

# Medical Coverage Policy



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## Corneal Remodeling

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### Related Coverage Resources

[Intraocular Lens Implant](#)

#### INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines

### 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 J3490) 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, such that adequate functional vision on a daily basis with contact lenses or spectacles can no longer be achieved

- 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/transepithelial) 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.**

### **Epikeratoplasty**

**Epikeratoplasty (CPT® code 65767) (epikeratophakia) is considered medically necessary for EITHER of the following indications:**

- acquired or congenital aphakia
- aphakia following cataract surgery in patients unable to receive intraocular lens

**Epikeratoplasty (CPT® code 65767) (epikeratophakia) is considered experimental, investigational or unproven for any other indication.**

### **Phototherapeutic Keratectomy (PTK)**

**Phototherapeutic keratectomy (PTK) (CPT® code 66999; HCPCS code S0812) is considered medically necessary for ANY of the following indications:**

- superficial corneal dystrophy (including granular, lattice and Reis-Bückler's dystrophy)
- epithelial membrane dystrophy
- irregular corneal surfaces due to Salzmann's nodular degeneration or keratoconus nodule
- corneal scars and opacities, including post-traumatic, postinfectious, postsurgical and secondary to pathology
- recurrent corneal erosions when more conservative measures (e.g., lubricants, hypertonic saline, patching, bandage contact lenses, gentle debridement of severely aberrant epithelium) have failed to halt the erosions

**Phototherapeutic keratectomy (PTK) (CPT® code 66999; HCPCS code S0812) is considered not medically necessary for any other indication.**

### **Intrastromal Corneal Ring Segments**

**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.**

### **Laser In Situ Keratomileusis (LASIK) & Photorefractive Keratectomy (PRK)**

**Correction of surgically-induced astigmatism and/or anisometropia 3.00 diopters (D) or greater with laser in situ keratomileusis (LASIK) (HCPCS code S0800), or photorefractive keratectomy (PRK) HCPCS code S0810), is considered medically necessary in an individual who has documented inadequate functional vision with glasses and/or contact lenses.**

**Laser in situ keratomileusis (LASIK) (HCPCS code S0800), or photorefractive keratectomy (PRK) HCPCS code S0810) is considered not medically necessary for any other indication.**

### **Other Procedures**

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

- clear lens extraction (CLE) (CPT® codes 66840; 66850; 66852; 66920; 66930; 66940; 66983; 66985; HCPCS codes C1780; Q1004; Q1005; S0596; S0800; S0810; V2630; V2631; V2632; V2687; V2688)
- conductive keratoplasty (CPT® code 65771)
- lamellar keratoplasty (nonpenetrating keratoplasty) (CPT® codes 65710; 0289T; 0290T)
- 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; 0289T; 0290T)
- phakic intraocular lens (PIOL) (HCPCS code S0596)
- radial keratotomy (CPT® code 65771)

**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)

## **Overview**

This Coverage Policy addresses procedures used for the correction of refractive errors.

## **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 nonaccommodating eye do not focus on the retina. The errors are imperfections in the functioning power of the eye due to an imperfectly shaped eyeball, cornea or lens, so that regarded 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 noninflammatory degenerative condition in which collagen fibers within the cornea weaken and progressively thin. As a result of 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 (Hayes 2016; Seyedian, et al., 2015). 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 (LASIK or 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 (Hersh, et al., Oct 2017; American Academy of Ophthalmology, 2013).

The need to correct refractive errors depends on the patient's symptoms and visual needs. Those with low refractive error 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 (American Academy of Ophthalmology [AAO], 2017).

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, 2017). There are several refractive procedures currently in use.

## **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, 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., Sept. 2017).

The original procedure, conventional CXL (C-CXL), also referred to as epithelium-off (Dresden protocol), involves total removal of the epithelium prior 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<sup>2</sup>). 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, 2018; 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 patients, age 14–65 years, with progressive keratoconus or for the treatment of corneal ectasia following refractive surgery. Patients with progressive deterioration in vision who are unable to obtain functional vision on a daily basis with contact lenses or spectacles are considered appropriate candidates. 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 (Hayes, 2018; Galvis, et al., 2017; 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 intraprocedure 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 reepithelialization. Few studies have investigated the safety and effectiveness of these modified corneal crosslinking procedures (Hayes, 2018; 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) and degenerative corneal diseases like Terrien Marginal Degeneration. 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 (Hayes, 2018; Zhu, et al., 2018; Chan et al., 2017; Galvis, et al., 2017; Craig, et al., 2014).

**US Food and Drug Administration (FDA):** On April 15, 2016, the FDA issued a new drug application (NDA) approval for Photrex Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%, and Photrex (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 age < 14 years and the clinical trials did not include patients who were age 65 years or older (FDA, 2016).

**Literature Review:** The available evidence in the published peer-reviewed medical literature evaluating the safety and effectiveness of primarily epithelial-off corneal collagen crosslinking consists of systematic reviews with meta-analysis, randomized controlled trials, case series and retrospective reviews. Although the studies primarily include small patient populations and short-term follow-ups, outcomes have overall, consistently reported a significant improvement in vision and cessation or slowing of the disease process. C-CXL has evolved into an accepted treatment option for a carefully defined subgroup of patients with progressive keratoconus and for corneal ectasia following refractive surgery.

**Conventional CXL (C-CXL) Epithelium-Off for Keratoconus:** Hersh et al. (Sept 2017) reported the results of a multicenter RCT (n=205) evaluating the safety and effectiveness of CXL for progressive keratoconus. Inclusion criteria were age 14 years or older, maximum keratometry of  $\geq 47.0$  diopters (D) on corneal topography, an inferior-to-superior ratio of  $> 1.5$  on topography mapping, corrected distance visual acuity (CDVA)  $< 20/20$ , and corneal thickness  $\geq 300$   $\mu$ m. Exclusion criteria included patients with a history of corneal surgery, including intracorneal ring segments, and a history of corneal disease that would interfere with healing after the procedure (e.g., chemical injury, history of delayed epithelial healing). Patients were randomized into a treatment (n=102) or sham control (n=103) group. The treatment group received standard ultraviolet A (UVA) riboflavin 0.1% CXL treatment,

while the sham patients received riboflavin 0.1% plus dextran ophthalmic solution alone without de-epithelialization. Outcomes included topography, visual acuity and refraction measurements. Maximum keratometry (i.e., steepness of keratoconic topographic distortion) was the primary efficacy outcome. A difference of at least 1.0 D in the mean change in maximum keratometry from baseline to the one-year follow-up when comparing the treatment and control groups was determined to be a clinically meaningful outcome to define study success. In the CXL treatment group, there was a significant decrease in the mean maximum keratometry value between baseline and 12 months after surgery ( $p<0.001$ ); a significant increase in the mean maximum keratometry value was found for those in the control group ( $p<0.001$ ). The difference in maximum keratometry change between treatment and control was 2.6 D, a statistically significant finding ( $p<0.0001$ ). The difference in CDVA change was also found to be statistically significant ( $p<0.01$  in favor of CXL treatment). At 12-month follow-up, adverse events of persistent corneal haze ( $n=2$  eyes), corneal scar ( $n=1$  eye), endothelial folds ( $n=1$  eye), and irregular corneal epithelium ( $n=1$  eye) were reported. Corneal stromal haze and/or a demarcation line were noted in 58 eyes (57%) throughout the study. At final follow-up, two eyes had retained stromal haze and one eye had a corneal scar. There was no statistically significant difference in cell count change between the two groups. The authors noted that a limitation of the study was that eyes in the control group were allowed to cross over to treatment at the three month follow-up which left only two control eyes were available at 12 months. The other noted limitation was that the epithelium was not removed in the control eyes.

