Anthem

Clinical UM Guideline

Subject: Corneal Collagen Cross-Linking
Guideline #: CG-SURG-105
Status: Reviewed

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Description

This document addresses corneal collagen cross-linking (CXL, also known as 3-CR or C3R), a photochemical treatment of progressive keratoconus and other corneal thinning processes, such as ectasia after laser in-situ keratomileusis (LASIK).

Note: Please see the following related documents for additional information:

- CG-SURG-72 Endothelial Keratoplasty
- CG-SURG-77 Refractive Surgery

Clinical Indications

Medically Necessary:

Corneal collagen cross-linking (CXL) is considered **medically necessary** as a treatment for progressive keratoconus when all of the following conditions are met:

A. Diagnosis of keratoconus based on keratometry and corneal mapping;**and**
B. Any of the following changes have occurred within 24 months:
    1. increase of 1.00 diopters (D) or more in the steepest keratometry measurement;**or**
    2. increase of 1.00 D or more in manifest cylinder;**or**
    3. increase of 0.50 D or more in manifest refraction spherical equivalent (MRSE);**and**
C. Age 14 years or older;**and**
D. Corrected distance visual acuity (CDVA) worse than 20/20 with properly fitted spectacles or contact lenses;**and**
E. Corneal thickness 300 microns or more; **and**
F. No history of corneal or systemic disease that would interfere with healing after the procedure such as chemical injury or delayed epithelial healing in the past.

Corneal collagen cross-linking (CXL) is considered **medically necessary** as a treatment for corneal ectasia resulting from refractive surgery (e.g. LASIK) when all of the following conditions are met:

A. Age 14 years of age or older;**and**
B. Axial topography pattern consistent with corneal ectasia;**and**
C. Corrected distance visual acuity (CDVA) worse than 20/20;**and**
D. Corneal thickness of at least 300 microns at the thinnest area;**and**
E. No history of corneal or systemic disease that would interfere with healing after the procedure such as chemical injury or delayed epithelial healing in the past.

Not Medically Necessary:

Corneal collagen cross-linking (CXL) is considered **not medically necessary** when the above criteria have not been met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
0402T	Collagen cross-linking of cornea including removal of the corneal epithelium, when performed, and intraoperative pachymetry, when performed
HCPCS	
J2787	Riboflavin 5'-phosphate, ophthalmic solution, up to 3 mL [Photrexa, Photrexa Viscous]
ICD-10 Diagnosis	
H18.601-H18.629	Keratoconus
H18.711-H18.719	Corneal ectasia

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed.

Discussion/General Information

The incidence of keratoconus has been estimated as approximately 1 in 2000 individuals. However, this estimate is drawn from a study that was conducted without the use of corneal topography and new studies suggest a prevalence as high as 1 in 375 individuals in certain populations (Asimellis, 2021). This progressive bilateral eye dystrophy is more prevalent in teens and young adults and is characterized by central steepening and stromal thinning of the cornea that impair visual acuity.

Initial treatment often consists of hard contact lenses. A penetrating keratoplasty (i.e., corneal graft) is the next line of treatment for those individuals who develop intolerance to contact lenses. While visual acuity is typically improved with a keratoplasty, there is an associated risk of perioperative complications, long-term topical steroid use is required and endothelial cell loss occurs over time, which is a particular concern in younger individuals.

As an alternative, a variety of keratorefractive procedures have been attempted. Subtractive techniques include LASIK, but in general, results of this technique have been poor. Implantation of intrastromal corneal ring segments represents an additive technique where the implants are intended to reinforce the cornea, prevent further deterioration and potentially obviate the need for a penetrating keratoplasty.

Corneal CXL is another potential alternative to immediate keratoplasty. This procedure is performed in the outpatient setting using topical anesthesia with the photosensitizer riboflavin (vitamin B2) and ultraviolet-A (UVA) irradiation. It involves removing approximately 8 mm of the central corneal epithelium to allow better diffusion of the photosensitizer into the stroma. Following de-epithelialization, a solution with riboflavin is applied to the cornea until the stroma is completely penetrated. The cornea is then irradiated for 30 minutes with 370 nm UVA. The interaction of riboflavin and UVA causes the formation of covalent bonds between collagen molecules. Preclinical studies demonstrated increased corneal rigidity and stability following CXL. CXL could potentially slow the progression of keratoconus.

