Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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Plan: Keystone First	**Submission Date**: 6/1/2024
Policy Number: ccp.1415	**Effective Date:** 6/2019 **Revision Date:** May 1, 2024
Policy Name: Corneal cross-linking	

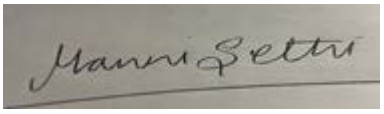
Type of Submission – Check all that apply:

New Policy
X Revised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Keystone First
Family of Health Plans

Corneal cross-linking

Clinical Policy ID: CCP.1415

Recent review date: 5/2024

Next review date: 9/2025

Policy contains: Collagen cross-linking; corneal ectasia; keratoconus; refractive surgery of cornea.

Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First's clinical policies are not guarantees of payment.

Coverage policy

Corneal cross-linking using the photo enhancer riboflavin 5′-phosphate ophthalmic solution and ultraviolet A radiation is clinically proven and, therefore, may be medically necessary when both criteria are met (American Academy of Ophthalmology, 2022; U.S. Food and Drug Administration, 2016).

- To treat either progressive keratoconus or corneal ectasia after refractive surgery.
- After conservative interventions have failed.

For any determinations of medical necessity for medications, refer to the applicable state-approved pharmacy policy.

Limitations

Relative contraindications to corneal cross-linking are (American Academy of Ophthalmology, 2018):

- Corneal stromal thickness below 400 µm.
- Prior herpes simplex virus keratitis.

Alternative covered services

- Routine patient evaluation and management by a network health care provider.
- Corrective glasses.
- Rigid and gas-permeable contact lenses.
- Intrastromal corneal ring segments.
- Keratorefractive surgery.
- Corneal transplant (keratoplasty).

Background

Keratoconus is a type of corneal ectasia that causes the normally round cornea to develop a cone-shaped bulge at its center, in areas where thinning is greatest. It causes blurry/distorted vision, sensitivity to light, and other vision problems. Other types of corneal ectasia include pellucid marginal degeneration, posterior keratoconus, and post-laser refractive surgery ectasia. Keratoconus is a rare ocular disease, affecting one in 2,000 Americans (National Organization for Rare Disorders, 2019).

The disorder often starts at puberty and is often observed in teenagers or young adults. Males, African Americans, and Latinos are at greater risk for developing the disease. Children with the disorder have a much greater proportion of severe (stage IV) cases than do adults. While no cause has been identified, environmental and genetic factors are suspected (National Organization for Rare Disorders, 2019).

Diagnosing the disease is feasible during a routine eye examination. Symptoms in the early stage include mild vision blurring, slightly distorted vision, sensitivity to light, and eye redness or swelling. Later stages include symptoms such as highly distorted nearsightedness and astigmatism, and inability to wear contact lenses due to the bulging cornea. Treatment of keratoconus often begins with corrective glasses or rigid and gas-permeable contact lenses to change the cornea back to its normal shape (Boyd, 2022).

Advanced treatments include intracorneal ring segments or a corneal transplant (keratoplasty) for failed response to conservative treatment. In children, treatment compliance is often poor. Corneal transplants have a higher risk of rejection and poor visual progress, and intracorneal ring segment implants are generally safe but have not been well studied in children (Olivo-Payne, 2019).

Corneal collagen cross-linking is a minimally invasive outpatient procedure that employs eye drops containing the photo enhancer riboflavin 5′-phosphate and local photo-polymerization using ultraviolet A light to strengthen the collagen bonds in the cornea. The standard Dresden protocol involves removing the outer layer of the corneal epithelium under topical anesthesia to allow penetration of riboflavin into the corneal tissue, followed by 30 minutes of eyedrop instillation using a slit lamp, followed by 30 minutes of ultraviolet A irradiation. Topical antibiotics and anti-inflammatory drops are usually prescribed after the procedure; in some cases, topical steroids may be necessary. One eye at a time is treated; repeat procedures may be necessary. Variations to the standard procedure include accelerated cross-linking (higher energy at a shorter duration), a transepithelial approach (epithelial-on), and a combination of cross-linking and either ring segment implantation or refractive surgery (Porter, 2022).

On April 15, 2016, the U.S. Food and Drug Administration approved corneal collagen cross-linking using Photrexa Viscous (riboflavin 5′-phosphate in 20% dextran ophthalmic solution) and Photrexa (riboflavin 5′-phosphate ophthalmic solution), intended for use with ultraviolet A irradiation administered with the KXL® system. It is approved for patients with progressive keratoconus or corneal ectasia after refractive surgery using the Dresden protocol. Data submitted to support regulatory approval included participants between the ages of 14 and 65 years. Cross-linking is marketed in the United States as iLink™ corneal cross-linking (Glaucos Corp., San Clemente, California) and is the only approved corneal cross-linking system as of this writing (Kaufman, 2016).