Seyedian et al. (2015) conducted an RCT ( $n=26$  subjects/52 eyes) of patients with bilateral progressive keratoconus who were treated with CXL. In each patient, one eye was randomly selected for treatment, and the contralateral eye served as the control. Inclusion criteria were age between 15 and 40 years, confirmed bilateral KCN based on clinical and topography findings, bilateral minimum corneal thickness of 400  $\mu\text{m}$ , maximum keratometry of 60 D in each eye based on Pentacam readings, and evidence of progressing KCN. Both eyes of each patient had to meet the criteria indicative of KCN progression over the previous 12 months. Exclusion criteria were corneal scarring in either eye, previous eye surgery, ocular surface or tear problems, and the coexistence of ocular disease other than KCN. The primary outcome measures were BSCVA, the maximum simulated keratometry (K-max) and mean keratometry (K-mean) based on Pentacam readings. A  $p<0.05$  was considered statistically significant. At one-year follow-up, the mean K-max values in treated eyes decreased by 0.22 D and increased by 0.41 D in the control group ( $p<0.001$ ). BSCVA improved slightly in the CXL group and decreased slightly in the control group ( $p=0.014$ ). There was no decrease in visual acuity attributable to complications of CXL in the treated eyes. At one-year, the keratometry in three (12%) treated eyes increased by more than 0.50 D and were considered cases of failed treatment. The authors commented that although this study provides some information on the safety and efficacy of CXL, more extensive studies with longer follow-up are necessary (Seyedian, et al., 2015).

Lang et al. (2015) published their results of a prospective, blinded, RCT (29 eyes) to evaluate the safety and efficacy of CXL in slowing the progression of keratoconus. Patients were randomized to receive treatment ( $n=15$ ) or placebo ( $n=14$ ). Inclusion criteria were early stage keratoconus defined as correction of refractive error possible with spectacles or contact lenses. The progression had to be either proven by measurement of the corneal topography (an increase of more than 1 diopter in Kmax within one year) or by a clinically significant change in refraction. Exclusion criteria were patient age  $< 12$  years, corneal thickness  $< 450$   $\mu\text{m}$ , additional pre-existing eye diseases, prior eye surgery, and pregnancy. Follow-up averaged 1098 days. The primary end-point was progression of keratoconus defined as an increase of 1 diopter per year in patients younger than 20 years and an increase of 0.2 diopters per year in the complete cohort. Progression was measured by the longitudinal change in keratometric corneal refraction. Secondary endpoints included minimal simulated K-readings, central corneal thickness, worsening of best corrected visual acuity and the occurrence of further adverse events. During the complete follow-up period, four patients in both the treatment and control groups experienced a significant worsening of the best corrected visual acuity. The treatment group showed significantly more haze (15/15 patients) than was observed in the control group (4/15 patients) ( $p<0.001$ ). After three years, 12/15 eyes showed a complete resolution of the haze. Acknowledged study limitations include small sample size and difficulty with blinding due to the lack of postoperative pain after sham treatment. The authors noted a need to determine the clinical parameters that will allow for a distinction of keratoconus patients who will derive the most benefit from the treatment.

Li et al. (2015) performed a systematic review and meta-analysis of the evidence ( $n=6$  RCTs) on CXL treatment ( $n=179$  eyes) of keratoconus versus control ( $n=182$  eyes). The control group of two studies received a sham

treatment in which riboflavin 0.1% eye drops were administered alone. RCTs were selected if they included patients 14 years of age or older, with a confirmed diagnosis of keratoconus, or documented progression of the disease. The primary outcome of interest was reduction in topographic measurements. Secondary outcomes included changes of visual acuity, refractive error, central corneal thickness (CCT) and IOP. The follow-up time frame ranged from three months to 36 months. The following outcome measures were demonstrated to have statistically significant improvement in the CXL group compared with the control group:

- decrease in mean keratometry value, maximum keratometry value and minimum keratometry values ( $p < 0.00001$ )
- improvement of best spectacle-corrected visual acuity ( $p < 0.00001$ )
- decrease in manifest cylinder error ( $p = 0.04$ )

The changes in CCT, uncorrected visual acuity and intraocular pressure were not statistically significant. Adverse events were found to be minimal and transient with primarily varying degrees of corneal haze. Acknowledged limitations of the meta-analysis include the small sample size and short-term follow-up in individual studies, as well as the paucity of RCTs available for CXL due to the ethical concerns of such studies.

A Cochrane review by Sykakis et al. (2015) ( $n = 3$  RCTs/225 eyes enrolled/ 219 eyes analyzed) evaluated the evidence to determine the safety and effectiveness of CXL for slowing the progression of keratoconus. The RCTs, conducted in Australia, the United Kingdom, and the United States, were included if CXL with UVA light and riboflavin was used to treat keratoconus and was compared to no treatment. The primary outcome was risk of disease progression. Only one study reported comparative data on review outcomes. There was indirect information on the risk of progression, defined as increase of 1.5D or more in maximum keratometry. The available data suggested that there may be an 80%–90% relative risk reduction in progression over 12 months, but there was uncertainty as to the size of the effect. Other data suggested that on average treated eyes had a less steep cornea and better uncorrected visual acuity, but the quality of the evidence for this finding was deemed to be very low as it was largely derived from one trial with high risk of bias. The data on corneal thickness were inconsistent. Adverse effects included corneal edema and recurrent corneal erosion. The authors found that overall the evidence was of low quality due to high risk of bias in all studies. Differences in measuring and reporting outcomes in studies prevented a pooling of the data. It was concluded that despite the fact that CXL seems to be accepted worldwide as a breakthrough treatment in the management of keratoconus, the available evidence is limited due to the lack of properly conducted RCTs. Within the context of this review, CXL for the treatment of keratoconus is not supported by high quality evidence.

Chunyu et al. (2014) performed a meta-analysis ( $n = 23$  trials/1557 eyes) to determine the effectiveness of CXL for the treatment of progressive keratoconus. Trials included RCTs ( $n = 4$ ), prospective controlled studies ( $n = 11$ ), and retrospective studies ( $n = 8$ ). A total of 18 trials reported follow-up results after one year, and six trials included a control group. The inclusion criteria were consistent in that all patients were reported to have progressive keratoconus, although the definition of “progressive” varied slightly and was undefined in some cases. The primary outcome measures included uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), refraction, corneal topography, and corneal thickness at baseline and through 18 months after CXL. In 14 studies, treated patients demonstrated a statistically significant improvement ( $p < 0.01$ ) in both UCVA and BCVA at 12 months of follow-up. After 18 months post-CXL, only BCVA ( $p < 0.001$ ) still showed significant improvement in five studies ( $n = 181$  patients). In a long-term follow-up of over 18-months, Kmax decreased significantly ( $p = 0.01$ ) based on the results of six studies, but Kavg was not found to be significantly different between treated patients and controls. CCT values were decreased at six and 12 months post-CXL ( $p < 0.05$ ); however, at the long-term follow-up of more than 18 months, the values showed no statistical difference ( $p > 0.05$ ). The authors noted limitations of this meta-analysis due to the varying criteria of individual trials (e.g., participant age, keratoconus stage, outcome measurement), and stated that additional research from RCTs is needed to confirm findings.

Craig et al. (2014) conducted a systematic review and meta-analysis of studies ( $n = 49$ ) for CXL for keratoconus and kerectasia. The evidence analyzed included RCTs ( $n = 8$  papers reporting 4 unique studies), prospective case series ( $n = 29$  studies), and case reviews ( $n = 12$  studies). The majority of the studies (39/49) were graded as very low quality evidence. The authors reported changes in the outcomes of visual acuity, topography, refraction

and astigmatism, and CCT. Statistically significant improvements were found in all efficacy outcomes at 12 months after the procedure and at 24 months where the quantity of data allowed for meta-analyses (Craig, et al., 2014):

Number of studies by outcome and measure included in each meta-analysis at 6, 12, and 24 months after CXL				
Outcome	Measure	6 months	12 months	24 months
<b>Topography</b>	Max Keratometry (K)	10	18	6
	Mean K	7	12	Not done (ND)
	Min K	4	8	ND
<b>Visual Acuity (VA)</b>	Uncorrected VA	12	18	6
	Corrected VA	15	22	7
<b>Refraction &amp; Astigmatism</b>	Astigmatism grouped	7	13	5
	Spherical equivalent grouped	8	10	ND
<b>Central Corneal Thickness (CCT)</b>	Micrometer (mm)	6	6	ND

In the three meta-analyses performed on the RCTs alone, significant improvements were found only for corrected VA at 12 months. Common side effects of CXL were pain, corneal edema, and corneal haze, which typically resolved within a few days after the procedure. It was noted that the quality of the evidence is limited by the lack of comparators, loss to follow-up and incomplete reporting in studies. The authors stated that long-term RCTs are needed to establish the potential benefit of epithelium-off CXL in avoiding or delaying disease progression and possibly reducing the need for corneal transplantation (Craig, et al., 2014).