Corneal CXL is also a potential treatment for post-LASIK ectasia. Ectasia also known as iatrogenic keratoconus or secondary keratoconus is a serious long-term complication of LASIK surgery. Reported treatments for the management of post-LASIK ectasia include hard contact lenses, intraocular pressure-lowering drugs, and intracorneal ring segments. Frequently, a penetrating keratoplasty is required.

Keratoconus

Several systematic reviews and meta-analyses of the published literature on corneal CXL for treating keratoconus have been published (Kobashi. 2017; Li, 2016; Meiri, 2016; Sarma, 2023; Sykakis, 2015).

For example, Kobashi and Rong (2017) conducted a review of randomized controlled trials (RCTs) evaluating corneal CXL for progressive keratoconus that had at least 1 year of follow-up. Studies on individuals with a history of corneal surgery and on combination treatment were excluded. Five trials with a total of 289 eyes met the review's inclusion criteria. The number of treated eyes in the RCTs ranged from 15 to 29. Three of the studies used the contralateral eye in the same individual as the control and the other two studies used different individuals matched for age and progression of keratoconus. A meta-analysis of data from four of the studies on best corrected visual acuity (BCVA) found a statistically significant increase in the corneal CXL group compared with the control group at 12 months (weighted mean difference [WMD], -0.09; 95% confidence interval [CI], -0.14 to -0.04; p<0.001). The authors noted that the difference between groups was not likely to be clinically significant because it was less than one line on an eye chart and is within the range of typical test-retest variability. A meta-analysis of data from three studies on change in thinnest corneal thickness did not differ significantly between groups at 12 months (WMD, 1.46; 95% CI, -2.77 to 5.68). Other outcomes were not pooled due to high heterogeneity. Maximum keratometry (Kmax), the steepest area of corneal distortion, was reported in all studies. In three studies, the Kmax was significantly reduced in the corneal CXL group compared with control and in the other two studies, the difference between groups was not statistically significant at the p<0.05 level. The authors concluded that CXL may be able to halt the progression of keratoconus for 1 year, but the evidence base is limited by the paucity of RCTs and significant heterogeneity among studies.

A 2015 Cochrane review included three randomized controlled trials (RCTs) that analyzed 219 eyes; 100 served as controls. The overall quality of the RCTs was deemed poor by the authors; all of the studies were hampered by a high risk for performance bias, detection bias and attrition bias. Outcome measures reported across the studies differed to the extent that pooling of data was not possible and no data was reported on quality of life outcomes. The authors concluded that, "The evidence for the use of CXL in the management of keratoconus is limited due to the lack of properly conducted RCTs."

RCT data submitted as part of Food and Drug Administration (FDA) approval on individuals with progressive keratoconus were published initially in 2011 and then in 2017 by Hersh and colleagues. The eligibility criteria for the RCT included age 14 or older, topography patterns consistent with keratoconus, CDVA worse than 20/20, and no previous corneal surgery. A total of 205 eyes were treated with CXL (n=102) or sham treatment with riboflavin plus dextran solution alone (n=103). Participants in the sham control group were able to cross over to the treatment group after 3 months. At 12 months, only 2 eyes (2%) remained in the control group; therefore the analysis used a last observation carried forward (LOCF) method. The number of actual control eyes was 96 (93%) at 3 months and 39 (38%) at 6 months.

The primary outcome in the Hersh study was mean change in Kmax from baseline to month 12. Using the LOCF method, Kmax decreased a mean of 1.6 D in the CXL group and increased a mean of 1.0 D in the control group. The difference between groups was statistically significant, p<0.0001. The between-group difference exceeded the 1.0 D difference that was pre-specified as being clinically meaningful. Using the LOCF method, the mean difference in CDVA was a 5.7 letter improvement in the treatment group and a 2.2 letter improvement in the control group. The between-group difference in CDVA was statistically significant, p<0.001.