Findings

Early keratoconus guidelines from European experts cited numerous studies that upheld the ability of corneal cross-linking to improve visual acuity and topographic indices in a safe manner for persons with keratoconus, since the technique’s introduction in the late 1990s (Alio, 2015; Andreanos, 2017).

An American Academy of Ophthalmology Preferred Practice Pattern summary (2022) states that, in patients with keratoconus, corneal cross-linking reduces the risk of progressive ectasia, particularly in its early stages, and stabilizes the cornea. No age limits were defined. Cross-linking also stabilizes cases of corneal ectasia occurring after keratorefractive surgery. More frequent follow-up (i.e., every three to six months) is warranted to assess for progression. Younger patients may also require more frequent follow-up.

Since then, multiple high-quality systematic reviews and meta-analyses have been published on collagen cross-linking. The majority of trial participants were adults or older juveniles with an even gender split. Most results of mixed populations were not stratified by age. Optimal treatment parameters beyond the approved Dresden protocol have not been determined. No consistent or clear definition of ectasia progression has been identified, but tomographic values and refractive changes are often reported.

The evidence from these analyses, presented below, consists of randomized controlled trials of mostly moderate quality. Standard epithelial-off cross-linking using the Dresden protocol is safe and effective for all age groups represented in the trials, for halting the progression of mild to moderate keratoconus with some improvement in visual structure and function, represented as corrected distance visual acuity, uncorrected distance visual acuity, and maximum keratometry (Kmax). Due to the aggressive and progressive nature of keratoconus, especially in younger patients, cross-linking may be particularly beneficial for avoiding or delaying corneal transplantation. Long-term effectiveness in pediatric patients has not been determined.

Complications caused by epithelial stripping and long exposure to ultraviolet radiation are intense postoperative ocular pain, subepithelial haze, sterile infiltration, and infectious keratitis. Modified cross-linking procedures may overcome some of these limitations. Compared to epithelium-off cross-linking, both transepithelial and accelerated modifications appear to have comparable visual and refractive outcomes and acceptable safety profiles, but are less effective at halting disease progression, which is the primary outcome of interest.

Further research is needed to determine the benefit of modified cross-linking procedures for younger pediatric populations or for patients with cornea thickness less than 400 µm (Li, 2017; Jiang, 2019; Nath, 2021; Shajari, 2019; Wen, 2018). There is insufficient evidence to determine the optimal combination or sequence of corneal surgical treatments (cross-linking, intrastromal corneal ring implants, and refractive surgery) for treating progressive keratoconus (Benoist d'Azy, 2019; Hashemi, 2018).

A systematic review/meta-analysis of 24 studies compared standard collagen cross-linking with modified cross-linking to reduce complications. The modified group was significantly inferior at delaying Kmax deterioration ($P = .03$). The spherical equivalent decreased significantly for the standard group ($P < .00001$) (Liu, 2017).

A meta-analysis of three randomized controlled trials (n = 244 eyes) found those who underwent standard corneal collagen cross-linking for keratoconus had more effective reduction in maximum keratometry at least 12 months post-operative. Significantly greater corrected distant visual acuity was observed in those who underwent transepithelial corneal collagen cross-linking, with similar results between groups in uncorrected distant visual acuity. Safety was similar for both groups (Li, 2017).

A systematic review/meta-analysis of 12 studies (n = 966) found the transepithelial approach to cross-linking inferior to the epithelium-off corneal approach, measured as change in maximal keratometry at 12 months ($P = .004$) and longest follow-up ($P < .001$) (Nath, 2021). Transepithelial cross-linking was associated with significantly fewer complications than the epithelium-off approach ($P = .020$) but also an increased rate of disease progression at 12 months after treatment ($P = .022$). Uncorrected distance visual acuity ($P = .386$) and corrected distance visual acuity ($P = .732$) outcomes were similar between groups. The mean age of all participants was 23.88 years (standard deviation, 9.03 years) and was similar between groups.

A meta-analysis of seven studies (n = 283 eyes) compared accelerated cross-linking with standard corneal cross-linking to treat keratoconus. The accelerated group experienced greater reductions of average keratometry (P < .01), while other outcomes were not significantly different between the two groups (Jiang, 2019).

Another meta-analysis of 22 studies (n = 1,158 eyes) found standard cross-linking yielded better results for minimum keratometry (P < .00001) and demarcation line depth (P < .00001) than accelerated procedures. Accelerated cross-linking had superior results when minimum corneal thickness was considered (P = .0005). Other measures showed no significant differences between the two groups (Shajari, 2019).

A meta-analysis (11 studies) of outcomes after transepithelial cross-linking with accelerated versus standard cross-linking for keratoconus yielded mixed results. Epithelium-off and transepithelial procedures had a greater reduction in maximum keratometry, while accelerated procedures had superior results in central corneal thickness and endothelial cell density (Wen, 2018).

