in which myopic subjects were assigned randomly to receive either LASEK or LASIK in one or both eyes. Patients were included in the studies who were between the ages of 18 and 60 years with myopia up to 12 D and/or myopic astigmatism of severity up to 3 D, and who did not have a history of prior refractive surgery. All trials enrolled participants with mild to moderate myopia (< -6.50 D); only one trial included subjects with severe myopia (> -6.00 D). The primary outcome measure was uncorrected visual acuity (UCVA) at 12 months. The evidence showed uncertainty as to whether there was a difference between LASEK and LASIK in UCVA at 12 months. People receiving LASEK were less likely to achieve a refractive error within 0.5 diopters of the target at 12 months follow-up (RR 0.69, 95% CI 0.48 to 0.99; 57 eyes; very low-certainty evidence). One trial reported mild corneal haze at six months in one eye in the LASEK group and none in the LASIK group (RR 2.11, 95% CI 0.57 to 7.82; 76 eyes; very low-certainty evidence). None of the included trials reported postoperative pain score or loss of visual acuity, spherical equivalent of the refractive error, or quality of life at 12 months. Patients receiving LASEK were less likely to achieve a refractive error within 0.5 diopters of the target at 12 months follow-up (very low-certainty evidence). In terms of adverse events, refractive regression was reported only in the LASEK group (8/37 eyes) compared to 0/39 eyes in the LASIK group in one trial (low-certainty evidence). Likewise, low-certainty evidence of one trial reported adverse events of corneal flap striae and refractive over-correction only in the LASIK group (5/39 eyes) compared to 0/37 eyes in the LASEK group. This review was limited by the small sample sizes in studies and the low quality of the available evidence. The authors concluded that large, well-designed RCTs are needed to estimate the magnitude of any difference in efficacy or adverse effects between LASEK and LASIK for treating myopia or myopic astigmatism.

Minimally Invasive RK (mini-RK): Radial keratotomy involves the use of radial incisions in the cornea to correct mild to moderate myopia. Mini-RK is a modified radial keratotomy procedure that reduces the millimeters of cornea incised. The goal is to maximize corneal flattening with a minimum length and number of incisions. Mini-RK is considered an investigational procedure.

Orthokeratology: Orthokeratology also called ortho-K, is the use of rigid gas-permeable contact lenses as a nonsurgical and reversible method for the treatment of mild to moderate myopia. The center of the contact lens is deliberately fitted flatter than the central corneal curvature to transiently induce central corneal flattening, by a thinning or molding of the epithelium, which is proposed to reverse myopia during the day when the lens is not worn. However, the corneas tend to revert back to their original shape when the lens is not worn. The most serious complication that has been associated with orthokeratology is microbial keratitis (Coats and Paysse, 2023).

Rigid gas permeable lens are approved by the FDA as 510(k) Class II devices. FDA published an industry Guidance for Premarket Submissions of Orthokeratology Rigid Gas Permeable Contact Lenses (FDA, last updated March 2018). In their discussion of types of contact lenses, the FDA requires that eye care professionals be trained and certified before using overnight Ortho-K lenses in their practice. An example of an FDA approved gas permeable contact lens is the Boston XO$_2$ (Bausch & Lomb, Inc., Rochester, NY). One of the approved intended uses of the lens is "daily wear for the correction of refractive ametropia (myopia, hyperopia, astigmatism and presbyopia) in aphakic and non-aphakic persons with non-diseased eyes. Also, the lenses may be prescribed in other wise non-diseased eyes that require a gas permeable contact lens for the management of irregular corneal conditions such as keratoconus, pellucid marginal degeneration, or following penetrating keratoplasty or refractive (e.g., LASIK) surgery" (FDA, 2007).

The updated 2022 AAO Preferred Practice Pattern on Refractive Errors stated that attempts to predict which patients would respond to orthokeratology based on ocular biomechanical or biometric parameters have not been successful. The effects of orthokeratology have been unpredictable and poorly controlled. There are substantial variations in changes in eye length among children and there is no way to predict the effect for individual subjects. There is a lack of evidence showing that orthokeratology can slow the progression of myopia. According to AAO, the safest way to incorporate contact lenses into clinical practice for reduction of axial elongation in young children remains to be determined.

There is insufficient evidence in the published, peer-reviewed literature to support the effectiveness of orthokeratology for the treatment of myopia. Studies are primarily in the form of case reports, retrospective reviews and case series with small patient populations, short-term follow-up and conflicting results. There is also a lack of data regarding a regimen for discontinuing ortho-k lenses (Tsai, et al., 2021; Zhong, et al., 2020; Kang, 2018; Si, et al., 2015; Sun, et al., 2015).