Wittig-Silva et al. (2014) published their results of a randomized, controlled trial (n=100 eyes) of corneal collagen crosslinking (n=50 eyes) in patients with keratoconus. Eyes randomized to the control group (n=50) did not receive sham treatment. Patients between the ages of 16 and 50 years with a confirmed diagnosis of progressive keratoconus were included. Exclusion criteria were a minimum corneal thickness less than 400  $\mu$ m, axial corneal scarring, previous refractive or other corneal surgery, a history of chemical burns, severe infections, and other corneal or ocular surface disorders. The primary outcome measure was the maximum simulated keratometry value (Kmax). Other outcome measures included uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA). At 36 months of follow-up, 27 eyes remained in the control group and 41 eyes in the experimental group. Overall, there was improvement in treated eyes with a flattening of Kmax by  $-1.03 \pm 0.19$  D at 36 months. An improvement of at least  $-2.00$  D between baseline and 36 months was observed in six eyes with a maximum improvement of  $-2.90$  D in 2 eyes. In the control group, no eyes improved by 2.00 D or more, and 19 eyes had documented progression of 2.00 D or more, with seven eyes in this group progressing by 4.00 D or more over 36 months. A comparison of the changes between control and treatment groups demonstrated statistically significant differences for all evaluated time points ( $p < 0.001$ ). For UCVA, the difference between the changes in both groups also was significant in favor of the treatment group at each follow-up ( $p < 0.001$ ). Compared to baseline values treated eyes significantly improved in BSCVA throughout 36 months of follow-up. The mean change in BSCVA for the control group was not significant at 36 months, and there was no significant difference in BSCVA between the 2 groups at any time point. Adverse events (n=2 eyes) of mild, diffuse corneal edema and a small paracentral infiltrate occurred in one week after CXL treatment. Study limitations include loss to follow-up and compassionate CXL being offered to select patients in the control group after a minimum of six months of follow-up. The authors noted that "this could lead to masking of progression in the control group and an underestimation of the treatment effect demonstrated in this study" (Wittig-Silva, et al., 2014). The results of this study suggest that CXL is associated with improved UCVA and BSCVA compared to no treatment for progressive keratoconus.



Hersh et al. (2011) conducted an RCT (n=58 patients/71 eyes) to evaluate corneal collagen crosslinking for treatment of keratoconus and corneal ectasia. The treatment group received standard corneal collagen crosslinking and the sham control group received riboflavin alone. Primary outcomes included uncorrected and corrected distance visual acuities, refraction, and astigmatism. At one year of follow-up, improvements were found in uncorrected ( $p=0.04$ ) and corrected ( $p<0.001$ ) distance visual acuities. Keratoconus patients had more improvement in topographic measurements than patients with ectasia. Limitations to this study include small sample size and short-term follow-up.

A prospective RCT (n=66 eyes/49 patients) by Wittig-Silva et al. (2008) evaluated the efficacy and safety of corneal collagen crosslinking for the management of progressive keratoconus. Eyes were separately randomized into either treatment or control groups. Interim analysis of treated eyes showed a statistically significant flattening of the steepest simulated keratometry value (K-max) by an average of 1.45 D ( $p=0.002$ ) at 12 months. A trend toward improvement in BSCVA was also observed. In the control group the mean K-max steepened by 1.28 D ( $p\leq 0.0001$ ) after 12 months. BSCVA decreased over 12 months ( $p=0.036$ ).

Cohort studies and case series investigating CXL treatment for progressive keratoconus have consisted of sample sizes ranging from 55-100 eyes with follow-up of 12-24 months (Khattak, et al., 2015; Lamy, et al., 2013; Viswanathan and Males, 2013; Kymionis, et al., 2010). Outcomes measured included keratometry, visual acuity, corneal thickness, and intraocular pressure measurements. The most consistent finding of these studies has been that corneal crosslinking causes a decrease in keratometry values that tends to be maintained over at least a year.

The evidence in the published peer-reviewed medical literature on the treatment of progressive keratoconus with corneal collagen crosslinking using riboflavin and ultraviolet is evolving. Additional results of well-designed controlled clinical trials are needed to firmly establish the role of this procedure in treating ectasia associated with keratoconus, and to determine the preferred technique i.e., epithelium-off, epithelium-on).

**Conventional CXL (C-CXL) Epithelium-Off for Corneal Ectasia Following Laser Refractive Surgery:** Hersh et al. (Oct 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  $\geq 14$  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  $> 300$   $\mu\text{m}$  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 ( $0.7\pm 2.1$  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 ( $0.6\pm 2.1$  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.

**Transepithelial CXL (T-CXL) Epithelium-On:** Studies investigating T-CXL are primarily in the form of case series or retrospective reviews with small patient populations and short-term follow-ups (Li, et al., 2012).

Rush et al. (2017) conducted a randomized controlled trial (n=144) to compare conventional corneal collagen crosslinking (C-CXL) (control group) to transepithelial 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. 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 transepithelial 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  $K_{max}$ ,  $K_{steep}$ , mean keratometry, and/or topographic cylinder value by >0.5 D over the previous six–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  $K_{max}$  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  $K_{max}$  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 transepithelial 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 transepithelial 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  $\geq 1$  D within the previous year) mild and moderate keratoconus (stages I and II on the Amsler–Krumeich scale), corneal thickness  $\geq 400$  mm, mean K  $\leq 53$  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 ( $K_{max}$ ). 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 transepithelial group stabilized or improved, and 19 patients (55%) progressed ( $p<0.0001$ ). Compared to baseline,  $K_{max}$  decreased significantly in the epithelium-off group and increased significantly in the transepithelial 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 transepithelial corneal crosslinking in slowing the progression of keratoconus.

**Corneal Crosslinking - Other Procedures:** 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); transepithelial 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/nonremoval 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.
- Transepithelial 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 reepithelialization.

**Professional Societies/Organizations:** The 2017 American Academy of Ophthalmology® (AAO) Summary Benchmark for Preferred Practice Pattern® (PPP) Guidelines on cornea/external disease includes a discussion of the initial and follow-up evaluation of corneal ectasia. The guideline listed collagen crosslinking as a treatment option that can improve corneal rigidity by increasing bonds between fibers.

In the 2017 Refractive Errors and Refractive Surgery Preferred Practice Pattern® 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 postrefractive corneal ectasia has been reported and recently received FDA approval.

### **Corneal Relaxing/Corneal Wedge Resection - Astigmatic Keratotomy (AK)**

AK procedures are those in which 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 postkeratoplasty 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. 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, 2017). As such, the use of LRIs to treat astigmatism that is not surgically induced is considered not medically necessary.

The effectiveness of AK for correction of other refractive errors has not been proven in the literature. The AAO Preferred Practice Pattern on Refractive Errors stated that there are few well-controlled, prospective clinical studies available on AK performed alone or in connection with other keratorefractive procedures" (AAO, Jul 2017).