Several adverse events occurred in at least 10% of individuals in the CXL group. The most frequent of these were corneal opacity (57%), punctate keratitis (25%), corneal striae (24%) and epithelial defect after 1 week (23%). In the control group, the only adverse event affecting more than 10% of participants was corneal striae (12%). A limitation of the study is that it had a cross-over design at 3 months and thus comparative data beyond 3 months are unreliable. There was significant attrition and thus LOCF imputation was used. LOCF requires an assumption that no improvement or worsening occurred after the last recorded measurement, which may or may not accurately reflect the true values.

Several smaller RCTs have also been published. A randomized sham and fellow-eye controlled prospective trial by Greenstein and colleagues (2011) involving 82 eyes with CDVA worse than 20/20, found that the cornea thins after CXL but then recovers toward baseline thickness by 6 months.

In 2014, Wittig-Silva and colleagues reported results from an open-label trial evaluating the efficacy and safety of CXL using 0.1% riboflavin and UVA in the management of progressive keratoconus. A total of 100 eyes were randomized to either a treatment (n=50) or control (n=50) group. (The authors only reported on number of eyes, not number of participants). The control group received usual care and was offered "compassionate CXL treatment" no earlier than 6 months after randomization. A total of 12 eyes received compassionate CXL and were excluded from further analysis. The final analysis at 36 months included 41 treatment eyes and 27 control eyes, 68% of the randomized study population. The primary outcome of Kmax increased by a mean of 1.20 ± 0.28 diopters, 1.70 ± 0.36 diopters, and 1.75 ± 0.38 diopters at 12, 24, and 36 months, respectively (all p<0.001) in the control group. In treated eyes, Kmax decreased by -0.72 ± 0.15 diopters, -0.96 ± 0.16 diopters, and -1.03 ± 0.19 diopters at 12, 24, and 36 months, respectively (all between-group comparisons p<0.001). The mean change in uncorrected visual acuity (UCVA) showed deterioration in the control group (+0.10 ± 0.04 logMAR; p=0.034) at 36 months, whereas in the treatment group, both UCVA (-0.15 ± 0.06 logMAR; p=0.009) and best spectacle-corrected visual acuity (BSCVA) (-0.09 ± 0.03 logMAR; p=0.006) improved at 36 months. A total of 2

eyes had minor complications that did not affect the final visual acuity. The study showed a positive effect of CXL compared with usual care but was limited by the relatively small sample size, substantial dropout rate at 36 months and lack of blinding or sham-control.

An RCT by Meyer and colleagues (2021) included 38 individuals aged 14 or older with bilateral progressive keratoconus, and randomly assigned one eye to undergo CXL and the other eye to a no treatment control group. Participants were offered "compassionate CXL" if the progression of keratoconus was observed in the control eye after a minimum of 6 months. Of the 38 participants, 3 dropped out before 6 months and 10 individuals had the control eye treated after 6 months. A total of 21 of the original participants (55%) returned for the 5-year visit. At 5 years, there was a 3.16 D difference in the mean change of Kmax between the treatment and control groups ($p<0.001$). This study had a high drop-out rate over 5 years.

Larkin and colleagues (2021) published an observer-masked RCT conducted in 60 individuals age 10-16 years of age with keratoconus. Participants were randomized to CXL (n=30) or standard care alone (n=30). At 18 months, individuals in the treatment group had less progression of keratoconus compared with the standard care group. The primary study outcome, mean corneal power in the steepest meridian (K2), was a mean of 49.7 D (SD, 3.8 D) in the treatment group versus 53.4 D (SD, 5.8 D) in the standard care group, for an adjusted mean difference of -3.0 D (95% CI, -4.93 to -1.08 D, $p=0.002$). Several secondary outcomes also significantly favored the treatment group, including uncorrected visual acuity and best-corrected visual acuity.

Additionally, a number of uncontrolled studies have been published on the use of CXL for keratoconus. Studies were conducted with adult populations (Asri 2011; Chatzis, 2012; Coskunseven, 2009; De Bernardo, 2014; Derakhshan, 2011; Grewal 2009; Hashemi, 2013; Raiskup-Wolf, 2015; Vinciguerra, 2012) and pediatric populations (Caporossi, 2012; Caporossi, 2010; Knutsson, 2018; Mazzotta, 2018).