Lawrenson et al. (2023) conducted a Cochrane systematic review and network meta-analysis of randomized controlled trials evaluating interventions for myopia control in children. The review included 11 studies (n=52-240 subjects) comparing orthokeratology lenses to single vision spectacle lenses (SVLs); single vision soft contact lenses (SVSCLs); rigid gas-permeable contact lenses (RGPs); atropine; or a combination of these interventions. Length of follow up was one to two years. The primary outcome for most studies was change in axial length. The authors judged the risk of bias as ranging from "some concerns" to "high risk". In the eight studies (n=787 subjects) comparing orthokeratology to SVLs or SVSCLs, a significant reduction in axial elongation was seen across two years (one year mean difference [MD] −0.19 millimeters [mm], 95% confidence interval [CI] −0.23 to −0.15; two year MD −0.28 mm, 95% CI −0.38 to −0.19). In two studies which compared low-dose atropine to orthokeratology, there was no significant difference in axial length between treatments. One-year data was based on 234 participants, and

two-year data was derived from 49 participants. Among contact lens interventions, adverse events were more common in orthokeratology, and included corneal infiltrates and corneal staining, with four cases of corneal staining graded 3 or higher. There were 12 documented withdrawals due to adverse events. The authors concluded topical antimuscarinic agents and orthokeratology appear to be effective treatments for slowing childhood myopia progression, but also stated that there was uncertainty regarding the risk-benefit of orthokeratology and other contact lens interventions in children. Adherence to treatment was not formally assessed, despite these studies often being associated with high dropout rates (over 50% in some studies).

In a systematic review and meta-analysis Si et al. (2015) reported that orthokeratology may slow the progression of myopia in children but due to the limited evidence large-scale studies are needed to substantiate the results and to investigate the long-term effects of orthokeratology in myopia control. Studies were included if they included myopic patients aged ≤ 18 years; compared orthokeratology with control subjects (single-vision spectacles or soft contact lenses); and reported axial length (AL) elongation or more information relevant to myopia progression (e.g., vitreous chamber depth elongation). Two randomized controlled trials and five nonrandomized controlled trials (n=435) met inclusion criteria with 218 children being treated with orthokeratology. Maximum follow-up was two years. Subjects were aged 6–16 years. The weighted mean difference was -0.26 mm (p< 0.001) for axial length elongation based on data from seven studies and -0.18 mm (p=0.02) for vitreous chamber depth elongation based on data from two studies showed significant improvement with ortho-K. The author-noted limitations were: small sample sizes, short-term follow up, limited the reliability of the results, and the heterogeneity of the patient population, study protocols and designs. The authors noted that because the mechanism of myopia progression is still debatable, additional studies are needed to further elucidate the potential biological mechanisms that are involved.

Sun et al. (2015) conducted a systematic review and meta-analysis to evaluate the clinical treatment effects of orthokeratology to slow the progression of myopia. Seven studies (n=546) met inclusion criteria including two were randomized controlled trials, two retrospective reviews and three observational studies. Subjects were ages 6–16 years and follow-ups were for two years. The main outcomes included axial length and vitreous chamber depth. All studies reported axial length changes after two years and two studies reported vitreous chamber depth changes. The pooled estimates indicated that change in axial length in the ortho-k group (n=218) was 0.27 mm less than the control group and myopic progression was reduced by approximately 45%. The combined results revealed that the difference in vitreous chamber depth between the two groups was 0.22 mm in favor of ortho-K. None of the studies reported severe adverse events. Limitations of the studies included: small patient populations, short-term follow-up, drop-out rates of 12.4%–46.2% and the retrospective study designs. Well-designed randomized controlled trials with large populations and long-term follow-ups are needed to assess the effectiveness of ortho-K for the treatment of myopia.

Van Meter et al. (2008) performed a technology assessment of case reports and noncomparative case series (n=75) to evaluate the safety of overnight orthokeratology for the treatment of myopia. It was found that overnight orthokeratology is associated with complications including infectious keratitis and induced astigmatism, however the prevalence and incidence of complications have not been determined. The authors noted that overnight orthokeratology puts patients at risk for vision-threatening complications they may not encounter otherwise. Large, well-designed randomized controlled studies are needed to provide a more reliable measure of the risks of treatment and to identify risk factors for complications Overnight orthokeratology for slowing the progression of myopia in children also needs well-designed and properly conducted controlled trials to investigate efficacy (Van Meter, et al., 2008).

Scleral Expansion Surgery: Scleral expansion surgery involves the use of scleral expansion band segments which are inserted beneath partial thickness scleral incisions (scleral belt loops) in each of the oblique quadrants. The procedure is claimed to improve accommodation and has been proposed as a treatment for presbyopia. The infrared laser has also been used to make deep scleral incisions to treat presbyopia presumably by mechanisms similar to scleral expansion bands (Kleinmann, et al., 2006). Many investigators dispute the proposed mechanism of scleral expansion to treat presbyopia, and the results of these various surgeries have not shown predictable or consistent effects on distance corrected near acuity or accommodative amplitude (Mercer, et al., 2023; AAO, 2022a).