#### **Epikeratoplasty (or Epikeratophakia)**

Epikeratoplasty is a refractive surgical procedure that involves placement of a precarved donor corneal lens on the surface of a patient's eye. Epikeratophakia is the surgical correction of aphakia and may be considered for the treatment of childhood aphakia (absence of lens) because contact lenses are difficult for children to use, and intraocular lens implants may result in long-term complications in children. This procedure may be used on scarred corneas and corneas affected with endothelial dystrophy. Epikeratophakia may also be considered acceptable in cases of adult aphakia when the secondary implantation of an intraocular lens might affect outcome (e.g., history of uveitis, significant corneal endothelial disease, gross corneal irregularity after trauma). The effectiveness of this procedure for the correction of refractive errors in other disorders has not been proven in the literature. The AAO Preferred Practice Pattern on Refractive Errors and Refractive Surgery states that epikeratoplasty results have been widely variable and there have been significant complications including poor wound healing, irregular astigmatism and infectious keratitis. According to the AAO (Jul 2017), this procedure has largely been abandoned for refractive correction.

#### **Phototherapeutic Keratectomy (PTK)**

PTK is used to correct refractive errors caused by a diseased cornea (e.g., granular, lattice, and Reis-Buckers' dystrophy; epithelial membrane dystrophy; irregular corneal surfaces due to Salzmann's nodular degeneration; or keratoconus nodules, corneal scars and opacities, and recurrent corneal erosions) or for the correction of visual impairment after cataract surgery. PTK uses an excimer laser, but does not alter the final refractive state of the eye. PTK should not be confused with photorefractive keratectomy (PRK). Although technically the same procedure, PTK is used for the correction of particular corneal diseases; whereas, PRK is used for the correction of refractive errors (e.g., myopia, hyperopia, astigmatism and presbyopia) in persons with otherwise nondiseased corneas.

#### **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  $\leq 1.0$  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, et al., 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, Jul 2017). 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.

**U.S. Food and Drug Administration (FDA):** The FDA has granted PMA approval to manufacturers of LASIK laser systems for the treatment of myopia, hyperopia, and astigmatism, and for PRK to treat hyperopia and astigmatism. On July 30, 1998, the Kremer Excimer Laser System® (PhotoMed, Inc., King of Prussia, PA) was granted premarket approval by the FDA for treatment of myopia and astigmatism (FDA, 2018). However, LASIK is considered not medically necessary for the treatment of myopia between -1.0 and -15.0 diopters (D), with or without astigmatism up to 5.0 D because this can be corrected satisfactorily with eyeglasses or contact lenses. LASIK has not been shown to be effective for the treatment of high myopia greater than -15.0 D, hyperopic astigmatism greater than 5.0 D, and for all other refractive errors

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 primary goal of LASIK after penetrating keratoplasty is to reduce the refractive error (e.g., astigmatism, anisometropia) to levels at which spectacle correction or contact lenses can be tolerated. The uncorrected visual acuity should remain a secondary goal (Wilkinson, et al., 2008). 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.

**Professional Societies/Organizations:** The AAO Ophthalmic Procedure Assessment of PRK concluded that "it appears to be a safe and effective procedure for the treatment of low to moderate degrees of myopia and astigmatism. Results for high degrees of myopia are associated with poorer outcomes, that is, longer stabilization periods, greater need for re-treatment, and increased loss of lines of BSCVA" (No authors listed, 1999). The AAO Preferred Practice Pattern on Refractive Errors states that published reports of PRK document a median rate of 92% of patients achieving 20/40 uncorrected vision and 70% of patients achieving 20/20 uncorrected vision at 12 or more months following PRK for myopia (AAO, Jul 2017).

Eye disorders such as keratoconus, where the cornea becomes progressively thinner and cone shaped, may result in a large amount of astigmatism resulting in poor vision that cannot be clearly corrected with spectacles. Keratoconus usually requires contact lenses for clear vision, and it may eventually progress to a point where a corneal transplant is necessary (American Optometric Association [AOA], Jul 2017).

## **Other Procedures**

**Clear Lens Extraction (CLE):** CLE, also referred to as refractive lens exchange, has been performed to correct refractive errors such as myopia, hyperopia, and presbyopia. The CLE technique is very similar to cataract extraction. The eye's natural lens is removed and replaced with a prescription intraocular lens. The replacement lens may be monofocal, multifocal or accommodating. Several studies have supported the safety and effectiveness of clear lens extraction using multifocal intraocular lenses (Leyland and Pringle, 2006; Dick, et al., 2002; Jacobi, et al., 2002). The AAO Preferred Practice Pattern on Refractive Errors and Refractive Surgery states that refractive lens exchange for myopia and hyperopia has been demonstrated to be predictable and effective, but no large-scale investigations on complications have been reported. Complications that may result in a permanent loss of vision are rare and include infectious endophthalmitis, intraoperative suprachoroidal hemorrhage, cystoid macular edema (CME), retinal detachment, corneal edema, and IOL dislocation (AAO, Jul 2017).

CLE for the treatment of refractive errors is considered not medically necessary because the correction of refractive errors can be achieved with eyeglasses or contact lenses.

**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 PMA approval 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. CK is considered not medically necessary for its FDA-approved indications, and is considered investigational for all other indications.

Currently, there is insufficient evidence in the peer-reviewed literature to support the effectiveness of CK for the treatment of presbyopia. Few case series with small sample sizes (n=10-27) and follow-ups of 1-3 years have

reported conductive keratoplasty to be safe and effective for symptomatic presbyopia (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 AAO (Jul 2017) 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. 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 CK):** 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, 2017). 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.

**Phakic Intraocular Lens (PIOL):** PIOL are synthetic lenses that are placed within the eye, along with the normal lens of the eye, to correct refractive errors. The PIOLs have a refractive power that exerts its effect on the overall refractive power of the eye. This results in improvement of refractive errors. PIOLs have the advantage of leaving the natural corneal curvature unchanged, whereas corneal refractive surgery creates abnormal corneal shapes, which may induce visual aberrations. While there is evidence to support short-term safety and efficacy, there are limited long-term data on potential complications such as the increased risk of cataract, corneal damage or retinal detachment (National Institute for Clinical Excellence [NICE], 2009). Other potential complications of PIOL implantation include endophthalmitis, chronic iridocyclitis, iris distortion, pigment dispersion, glaucoma, and intraocular lens (IOL) dislocation.

FDA PMA approved devices include Visian ICL (implantable collamer lens) (Staar Surgical Co., Aliso Viejo, CA) and Artisan (Model 206 and 204) PIOL, also known as Verisyse (VRSM5US and VRSM6US) (Ophtec BV, Groningen, Netherlands). According to the FDA, the Visian ICL is indicated for adults 21–45 years of age to

correct myopia ranging from -3.0 D to < -15.0 D with  $\leq 2.5$  D of astigmatism, or to reduce myopia ranging from > -15.0 D to -20.0 D with  $\leq 2.5$  D of astigmatism. The Artisan Myopia IOLs are indicated for the reduction or elimination of myopia in adults with myopia ranging from -5 to -20 D with less than or equal to 2.5 D of astigmatism.

PIOLs are considered not medically necessary for FDA-approved indications and investigational for all other indications.

**Radial Keratotomy (RK):** RK involves the use of radial incisions in the cornea to correct mild to moderate myopia. RK has been performed infrequently since the advent of photorefractive keratectomy (PRK) and LASIK (AAO, Jul 2017). RK is considered not medically necessary for treatment of myopia ranging from -2.00 to -8.00 D, because this refractive error can be corrected satisfactorily with eyeglasses or contact lenses. Radial keratotomy is considered investigational for treatment of myopia greater than -8.00 D. It is also considered investigational for the treatment of all other refractive errors because of the high rate of complications that include starbursts, anterior chamber perforation and infectious keratitis. Minimally invasive RK (mini-RK) is a modified RK 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.

**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 Preferred Practice Pattern on Refractive Errors 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, Jul 2017).

**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 (AAO, 2015). 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 subject 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 is 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  $\leq 0.75$  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

Contraindications to device implantation are similar to those for the Kamra inlay and also include having a corneal thickness that does not allow for a minimum of 300 microns of stromal bed thickness below the flap or an abnormal corneal topographic map of the eye to be implanted. 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  $\geq 20/40$  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%. Post-approval studies are underway to evaluate long-term safety and effectiveness (FDA, 2016).