Several of the case series provided long-term follow-up data. Raiskup-Wolf and colleagues (2015) published 10-year follow-up data from a retrospective case series that enrolled 24 individuals (34 eyes) with progressive keratoconus who were treated with corneal CXL. Kmax was lower after 10 years than at baseline ($p<0.001$). Mean CDVA improved by 0.14 logMAR at follow-up, which was significantly better than at baseline. Two individuals had repeat CXL due to symptom progression.

In 2018, Mazzotta and colleagues reported 10-year follow-up of a study of CXL in pediatric subjects age 18 years and younger. The study cohort originally consisted of 152 eyes, but only 62 eyes (40%) in 47 individuals were available for follow-up at 10 years. The mean age at baseline of the evaluable individuals was 14 years (range: 8 to 18 years). Mean CVDA and mean uncorrected distance visual acuity (UVDA) improved at all follow-up visits compared with baseline. The improvement was significantly better than baseline each year through year 10 ($p=0.001$). Kmax improved significantly starting 6 months after treatment ($p=0.0454$) and continuing through the eighth year of follow-up. The 10-year keratoconus progression rate was 26% of participants and 24% of eyes.

Corneal Ectasia

A 2017 RCT by Hersh and colleagues focused on corneal CXL for treating corneal ectasia after laser refractive surgery. The study pooled data on individuals with corneal ectasia from two pivotal trials. In both trials, the eligibility criteria included age 14 or older, topography patterns consistent with corneal ectasia, CDVA worse than 20/20, and no previous corneal surgery other than corneal refractive surgery. A total of 179 eyes were randomized to treatment with CXL (n=91) or sham treatment with riboflavin alone (n=88). Participants in the sham control group were able to cross over to the treatment group after 3 months. At 12 months, only 2 eyes (2%) remained in the control group; therefore the analysis used a LOCF method. The number of actual control eyes was 85 (97%) at 3 months and 32 (36%) at 6 months.

The primary outcome was mean change in Kmax from baseline to month 12. Using the LOCF method, at 12 months Kmax decreased a mean of 1.3 D in the CXL group and increased a mean of 0.8 D in the control group, a statistically significant difference, $p<0.0001$. The between-group difference exceeded the 1.0 D difference that was pre-specified as being clinically meaningful. Using the LOCF method, the difference in CDVA was a 5 letter improvement in the treatment group and a 0.3 letter decrease in the control group. The between-group difference in CDVA was statistically significant, $p<0.001$. There were a number of ocular adverse events that occurred in at least 5% of individuals in the CXL group. The most frequent of these were corneal opacity (68%), epithelial defect after 1 week (26%) and eye pain (26%), punctate keratitis (20%) and photophobia (19%). A limitation of the study is that it had a cross-over design at 3 months and thus comparative data beyond 3 months are unreliable. There was significant attrition requiring use of LOCF imputation. There is a lack of comparative data on long-term outcomes after corneal CXL for corneal ectasia.

In April 2016, the FDA granted approval for Photrexa® (riboflavin 5'-phosphate ophthalmic solution) 0.146% and Photrexa Viscous® (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) 0.146% to be used along with the KXL® collagen cross-linking system (Avedro Inc.; Waltham, MA) for treatment of progressive keratoconus and corneal ectasia following refractive surgery. According to the Product Information (PI) Label (2016), approval of Avedros' CXL system was based on three open-label Phase III clinical trials conducted in the United States (n=364). Kmax was the primary outcome.

Other Potential Indications

A 2020 Cochrane review (Davis, 2020) evaluated published literature on photoactivated chromophore for collagen cross-linking (PACK-CXL) for bacterial infectious keratitis. The authors identified two RCTs and one quasi-RCT, with a total of 59 participants, comparing PACK-CXL to standard therapy such as medication treatment. All of the studies were conducted outside of the U.S. The authors did not pool study findings because primary outcomes differed in each of the studies. They judged the certainty of the evidence to be very low because of the small sample sizes in individual studies as well as the small number of total participants, and heterogeneity of the study populations and outcomes.

Transepithelial Approach to Corneal CXL

The conventional corneal CXL procedure involves removal of corneal epithelium to facilitate adequate penetration of riboflavin into the corneal stroma. Transepithelial approaches that leave the epithelium intact are proposed to minimize risks of infection and scarring associated with removal of epithelium. Meta-analyses of available literature have been published comparing transepithelial versus epithelium-off corneal collagen cross-linking in individuals with progressive keratoconus (Ng, 2021) and in individuals with corneal ectasia (Nath, 2021).