There is insufficient evidence in the peer-reviewed literature to support the effectiveness of scleral expansion surgery for the treatment of presbyopia.

Use Outside of the US
The National Institute for Health and Clinical Excellence (NICE) (United Kingdom) (2013) conducted a review of the evidence on photochemical corneal collagen cross-linkage (CXL). According to NICE, the majority of the published evidence on the procedure using riboflavin and ultraviolet A (UVA) for keratoconus and keratectasia relates to the 'epithelium-off' technique. NICE stated that the current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia is adequate in quality and quantity. NICE found the safety and efficacy evidence for epithelium-on CXL and the combination (CXL-plus) procedures to be of inadequate quantity and quality and therefore recommended that the procedures only be used with special arrangements for clinical governance, consent and audit or research.

The 2013 NICE guidance on corneal inlay implantation for correction of presbyopia stated that the evidence was limited in quantity and quality and came predominantly from case series. There was some evidence of efficacy in the short term. However, there were reports that adverse effects occur frequently. Therefore the procedure should only be used with special arrangements for clinical governance, consent and audit or research.

NICE issued guidance on the use of corneal implants for the correction of refractive error, stating that the available evidence on the efficacy of corneal implants for the correction of refractive error showed limited and unpredictable benefit. In addition, NICE stated there were concerns about the safety of the procedure for patients with refractive error which can be corrected by other means, such as spectacles, contact lenses, or laser refractive surgery. Therefore, corneal implants should not be used for the treatment of refractive error in the absence of other ocular pathology such as keratoconus (NICE, 2007b).

The NICE guidance on the use of corneal implants for the management of keratoconus stated that current evidence on the safety and efficacy of corneal implants for keratoconus appears adequate to support the use of this procedure, provided that normal arrangements are in place for consent, audit and clinical governance (NICE, 2007a).

The 2006 NICE guidance on photorefractive laser surgery for refractive errors supported the treatment in appropriately selected patients. Supported techniques included photorefractive keratectomy (PRK), laser epithelial keratomileusis (LASEK) and laser in situ keratomileusis (LASIK) (NICE, 2006).

In 2004, NICE issued guidance on the use of scleral expansion bands in which it was stated that the current evidence on the safety and efficacy of scleral expansion surgery for presbyopia is very limited. NICE found no evidence of efficacy in the majority of patients and also noted that there were concerns about the potential risks of the procedure. It was recommended that the procedure not be used (NICE, 2004).

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Refractive Keratoplasty (80.7)	5/1/1997
LCD		No Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:
1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

Conventional, epithelium-off, corneal collagen crosslinking

CPT®* Codes	Description
0402T	Collagen crosslinking of cornea including removal of the corneal epithelium, when performed, and intraoperative pachymetry, when performed

HCPCS Codes	Description
J2787	Riboflavin 5'-phosphate, ophthalmic solution, up to 3ml

Corneal Relaxing Incision/Corneal Wedge Resection

CPT®* Codes	Description
65772	Corneal relaxing incision for correction of surgically induced astigmatism
65775	Corneal wedge resection for correction of surgically induced astigmatism

Intrastromal Corneal Ring Segments

CPT®* Codes	Description
65785	Implantation of intrastromal corneal ring segments

Considered Not Medically Necessary when used to report correction of refractive errors:

CPT®* Codes	Description
65710	Keratoplasty (corneal transplant); anterior lamellar
65730	Keratoplasty (corneal transplant); penetrating (except in aphakia or pseudophakia)

CPT®* Codes	Description
65750	Keratoplasty (corneal transplant); penetrating (in aphakia)
65755	Keratoplasty (corneal transplant); penetrating (in pseudophakia)
65756	Keratoplasty (corneal transplant); endothelial
66999	Unlisted procedure, anterior segment of eye

ICD-10-CM Diagnosis Codes	Description
H52.00-H52.7	Disorders of refraction and accommodation

Considered Experimental/Investigational/Unproven when used to report correction of refractive error:

CPT®* Codes	Description
65760	Keratomileusis
65765	Keratophakia
66999	Unlisted procedure, anterior segment of eye

HCPCS Codes	Description
V2599	Contact lens, other type

*Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.

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Revision Details

Type of Revision	Summary of Changes	Date
Annual review	• Updated to new template and formatting standards. • Removed laser in situ keratomileusis, photorefractive keratectomy, and radial keratotomy from policy statement.	10/15/2023