Currently under investigation is the Presbia Flexivue Microlens™ (PresbiBio, LLC., Sandyford Dublin) 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 Presbia 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  $\mu\text{m}$  to 20  $\mu\text{m}$ . The Microlens received its CE Mark in 2009 and is approved in 42 countries. Presbia is not currently FDA approved but is in a Phase III trial for FDA approval and has completed enrollment (Moarefi, et al., 2017; Presbia, 2018).

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 (Hayes, 2017; Linn, et al., 2017; Verdoorn, 2017; Whang, et al., 2017; Jalali, et al., 2016; Yoo, et al., 2015; Yilmaz, et al., 2011; Dexl, et al., 2012; Seyeddain, et al., 2010). These studies included small patient populations (n=24-60) 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  $\geq 500$   $\mu\text{m}$ , corneal power  $\geq 41.00$  D and  $\leq 47.00$  D in all meridians and an endothelial cell count of more than 2000 cells/ $\text{mm}^2$ . The primary outcome was the percentage of eyes with a UNVA  $\geq 20/40$ . 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  $\geq 2$  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, as newer techniques in refractive surgery have been developed.

**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 AAO Preferred Practice Pattern on Refractive Errors and 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 on Refractive Errors and Refractive Surgery stated that the potential for the development of corneal haze remains a concern since LASEK is a modification of PRK (AAO, Jul 2017). 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):** 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.

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 Mar 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 (FDA, last updated Jan 2018). An example of an FDA approved gas permeable contact lens is the Boston XO<sub>2</sub> (Bausch & Lomb, Inc., Rochester, NY). One of the approved intended uses of the lens is “for daily wear in an orthokeratology fitting program for the temporary reduction of myopia of up to 5.00 diopters in nondiseased eyes. Note: To maintain the orthokeratology effect of myopia reduction, lens wear must be continued on a prescribed wearing schedule” (FDA, 2007).

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 the Ortho-K (Kang, 2018; Si, et al., 2015; Sun, et al., 2015).

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 authors noted that the small sample sizes, limited the reliability of the results, as well as the heterogeneity of the patient population, study protocols and designs. The short-term follow-up was another limitation. 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).

The Jul 2017 AAO Preferred Practice Pattern on Refractive Errors and Refractive Surgery 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 lens into clinical practice for reduction of axial elongation in young children remains to be determined.

**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). According to the AAO, 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 (AAO, Jul 2017).

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 crosslinkage (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.

The National Institute for Health and Clinical Excellence (NICE) has issued guidance on the use of corneal implants for the correction of refractive error. NICE states that the available evidence on the efficacy of corneal implants for the correction of refractive error shows limited and unpredictable benefit. In addition, NICE states

there are 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 states 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).

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).

## Coding/Billing Information

**Note:** 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 and intraoperative pachymetry when performed)

HCPSC Codes	Description
J3490	Unclassified drugs

### 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

### Epikeratoplasty (epikeratophakia)

CPT®* Codes	Description
65767	Epikeratoplasty

### Phototherapeutic Keratectomy (PTK)

HCPSC Codes	Description
S0812	Phototherapeutic keratectomy (PTK)

### Intrastromal Corneal Ring Segments

<b>CPT®*</b> <b>Codes</b>	<b>Description</b>
65785	Implantation of intrastromal corneal ring segments

**Laser In Situ Keratomileusis (LASIK), Photorefractive Keratectomy (PRK)**

<b>HCPCS</b> <b>Codes</b>	<b>Description</b>
S0800	Laser in situ keratomileusis (LASIK)
S0810	Photorefractive keratectomy (PRK)

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

<b>CPT®*</b> <b>Codes</b>	<b>Description</b>
65710	Keratoplasty (corneal transplant); anterior lamellar
65730	Keratoplasty (corneal transplant); penetrating (except in aphakia or pseudophakia)
65750	Keratoplasty (corneal transplant); penetrating (in aphakia)
65755	Keratoplasty (corneal transplant); penetrating (in pseudophakia)
65756	Keratoplasty (corneal transplant); endothelial
65771	Radial keratotomy
66840	Removal of lens material; aspiration technique, 1 or more stages
66850	Removal of lens material; phacofragmentation technique (mechanical or ultrasonic) (eg, phacoemulsification), with aspiration
66852	Removal of lens material; pars plana approach, with or without vitrectomy
66920	Removal of lens material; intracapsular
66930	Removal of lens material; intracapsular, for dislocated lens
66940	Removal of lens material; extracapsular (other than 66840, 66850, 66852)
66983	Intracapsular cataract extraction with insertion of intraocular lens prosthesis (1 stage procedure)
66985	Insertion of intraocular lens prosthesis (secondary implant), not associated with concurrent cataract removal
66999	Unlisted procedure, anterior segment of eye
0290T	Corneal incisions in the recipient cornea created using a laser, in preparation for penetrating or lamellar keratoplasty (List separately in addition to code for primary procedure)

<b>HCPCS</b> <b>Codes</b>	<b>Description</b>
C1780	Lens, intraocular (new technology)
Q1004	New technology, intraocular lens, category 4 as defined in Federal Register notice
Q1005	New technology, intraocular lens, category 5 as defined in Federal Register notice
S0596	Phakic intraocular lens for correction of refractive error
S0800	Laser in situ keratomileusis (LASIK)
S0810	Photorefractive keratectomy (PRK)
V2630	Anterior chamber intraocular lens
V2631	Iris supported intraocular lens
V2632	Posterior chamber intraocular lens
V2787	Astigmatism correcting function of intraocular lens
V2788	Presbyopia correcting function of intraocular lens

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®) ©2017 American Medical Association: Chicago, IL.**

## References

1. Aixinjueluo W, Usui T, Miyai T, Toyono T, Sakisaka T, Yamagami S. Accelerated transepithelial corneal crosslinking for progressive keratoconus: a prospective study of 12 months. Br J Ophthalmol. 2017 Sep;101(9):1244-1249.
2. Al Fayed MF, Alfayez S, Alfayez Y. Transepithelial Versus Epithelium-Off Corneal Collagen Crosslinking for Progressive Keratoconus: A Prospective Randomized Controlled Trial. Cornea. 2015 Oct;34 Suppl 10:S53-6.
3. American Academy of Ophthalmology (AAO). Preferred Practice Pattern. Corneal Ectasia. 2013 Accessed Jul 6, 2018. Available at URL address: <https://www.aao.org/about-preferred-practice-patterns>
4. American Academy of Ophthalmology (AAO). Cornea/external disease summary benchmarks – 2017. Nov. 2017. Accessed Jun 28, 2018. Available at URL address: <https://www.aao.org/about-preferred-practice-patterns>
5. American Academy of Ophthalmology (AAO). Preferred Practice Pattern. Refractive Errors & Refractive Surgery. September 2007; Updated July 2017. Accessed Jun 21, 2018. Available at URL address: <https://www.aao.org/guidelines-browse>
6. American Academy of Ophthalmology (AAO). Corneal inlays. Aug 28, 2015. Accessed Jun 26, 2018. Availabel at URL address: [http://eyewiki.aao.org/Corneal\\_inlays](http://eyewiki.aao.org/Corneal_inlays)
7. American Optometric Association (AOA). Center for Healthy Vision. Astigmatism. ©2017. American Optometric Association. Accessed Jun 26, 2018. Available at URL address: <http://www.aoa.org/Astigmatism.xml>
8. Beer SMC, Santos R, Nakano EM, Hirai F, Nitschke EJ, Francesconi C, Campos M. One-Year Clinical Outcomes of a Corneal Inlay for Presbyopia. Cornea. 2017 Jul;36(7):816-820.
9. Boxer Wachler BS, Christis JP, Chandra NS, Chou B, Korn T, Nepomuceno R. Intacs for keratoconus. Ophthalmology. 2003 May;110(5):1031-1040.