A Cochrane systematic review (Ng, 2021) included 13 RCTs comparing transepithelial and epithelium-off cross-linking for treatment of progressive keratoconus; 9 of these RCTs were included in the quantitative meta-analysis. The primary outcome of interest was K and the timepoints of interest were 12 and 24 months after treatment. A meta-analysis of 5 RCTs found no statistically significant difference change in Kmax at 12 months (mean difference, 0.99, 95% CI: -0.11 to 2.09). There were not enough studies reporting any other outcome related to K to conduct pooled analyses. The authors also stated that heterogeneity among studies made it inappropriate to conduct pooled analyses for other outcomes such as visual acuity. A pooled analysis of 4 RCTs reporting the adverse outcomes of corneal haze or scarring found significantly more corneal haze or scarring after epithelium-off cross-linking compared with transepithelial cross-linking (RR, 1.07, 95% CI, 1.01 to 1.14).

Nath and colleagues (2021) identified 12 RCTs involving a total of 966 eyes comparing transepithelial and epithelium-off cross-linking for corneal ectasia. The primary outcome for the meta-analysis was change in Kmax (measured in D) as evaluated by topography at 12 months after the procedure. In a pooled analysis of 9 RCTs, Kmax was significantly larger in the epithelium-off group at 12 months than the transepithelial group (mean difference, 0.75, 95% CI, 0.23 to 1.28, p=0.004). Moreover, a meta-analysis of 4 RCTs found that the incidence of disease progression at 12 months was significantly higher after transepithelial cross-linking (7%) than epithelium-off cross-linking (2%), RR, 4.49 (95% CI, 1.24 to 16.25, p=0.22). However, meta-analyses found no significant differences in visual and refractive outcomes after transepithelial versus epithelium-off procedures, including uncorrected distance visual acuity (UDVA) (mean difference, 0.04 logMAR, 95% CI, -0.06 to 0.14, p=0.386), CDVA (mean difference, -0.01 logMAR, 95% CI, -0.06 to 0.09, p=0.732) and spherical equivalent (mean difference, -0.26 D, 95% CI, -0.81 to 0.28, p=0.360). Additionally, a meta-analysis of 5 RCTs found that the incidence of complications was significantly lower after transepithelial cross-linking (2%) than with epithelium-off cross-linking (4%), RR, 0.22 (95% CI, 0.06 to 0.79).

Conclusion

The pivotal trials on corneal CXL for treating keratoconus and corneal ectasia have positive 12-month findings using imputed data. For keratoconus, the smaller open-label Wittig-Silva trial found better outcomes at 3 years in the corneal crosslink group compared with standard care and case series have found a durable impact of corneal CXL on health outcomes in both adults and children at up to 10 years. However, there remains a paucity of long-term comparative data on safety and efficacy for any indication. In addition, there is growing consensus in the ophthalmology practice community that corneal CXL for treating keratoconus and corneal ectasia provides significant benefits over standard care in terms of improving health outcomes. The evidence base to support any other indications for corneal CXL remains limited. Meta-analyses of studies evaluating transepithelial versus epithelium-off corneal CXL did not find that one approach is clearly superior to the other.

Definitions

Astigmatism: The astigmatism is the difference in any two meridians of the cornea and the crystalline lens in the eye. Typically, it is measured the two meridians that are 90 degrees apart from one another. The astigmatism in your glasses neutralizes the astigmatism in the eye. Normally, most of the astigmatism is in the cornea.

Cornea: The outermost layer of the eye; dome shaped and covers the front of the eye.

Corneal stria: also known as Vogt's striae: Lines seen in Descemet's membrane caused by undulations in stromal collagen lamellae. Although present in many normal eyes, they are more numerous and more likely to be vertical in keratoconus eyes. In keratoconus, they are associated with deeper anterior chambers, thinner corneas, worse visual acuity, and more abnormal tomography.

Ectasia: A condition that occurs when the cornea is so thin that pressure within the eye leads to bulging of the cornea.

Keratoconus: Cone-shaped cornea with the apex of the cone being forward; also called conical cornea.

Keratometry (K): Measurement of the corneal radius of curvature.