A systematic review/meta-analysis of 17 studies assessed outcomes of three groups that 1) combined intracorneal ring segment and corneal collagen cross-linking the same day, 2) performed the ring segment at an earlier day, and 3) performed collagen cross-linking at an earlier day. After 12 months, there was no difference between the groups in best-corrected visual acuity and cylindrical refractive error (Hashemi, 2018).

A systematic review/meta-analysis of 95 studies (n = 4,560) showed treatment of keratoconus with a combination of intracorneal ring segment implantation, collagen cross-linking, and photorefractive keratectomy is superior to the implantation alone in all measures except for the correction of spherical equivalent, and could be proposed to young people with keratoconus (Benoist d'Azy, 2019).

In 2022, we deleted several older references based on the findings from a quality assessment of systematic reviews of treatments for corneal diseases produced for the American Academy of Ophthalmology (Saldanha, 2019). We added an updated Cochrane review (Ng, 2021) and guidance from the American Academy of Ophthalmology (2018, 2021) that confirm previous findings. We added relative contraindications to the limitations section based on American Academy of Ophthalmology (2018) guidance.

In 2023, we updated the American Academy of Ophthalmology (2022) guidance and added several systematic reviews, meta-analyses, and large observational studies. Two analyses addressed pediatric keratoconus (Achiron, 2022; Li, 2022), two addressed protocol variations (Borchert, 2022; Karam, 2023), and two addressed long-term outcomes (Ferdi, 2023; Seifert, 2022). The results confirm previous findings, and no policy changes are warranted.

For pediatric keratoconus, the risk of progression after standard epithelium-off collagen cross-linking was 9.9% (95% confidence interval 6.1% to 14.6%, P < .0001) as measured by an increase in Kmax, Kmean, or Ksteep ≥ 1.0 diopter over various time periods (Achiron, 2022; 37 studies; n = 2,078 eyes). In a second meta-analysis, compared to accelerated collagen cross-linking, standard collagen cross-linking resulted in a higher incidence of adverse effects but a significantly greater improvement in best corrected visual acuity at 24-month follow-up (P = .03). Other acuity and keratometric outcomes were comparable (Li, 2022; 11 studies; n = 888 eyes).

For protocol variation, Borchert (2022) examined the effect of oxygen added in epithelium-on corneal cross linking protocols on visual acuity and keratometry. The systematic review included six studies, and the meta-analysis included five studies. After six months of follow-up, participants with oxygen added experienced a significant decrease in mean maximum keratometry of 1.2 diopter (95% confidence interval 0.2 to 2.3, P = .02) and an increase in mean corrected distance visual acuity by 0.08 logMAR (95% confidence interval 0.02 to 0.13, P = .01), compared to controls. No serious adverse events were reported. Controlled trials with long-term follow-up across a range of treatment protocols are needed to inform clinical practice.

A systematic review and meta-analysis of four studies (n = 329 eyes) compared the outcomes of 10-minute and five minute accelerated corneal cross-linking protocols. Compared to the 5-minute protocol, the 10-minute

protocol resulted in significantly improved keratometry (P < 0.00001), corneal high-order aberration (*P* = .0002), and corneal coma (*P* = .00001) outcomes. No statistically significant differences were observed in the other outcomes (Karam, 2023).

Regarding long-term outcomes, a multinational, observational registry study examined outcome data at year 1 (n = 794 patients, 976 eyes) and at year 5 (n = 162). From year 1 to year 5, in the majority of participants, mean visual acuity significantly improved from baseline (3.7 logMAR letters at year 1, *P* < .001; 6.9 logMAR letters at year 5, *P* < 0.001). Keratometry values improved in year 1 and remained stable in subsequent years. However, over the five-year period, approximately 4.1% patients were poor responders to corneal cross-linking based on reduced visual acuity, and 5.9% to 7.5% were poor responders based on keratometry (Ferdi, 2023).

A retrospective consecutive case series of 131 participants (131 eyes) followed for up to 10 years (n = 44 participants at year 10) showed the ability of collagen crosslinking to slow or halt keratoconus progression and improve corrected distance visual acuity over the long-term. However, the percentage of non-responders rose from 16% after 5 years to 33% after 10 years. Risk factors for non-response were young age, high astigmatism (> 4.3 D), thin cornea (< 480 µm), poor initial visual acuity (corrected distance visual acuity ≥ 0.3 D), and atopic dermatitis. Re-treatment may be indicated (Seifert, 2022).

In 2024, no new policy references were found and no policy changes warranted.

References

On April 8, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “cross-linking,” “keratoconus;” “collagen,” and “riboflavin.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

4/2019: initial review date and clinical policy effective date: 6/2019

5/2020. Policy references updated.

5/2021: Policy references updated.

5/2022: Policy references updated. Limitations modified.

5/2023: Policy references updated.
5/2024: Policy references updated.