10. Boyd, K. PEARL. A promising new treatment for presbyopia. Nov 21, 2016. Accessed Jul 6, 2018. Available at URL address: <https://www.aao.org/eye-health/news/pearl-promising-new-treatment-presbyopia>
11. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T, Denaro R. Age-Related Long-Term Functional Results after Riboflavin UV A Corneal Crosslinking. *J Ophthalmol*. 2011;2011:608041. Epub 2011 Aug 4.
12. Chan TCY, Ng ALK, Chan KKW, Cheng GPM, Wong IYH, Jhanji V. Combined application of prophylactic corneal crosslinking and laser in-situ keratomileusis - a review of literature. *Acta Ophthalmol*. 2017 Nov;95(7):660-664.
13. Chang DH, Davis EA. Phakic intraocular lenses. *Curr Opin Ophthalmol*. 2006 Feb;17(1):99-104.
14. Charm J, Cho P. High myopia-partial reduction ortho-k: a 2-year randomized study. *Optom Vis Sci*. 2013 Jun;90(6):530-9. doi: 10.1097/OPX.0b013e318293657d.
15. Cho P, Cheung SW. Retardation of myopia in Orthokeratology (ROMIO) study: a 2-year randomized clinical trial. *Invest Ophthalmol Vis Sci*. 2012 Oct 11;53(11):7077-85. doi: 10.1167/iovs.12-10565.
16. Choi JA, Kim MS. Progression of keratoconus by longitudinal assessment with corneal topography. *Invest Ophthalmol Vis Sci*. 2012 Feb 23;53(2):927-35. doi: 10.1167/iovs.11-8118.
17. Chunyu T, Xiujun P, Zhengjun F, Xia Z, Feihu Z2. Corneal collagen crosslinking in keratoconus: a systematic review and meta-analysis. *Sci Rep*. 2014 Jul 10;4:5652.
18. Colin J. European clinical evaluation: Use of Intacs for the treatment of keratoconus. *J Cataract Refract Surg*. 2006 May;32(5):747-55.
19. Colin J, Cochener B, Savary G, Malet F, Holmes-Higgin D. INTACS inserts for treating keratoconus: one-year results. *Ophthalmology*. 2001 Aug;108(8):1409-14.
20. Colin J, Malet FJ. Intacs for the correction of keratoconus: two-year follow-up. *J Cataract Refract Surg*. 2007 Jan;33(1):69-74.
21. Craig JA, Mahon J, Yellowlees A, Barata T, Glanville J, Arber M, et al. Epithelium-off photochemical corneal collagen crosslinkage using riboflavin and ultraviolet a for keratoconus and keratectasia: a systematic review and meta-analysis. *Ocul Surf*. 2014 Jul;12(3):202-14.
22. Dexl AK, Jell G, Strohmaier C, Seyeddain O, Riha W, Rückl T, et al. Long-term outcomes after monocular corneal inlay implantation for the surgical compensation of presbyopia. *J Cataract Refract Surg*. 2015 Mar;41(3):566-75.
23. Dick HB, Gross S, Tehrani M, Eisenmann D, Pfeiffer N. Refractive lens exchange with an array multifocal intraocular lens. *J Refract Surg*. 2002 Sep-Oct;18(5):509-18.
24. Ertan A, Kamburoğlu G, Bahadır M. Intacs insertion with the femtosecond laser for the management of keratoconus: one-year results. *J Cataract Refract Surg*. 2006 Dec;32(12):2039-42.
25. Galvis V, Tello A, Ortiz AI, Escaf LC. Patient selection for corneal collagen crosslinking: an updated review. *Clin Ophthalmol*. 2017 Apr 7;11:657-668.
26. Greenstein SA, Shah VP, Fry KL, Hersh PS. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011 Apr;37(4):691-700. doi: 10.1016/j.jcrs.2010.10.052.



27. Greenstein SA1, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg.* 2011 Jul;37(7):1282-90. doi: 10.1016/j.jcrs.2011.01.029.
28. HAYES Directory Report™. Conventional Corneal Crosslinking for Treatment of Keratoconus. Lansdale, PA: HAYES, Inc., ©2016 Winifred S. Hayes, Inc. November 2016.
29. HAYES Directory Report™. Comparative effectiveness review. Corneal Crosslinking for treatment of keratoconus. PA: HAYES, Inc., ©2018 Winifred S. Hayes, Inc. Feb 2018.
30. Hayes search and summary. Raindrop Near Vision Inlay (ReVision Optics Inc.) for presbyopia. Jul 13, 2017. Accessed Jul 9, 2018. Available at URL address: <https://www.hayesinc.com/subscribers/subscriberArticlePDF.pdf?articleId=68686>
31. Hersh P. U.S. Multicenter Clinical Trial of Corneal Collagen crosslinking for Treatment of Corneal Ectasia after Refractive Surgery. *Ophthalmology.* 2017 October; 124(10): 1475-1484.
32. Hersh PS, Stulting RD, Muller D, Durrie DS, Rajpal RK; United States Crosslinking Study Group. United States Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment. *Ophthalmology.* 2017 Sep;124(9):1259-1270.
33. Hersh PS, Greenstein SA, Fry KL Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. *J Cataract Refract Surg.* 2011 Jan;37(1):149-60.
34. Jacobi PC, Dietlein TS, Lüke C, Jacobi FK. Multifocal intraocular lens implantation in prepresbyopic patients with unilateral cataract. *Ophthalmology.* 2002 Apr;109(4):680-6.
35. Jalali S, Aus der Au W, Shaarawy T. Acufocus Corneal Inlay to Correct Presbyopia Using Femto-LASIK. One Year Results of a Prospective Cohort Study. *Klin Monbl Augenheilkd.* 2016 Apr;233(4):360-4.
36. Kanellopoulos AJ, Pe LH, Perry HD, Donnenfeld ED. Modified intracorneal ring segment implantations (INTACS) for the management of moderate to advanced keratoconus: efficacy and complications. *Cornea.* 2006 Jan;25(1):29-33.
37. Kanellopoulos AJ. Long term results of a prospective randomized bilateral eye comparison trial of higher fluence, shorter duration ultraviolet A radiation, and riboflavin collagen cross linking for progressive keratoconus. *Clin Ophthalmol.* 2012;6:97-101. doi: 10.2147/OPHTH.S27170. Epub 2012 Jan 11.
38. Kang P. Optical and pharmacological strategies of myopia control. *Clin Exp Optom.* 2018 May;101(3):321-332.
39. Khattak A, Nakhli FR, Cheema HR. Corneal collagen crosslinking for progressive keratoconus in Saudi Arabia: One-year controlled clinical trial analysis. *Saudi J Ophthalmol.* 2015 Oct-Dec;29(4):249-54.
40. Kobashi H, Rong SS Corneal Collagen Crosslinking for Keratoconus: Systematic Review. *Biomed Res Int.* 2017;2017:8145651.
41. Kuryan J, Cheema A, Chuck RS. Laser-assisted subepithelial keratectomy (LASEK) versus laser-assisted in-situ keratomileusis (LASIK) for correcting myopia. *Cochrane Database Syst Rev.* 2017 Feb 15;2:CD011080.
42. Kymionis GD, Grentzelos MA, Kounis GA, Portaliou DM, Detorakis ET, Magarakis M, et al. Intraocular pressure measurements after corneal collagen crosslinking with riboflavin and ultraviolet A in eyes with keratoconus. *J Cataract Refract Surg.* 2010 Oct;36(10):1724-7.