Last Observation Carried Forward (LOCF): An imputation method used to manage missing data points in longitudinal series. In this method, the last recorded value is assigned to a later measurement when data for that measurement is missing. LOCF requires an assumption that there is no improvement or worsening in the measured value in the intervening period.

Manifest cylinder: A subjective measure of a change in the cylinder (astigmatism). For example, an increase of 1.00 D or more in manifest cylinder indicates that the glasses prescription astigmatism has changed by 1 or more.

Manifest refraction spherical equivalent (MRSE): A subjective measure of a change in the cylinder (astigmatism). It is calculated arithmetically by adding the sphere power and half of the cylinder power. MRSE is used in the calculation of spherical equivalent.

Maximum keratometry (Kmax): Refers to the curvature in the steepest portion of the cornea.

Transepithelial: Through or across an epithelium.

References

Peer Reviewed Publications:

1. Asimellis G, Kaufman EJ. Keratoconus. 2021 Aug 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan.
2. Asri D, Touboul D, Fournié P, et al. Corneal collagen crosslinking in progressive keratoconus: multicenter results from the French National Reference Center for Keratoconus. J Cataract Refract Surg. 2011; 37(12):2137-2143.
3. Bamdad S, Malekhosseini H, Khosravi A. Ultraviolet A/riboflavin collagen cross-linking for treatment of moderate bacterial corneal ulcers. Cornea. 2015; 34(4):402-406.
4. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. Am J Ophthalmol. 2010; 149(4):585-593.
5. Caporossi A. Mazzotta C. Baiocchi S, et al. Riboflavin-UVA-induced corneal collagen cross-linking in pediatric patients. Cornea. 2012; 31(3):227-231.
6. Chatzis N. Hafezi F. Progression of keratoconus and efficacy of pediatric corneal collagen cross-linking in children and adolescents. J Refract Surg. 2012; 28(11):753-758.
7. Chunyu T, Xiujun P, Zhengjun F, et al. Corneal collagen cross-linking in keratoconus: a systematic review and meta-analysis. Sci Rep. 2014; 4:5652.
8. Coskunseven E, Jankov MR, Hafezi F. Contralateral eye study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus. J Refract Surg. 2009; 25(4):371-376.
9. De Bernardo M, Capasso L, Tortori A, et al. Trans epithelial corneal collagen crosslinking for progressive keratoconus: 6 months follow up. Cont Lens Anterior Eye. 2014; 37(6):438-441.
10. Derakhshan A, Shandiz JH, Ahadi M, et al. Short-term outcomes of collagen crosslinking for early keratoconus. J Ophthalmic Vis Res. 2011; 6(3):155-159.
11. 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; 37(4):691-700.
12. Grewal DS, Brar GS, Jain R, et al. Corneal collagen crosslinking using riboflavin and ultraviolet-A light for keratoconus: one-year analysis using Scheimpflug imaging. J Cataract Refract Surg. 2009; 35(3):425-432.
13. Hashemi H, Seyedian MA, Miraftab M, et al. Corneal collagen cross-linking with riboflavin and ultraviolet a irradiation for keratoconus: long-term results. Ophthalmology. 2013; 120(8):1515-1520.
14. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J