43. Kymionis GD, Siganos CS, Tsiklis NS, Anastasakis A, Yoo SH, Pallikaris AI, et al. Long-term follow-up of Intacs in keratoconus. *Am J Ophthalmol*. 2007 Feb;143(2):236-244.
44. Lang SJ, Messmer EM, Geerling G, Mackert MJ, Brunner T, Dollak S, et al. Prospective, randomized, double-blind trial to investigate the efficacy and safety of corneal crosslinking to halt the progression of keratoconus. *BMC Ophthalmol*. 2015 Jul 21;15:78.
45. Lamy R, Netto CF, Reis RG, Procopio B, Porco TC, Stewart JM, et al. Effects of corneal crosslinking on contrast sensitivity, visual acuity, and corneal topography in patients with keratoconus. *Cornea*. 2013 May;32(5):591-6.
46. Leyland M, Pringle E. Multifocal versus monofocal intraocular lenses after cataract extraction. *Cochrane Database Syst Rev*. 2006 Oct 18;(4):CD003169.
47. Li G, Fan ZJ, Peng XJ. Corneal collagen crosslinking for corneal ectasia of post-LASIK: one-year results. *Int J Ophthalmol*. 2012;5(2):190-5.
48. Li J, Ji P, Lin X. Efficacy of corneal collagen crosslinking for treatment of keratoconus: a meta-analysis of randomized controlled trials. *PLoS One*. 2015 May 18;10(5):e0127079.
49. Li SM, Zhan S, Li SY, Peng XX, Hu J, Law HA, Wang NL. Laser-assisted subepithelial keratectomy (LASEK) versus photorefractive keratectomy (PRK) for correction of myopia. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD009799. DOI: 10.1002/14651858.CD009799.pub2.
50. Linn SH, Skanchy DF, Quist TS, Desautels JD, Moshirfar M. Stereoacuity after small aperture corneal inlay implantation. *Clin Ophthalmol*. 2017 Jan 24;11:233-235.
51. McDonald MB, Durrie D, Asbell P, Maloney R, Nichamin L. Treatment of presbyopia with conductive keratoplasty: six-month results of the 1-year United States FDA clinical trial. *Cornea*. 2004 Oct;23(7):661-8.
52. Moarefi MA, Bafna S, Wiley W. A Review of Presbyopia Treatment with Corneal Inlays. *Ophthalmol Ther*. 2017 Jun;6(1):55-65.
53. Moshirfar M, Desautels JD, Wallace RT, Koen N, Hoopes PC. Comparison of FDA safety and efficacy data for KAMRA and Raindrop corneal inlays. *Int J Ophthalmol*. 2017 Sep 18;10(9):1446-1451. doi: 10.18240/ijo.2017.09.18. eCollection 2017.
54. National Institute for Health and Clinical Excellence (NICE). Corneal implants for keratoconus: Guidance IPG227. July 2007a. Accessed June 26, 2018. Available at URL address: <https://www.nice.org.uk/guidance/IPG227>
55. National Institute for Health and Clinical Excellence (NICE). Corneal implants for the correction of refractive error: Guidance IPG225. July 2007b. Accessed June 26, 2018. Available at URL address: <https://www.nice.org.uk/guidance/ipg225>
56. National Institute for Health and Clinical Excellence (NICE). Corneal inlay implantation for correction of presbyopia: Guidance IPG455. Apr 2013. Accessed June 26, 2018. Available at URL address: <https://www.nice.org.uk/guidance/ipg455>
57. National Institute for Health and Clinical Excellence (NICE). Intraocular lens insertion for correction of refractive error, with preservation of the natural lens Guidance IPG289. Feb 2009. Accessed Jun 26, 2018. Available at URL address: <https://www.nice.org.uk/search?q=Phakic+Intraocular+Lens+>

58. National Institute for Health and Clinical Excellence (NICE). Photochemical corneal collagen crosslinkage using riboflavin and ultraviolet A for keratoconus and keratectasia IPG466. September 2013. Accessed June 26, 2018. Available at URL address: <https://www.nice.org.uk/guidance/IPG466>
59. National Institute for Health and Clinical Excellence (NICE). Photorefractive (laser) surgery for the correction of refractive error: Guidance IPG164. March 2006. Accessed Jun 26, 2018. Available at URL address: <https://www.nice.org.uk/guidance/ipg164>
60. National Institute for Health and Clinical Excellence (NICE). Scleral expansion surgery for presbyopia: guidance IPG70. July, 2004. Accessed Jun 26, 2018. Available at URL address: <https://www.nice.org.uk/guidance/ipg70>
61. No authors listed. Excimer laser photorefractive keratectomy (PRK) for myopia and astigmatism. American Academy of Ophthalmology. Ophthalmology. 1999 Feb;106(2):422-37.
62. No authors listed. Radial keratotomy for myopia. American Academy of Ophthalmology. Ophthalmology. 1993 Jul;100(7):1103-15.
63. No authors listed. Keratophakia and keratomileusis: safety and effectiveness. American Academy of Ophthalmology. Ophthalmology. 1992 Aug;99(8):1332-41.
64. Presbia. The Presbia Flexivue Microlens™. 2018. Accessed Jul 6, 2018. Available at URL address: <https://presbia.com/the-microlens-solution/>
65. Raiskup F, Theuring A, Pillunat LE, Spoerl E. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. J Cataract Refract Surg 2015;41(1):41–46.
66. Rapuano CJ, Sugar A, Koch DD, Agapitos PJ, Culbertson WW, de Luise VP, et al. Intrastromal corneal ring segments for low myopia: a report by the American Academy of Ophthalmology. Ophthalmology. 2001 Oct;108(10):1922-8.
67. Rush SW, Rush RB. Epithelium-off versus transepithelial corneal collagen crosslinking for progressive corneal ectasia: a randomised and controlled trial. Br J Ophthalmol. 2017 Apr;101(4):503-508.
68. Sadoughi MM, Einollahi B, Baradaran-Rafii A, Roshandel D, Hasani H, Nazeri M. Accelerated versus conventional corneal collagen crosslinking in patients with keratoconus: an inpatient comparative study. Int Ophthalmol. 2018 Feb;38(1):67-74.
69. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutiérrez-Ortega R, Sugimoto K. Long-term Efficacy of Orthokeratology Contact Lens Wear in Controlling the Progression of Childhood Myopia. Curr Eye Res. 2017 May;42(5):713-720.
70. Seyeddain O, Riha W, Hohensinn M, Nix G, Dexl AK, Grabner G. Refractive surgical correction of presbyopia with the AcuFocus small aperture corneal inlay: two-year follow-up. J Refract Surg. 2010 Oct;26(10):707-15.
71. Seyedian MA, Aliakbari S, Miraftab M, Hashemi H, Asgari S, Khabazkhoob M. Corneal Collagen Crosslinking in the Treatment of Progressive Keratoconus: A Randomized Controlled Contralateral Eye Study. Middle East Afr J Ophthalmol. 2015 Jul-Sep;22(3):340-5. doi: 10.4103/0974-9233.159755.
72. Shortt AJ, Allan BD. Photorefractive keratectomy (PRK) versus laser-assisted in-situ keratomileusis (LASIK) for myopia. Cochrane Database Syst Rev. 2006 Apr 19;(2):CD005135.
73. Si JK, Tang K, Bi HS, Guo DD, Guo JG, Wang XR. Orthokeratology for myopia control: a meta-analysis. Optom Vis Sci. 2015 Mar;92(3):252-7.