Cataract Refract Surg. 2011; 37(1):149-160.
15. Hersh PS, Stulting D, Muller D, et al. United States multicenter clinical trial of corneal collagen crosslinking for keratoconus treatment. Ophthalmology. 2017; 124(9):1259-1270.
16. Hersh PS, Stulting RD, Muller D, et al. U.S. Multicenter clinical trial of corneal collagen crosslinking for treatment of corneal ectasia after refractive surgery. Ophthalmology. 2017; 124(10):1475-1484.
17. Knutsson KA, Paganoni G, Matuska S, et al. Corneal collagen cross-linking in paediatric patients affected by keratoconus. Br J Ophthalmology. 2018; 102(2):248-252.
18. Kobashi H, Rong SS. Corneal collagen cross-linking for keratoconus: systematic review. Biomed Res Int. 2017; 2017:8145651.
19. Larkin DFP, Chowdhury K, Burr JM et al. Effect of corneal cross-linking versus standard care on keratoconus progression in young patients: The KERALINK randomized controlled trial. Ophthalmology. 2021; 128(11):1516-1526.
20. Li J, Ji P, Lin X. Efficacy of corneal collagen cross-linking for treatment of keratoconus: a meta-analysis of randomized controlled trials. PLoS One. 2015; 10(5):e0127079.
21. Mazzotta C, Traversi C, Baiocchi S, et al. Corneal collagen cross-linking with riboflavin and ultraviolet A light for pediatric keratoconus: ten-year results. Cornea. 2018; 37(5):560-566.
22. McAnena L, Doyle F, O'Keefe M. Cross-linking in children with keratoconus: a systematic review and meta-analysis. Acta Ophthalmol. 2017; 95(3):229-239.
23. Meiri Z, Keren S, Rosenblatt A, et al. Efficacy of corneal collagen cross-linking for the treatment of keratoconus: a systematic review and meta-analysis. Cornea. 2016; 35(3):417-428.
24. Meyer JJ, Jordan CA, Patel DV et al. Five-year results of a prospective, randomised, contralateral eye trial of corneal crosslinking for keratoconus. Clin Exp Ophthalmol. 2021; 49(6):542-549.
25. Nath S, Shen C, Koziarz A et al. Transepithelial versus epithelium-off corneal collagen cross-linking for corneal ectasia: A systematic review and meta-analysis. Ophthalmology. 2021; 128(8):1150-1160.
26. 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.
27. Sarma P, Kaur H, Hafezi F et al. Short- and long-term safety and efficacy of corneal collagen cross-linking in progressive keratoconus: A systematic review and meta-analysis of randomized controlled trials. Taiwan J Ophthalmol. 2022;13(2):191-202.
28. Seyedian MA, Aliakbari S, Miraftab M, et al. Corneal collagen cross-linking in the treatment of progressive keratoconus: a randomized controlled contralateral eye study. Middle East Afr J Ophthalmol. 2015; 22(3):340-345.
29. Vinciguerra P, Albe E, Frueh BE, et al. Two-year corneal cross-linking results in patients younger than 18 years with documented progressive keratoconus. Am J Ophthalmol. 2012; 154(3):520-526.
30. Wittig-Silva C, Chan E, Islam FM, et al. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. Ophthalmology. 2014; 121(4):812-821.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Academy of Ophthalmology (AAO). Corneal Ectasia PPP – 2018. For additional information visit the AAO website: https://www.aao.org/preferred-practice-pattern/corneal-ectasia-ppp-2018. Accessed on November 6, 2023.
2. Davis SA, Bovelle R, Han G, Kwagyan J. Corneal collagen cross-linking for bacterial infectious keratitis. Cochrane Database Syst Rev. 2020 Jun17;6(6):CD013001.
3. Highlights of prescribing information. Photrexa Viscous and Photrexa Photrexa [Product Information], Waltham, MA. Avedro Inc. Last updated July 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203324s000lbl.pdf. Accessed on August 29, 2023.
4. Ng SM, Ren M, Lindsley KB et al. Transepithelial versus epithelium-off corneal cross-linking for progressive keratoconus. Cochrane Database Syst Rev. 2021; 23;3(3):CD013512.
5. Sykakis E, Karim R, Evans JR, et al. Corneal collagen cross-linking for treating keratoconus. Cochrane Database Syst Rev. 2015;(3):CD010621.

Websites for Additional Information

1. National Eye Institute (NEI). Facts about the cornea and corneal disease. Available at: https://nei.nih.gov/health/cornealdisease/. Accessed on September 11, 2023.

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Corneal cross-linking (CXL)
KXL System

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Discussion/General Information and References sections.
Reviewed	11/10/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Description, Discussion/General Information and References sections updated. Updated Coding section with 7/1/2022 descriptor change for 0402T, removed NOC code 66999 no longer applicable.
Reviewed	11/11/2021	MPTAC review. Description, Discussion/General Information and References sections updated. Updated Coding section; added 66999 NOC code.
Reviewed	11/05/2020	MPTAC review. Discussion/General Information and References sections updated. Reform atted Coding section.
New	11/07/2019	MPTAC review. Initial document development. Moved content of MED.00109 to new clinical utilization management guideline document with the same title. Edited criterion B in medically necessary statement on progressive keratoconus for clarification.

Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to adopt a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.

Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan's or line of business's members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.