74. Siganos CS, Kymionis GD, Kartakis N, Theodorakis MA, Astyrakakis N, Pallikaris IG. Management of keratoconus with Intacs. *Am J Ophthalmol*. 2003 Jan;135(1):64-70.
75. Soeters N, Wisse RP, Godefrooij DA, Imhof SM, Tahzib NG. Transepithelial versus epithelium-off corneal crosslinking for the treatment of progressive keratoconus: a randomized controlled trial. *Am J Ophthalmol*. 2015 May;159(5):821-8.e3.
76. Stahl JE. Conductive keratoplasty for presbyopia: 3-year results. *J Refract Surg*. 2007 Nov;23(9):905-10.
77. Sugar A, Rapuano CJ, Culbertson WW, Huang D, Varley GA, Agapitos PJ, et al. Laser in situ keratomileusis for myopia and astigmatism: safety and efficacy: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2002 Jan;109(1):175-87.
78. Sun Y, Xu F, Zhang T, Liu M, Wang D, Chen Y, Liu Q. Orthokeratology to control myopia progression: a meta-analysis. *PLoS One*. 2015 Apr 9;10(4):e0124535.
79. Sykakis E, Karim R, Evans JR, Bunce C, Amissah-Arthur KN, Patwary S, et al. Corneal collagen crosslinking for treating keratoconus. *Cochrane Database Syst Rev*. 2015 Mar 24;3:CD010621. doi: 10.1002/14651858.CD010621.pub2.
80. Torquetti L, Berbel RF, Ferrara P. Long-term follow-up of intrastromal corneal ring segments in keratoconus. *J Cataract Refract Surg*. 2009 Oct;35(10):1768-73.
81. Ulusoy DM, Göktaş E, Duru N, Özköse A, Ataş M, Yuvacı İ, et al. Accelerated corneal crosslinking for treatment of progressive keratoconus in pediatric patients. *Eur J Ophthalmol*. 2017 May 11;27(3):319-325. doi: 10.5301/ejo.5000848. Epub 2016 Jul 20.
82. U.S. Food and Drug Administration (FDA). 510(k) summary. Boston X0<sub>2</sub> (hexafocon B) Rigid Gas Permeable Contact Lenses for Daily Wear. Aug 15, 2007. Accessed Jul 9, 2018. Available at URL address:  
<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ContactLenses/ucm062319.htm#orthok>
83. U.S. Food and Drug Administration (FDA). Contact lenses. Last updated Jan 2018. Accessed Jul 9, 2018. Available at URL address:  
<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/ContactLenses/ucm062319.htm#orthok>
84. U.S. Food and Drug Administration (FDA). FDA-approved lasers for LASIK. Last updated: March 12, 2018. Accessed October Jun 26, 2018. Available at URL address:  
<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/ucm192109.htm>
85. U.S. Food and Drug Administration (FDA). Guidance for Premarket Submissions of Orthokeratology Rigid Gas Permeable Contact Lenses - Guidance for Industry. Last updated Mar 2018. Accessed Jul 9, 2018. Available at URL address:  
<https://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm073739.htm>
86. U.S. Food and Drug Administration (FDA). List of FDA-approved lasers for LASIK. Updated Mar 12, 2018. Accessed Jul 10, 2018. Available at URL address:  
<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/ucm192109.htm>
87. U.S. Food and Drug Administration (FDA). New Drug Application (NDA) Approval. NDA 203324/Original 2: Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%, Photrexa

- (riboflavin 5'phosphate ophthalmic solution) 0.146%, with the KXL System. July 2016. Accessed Jun 26, 2018. Available at URL address:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2016/203324Orig2s000ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/203324Orig2s000ltr.pdf)
88. U.S. Food and Drug Administration (FDA). New Drug Application (NDA) Label. NDA 203324/Original 2: Photrex Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146%, Photrex (riboflavin 5'phosphate ophthalmic solution) 0.146%, with the KXL System. July 2016. Accessed Jun 26, 2018. Available at URL address:  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/203324s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203324s000lbl.pdf)
  89. U.S. Food and Drug Administration (FDA). New Humanitarian Device Approval. INTACS® Prescription Inserts for Keratoconus - H040002. Updated September 21, 2004. Accessed Jun 26, 2018. Available at URL address: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf4/H040002A.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf4/H040002A.pdf)
  90. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED). KAMRA® inlay - P120023. April 2015. Accessed Jun 26, 2018. Available at URL address:  
[http://www.accessdata.fda.gov/cdrh\\_docs/pdf12/P120023b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120023b.pdf)
  91. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data. KeraVision Intacs™. P980031. Aug 30, 1999. Accessed Jun 26, 2018. Available at URL address:  
[https://www.accessdata.fda.gov/cdrh\\_docs/pdf/P980031B.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf/P980031B.pdf)
  92. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data. Raindrop® Near Vision Inlay - P150034. June 2016. Accessed Jun 26, 2018. Available at URL address:  
[https://www.accessdata.fda.gov/cdrh\\_docs/pdf15/P150034b.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150034b.pdf)
  93. U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data. ViewPoint™ CK System. P010018. Apr 11, 2002. Accessed Jun 26, 2018. Available at URL address:  
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P010018>
  94. Van Meter WS, Musch DC, Jacobs DS, Kaufman SC, Reinhart WJ, Udell IJ; American Academy of Ophthalmology. Safety of overnight orthokeratology for myopia: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2008 Dec;115(12):2301-2313.e1.
  95. Varley GA, Huang D, Rapuano CJ, Schallhorn S, Boxer Wachler BS, Sugar A; Ophthalmic Technology Assessment Committee Refractive Surgery Panel, American Academy of Ophthalmology. LASIK for hyperopia, hyperopic astigmatism, and mixed astigmatism: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2004 Aug;111(8):1604-17.
  96. Verdoorn C. Comparison of a hydrogel corneal inlay and monovision laser in situ keratomileusis in presbyopic patients: focus on visual performance and optical quality. *Clin Ophthalmol*. 2017 Sep 20;11:1727-1734. doi: 10.2147/OPTH.S142075. eCollection 2017.
  97. Viswanathan D, Males J. Prospective longitudinal study of corneal collagen crosslinking in progressive keratoconus. *Clin Exp Ophthalmol*. 2013 Aug;41(6):531-6.
  98. Vukich JA, Durrie DS, Pepose JS, Thompson V, van de Pol C, Lin L. Evaluation of the small-aperture intracorneal inlay: Three-year results from the cohort of the U.S. Food and Drug Administration clinical trial. *J Cataract Refract Surg*. 2018 May;44(5):541-556.
  99. Whang WJ, Yoo YS, Joo CK, Yoon G. Changes in Keratometric Values and Corneal High Order Aberrations After Hydrogel Inlay Implantation. *Am J Ophthalmol*. 2017 Jan;173:98-105.
  100. Wilkinson PS, Davis EA, Hardten DR. LASIK. In: Yanoff & Duker: *Ophthalmology*, 3rd ed. Maryland Heights, MO: Mosby Inc., An Imprint of Elsevier, Copyright © 2008. pp 155-156.

101. Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen crosslinking in progressive keratoconus: three-year results. *Ophthalmology*. 2014 Apr;121(4):812-21.
102. Wittig-Silva C, Whiting M, Lamoureux E, Lindsay RG, Sullivan LJ, Snibson GR. A randomized controlled trial of corneal collagen crosslinking in progressive keratoconus: preliminary results. *J Refract Surg*. 2008 Sep;24(7):S720-5.
103. Ye P, Xu W, Tang X, Yao K, Li Z, Xu H, et al. Conductive keratoplasty for symptomatic presbyopia following monofocal intraocular lens implantation. *Clin Experiment Ophthalmol*. 2011 Jul;39(5):404-11.
104. Yilmaz OF, Alagöz N, Pekel G, Azman E, Aksoy EF, Cakır H, et al. Intracorneal inlay to correct presbyopia: Long-term results. *J Cataract Refract Surg*. 2011 Jul;37(7):1275-81.
105. Yoo A, Kim JY, Kim MJ, Tchah H. Hydrogel Inlay for Presbyopia: Objective and Subjective Visual Outcomes. *J Refract Surg*. 2015 Jul;31(7):454-60.
106. Zhao LQ, Zhu H, Li LM. Laser-Assisted Subepithelial Keratectomy versus Laser In Situ Keratomileusis in Myopia: A Systematic Review and Meta-Analysis. *ISRN Ophthalmol*. 2014 Jun 12;2014:672146. doi: 10.1155/2014/672146. eCollection 2014.
107. Zhu W, Han Y, Cui C, Xu W, Wang X, Dou X, Xu L, Xu Y, Mu G. Corneal Collagen Crosslinking Combined with Phototherapeutic Keratectomy and Photorefractive Keratectomy for Corneal Ectasia after Laser in situ Keratomileusis. *Ophthalmic Res*. 2018;59(3):135-141.

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