Medical Policy

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Title: Corneal Collagen Cross-Linking

Related Policies:	▪ *Corneal Topography/Computer-Assisted Corneal Topography/Photokeratoscopy*

Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With progressive keratoconus	Interventions of interest are: • Corneal collagen cross-linking using riboflavin and ultraviolet A	Comparators of interest are: • Observation • Rigid or specialty contact lens • Intracorneal ring segments • Corneal transplant	Relevant outcomes include: • Change in disease status • Functional outcomes • Treatment-related morbidity
Individuals: • With corneal ectasia after refractive surgery	Interventions of interest are: • Corneal collagen cross-linking using riboflavin and ultraviolet A	Comparators of interest are: • Observation • Rigid or specialty contact lens • Intracorneal ring segments • Corneal transplant	Relevant outcomes include: • Change in disease status • Functional outcomes • Treatment-related morbidity

DESCRIPTION

Corneal collagen cross-linking is a photochemical procedure approved by the U.S. Food and Drug Administration (FDA) for the treatment of progressive keratoconus and corneal ectasia following refractive surgery. Keratoconus is a dystrophy of the cornea characterized by progressive deformation (steepening) of the cornea, while corneal ectasia is keratoconus that occurs following refractive surgery. Both conditions can lead to functional loss of vision and need for corneal transplantation.

OBJECTIVE

The objective of this evidence review is to assess whether the use of corneal collagen cross-linking using riboflavin and ultraviolet A improves the net health outcome for individuals with progressive keratoconus and corneal ectasia after refractive surgery.

BACKGROUND

Treatment of Keratoconus and Ectasia

The initial treatment for keratoconus often consists of hard contact lenses. A variety of keratorefractive procedures have also been attempted, broadly divided into subtractive and additive techniques. Subtractive techniques include photorefractive keratectomy or laser in situ keratomileuses, although generally, results of these techniques have been poor. Implantation of intrastromal corneal ring segments is an additive technique in which the implants are intended to reinforce the cornea, prevent further deterioration, and potentially obviate the need for penetrating keratoplasty. Penetrating keratoplasty (ie, corneal grafting) is the last line of treatment. About 20% of patients with keratoconus will require corneal transplantation. All of these treatments attempt to improve the refractive errors but are not disease-modifying.

Treatment options for ectasia include intraocular pressure-lowering drugs and intracorneal ring segments. Frequently, penetrating keratoplasty is required.

None of the currently available treatment options for keratoconus and corneal ectasia halt the progression of the disease, and corneal transplantation is the only option available when functional vision can no longer be achieved.

Corneal collagen cross-linking has the potential to slow the progression of the disease. It is performed with the photosensitizer riboflavin (vitamin B2) and ultraviolet A irradiation. There are 2 protocols for corneal collagen cross-linking:

1. Epithelium-off corneal collagen cross-linking (also known as "epi-off"): In this method, about 8 mm of the central corneal epithelium is removed under topical anesthesia to allow better diffusion of the photosensitizer riboflavin into the stroma. Following de-epithelialization, a solution with riboflavin is applied to the cornea (every 1 to 3 minutes for 30 minutes) until the stroma is completely penetrated. The cornea is then irradiated for 30 minutes with ultraviolet A 370 nm, a maximal wavelength for absorption by riboflavin, while the riboflavin continues to be applied. The interaction of riboflavin and ultraviolet A causes the formation of reactive oxygen species, leading to additional

covalent bonds (cross-linking) between collagen molecules, resulting in stiffening of the cornea. Theoretically, by using a homogeneous light source and absorption by riboflavin, the structures beyond a 400-mm thick stroma (endothelium, anterior chamber, iris, lens, retina) are not exposed to an ultraviolet dose that is above the cytotoxic threshold.

2. Epithelium-on corneal collagen cross-linking (also known as "epi-on" or transepithelial): In this method, the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed.

Historically, the only corneal collagen cross-linking treatment approved by the U.S. Food and Drug Administration (FDA) was the epithelium-off method. In 2025, the first epithelium-on corneal collagen cross-linking treatment was approved (riboflavin 5'-phosphate ophthalmic solution, 0.177% and 0.239%; Epioxa™). Epoxia is anticipated to enter the market during quarter 1 of 2026. Corneal collagen cross-linking is being evaluated primarily for corneal stabilization in patients with progressive corneal thinning, such as keratoconus and corneal ectasia following refractive surgery. Corneal collagen cross-linking may also have anti-edematous and antimicrobial properties.

REGULATORY STATUS

In 2016, riboflavin 5'-phosphate in 20% dextran ophthalmic solution (Photrexa Viscous™; Avedro now Glaukos) and riboflavin 5'-phosphate ophthalmic solution (Photrexa™; Avedro) were approved by the FDA for use with the KXL System in corneal corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia after refractive surgery.[2,] In 2025, riboflavin 5'-phosphate 0.177% and 0.239% ophthalmic solution (Epioxa™ and Epioxa HD™; Glaukos) was approved for treatment of keratoconus in adults and children aged 13 years and older. Epioxa uses the O_2n System™ and Boost Googles® for its proprietary epithelium-on corneal collagen cross-linking technology. Photrexa products are planned to be discontinued from the market effective January 20, 2026 with manufacturing set to end February 2026.

POLICY

A. Corneal collagen cross-linking using riboflavin and ultraviolet A may be considered **medically necessary** as a treatment of progressive keratoconus or corneal ectasia resulting from refractive surgery in individuals who have failed conservative treatment (e.g., spectacle correction, rigid contact lens) (see Policy Guidelines).

B. Corneal collagen cross-linking using riboflavin and ultraviolet A is considered **experimental / investigational** for all other indications.

POLICY GUIDELINES

A. The American Academy of Ophthalmology has not set forth definitive criteria defining progressive keratoconus but has suggested that signs of progression include changes in refraction, visual acuity and corneal shape (https://eyewiki.aao.org/Corneal_Collagen_Cross-Linking). In the trials leading to FDA approval of corneal collagen cross-linking, progressive keratoconus or corneal ectasia were defined as one or more of the following:
   1. An increase of 1 diopter (D) in the steepest keratometry value
   2. An increase of 1 D in regular astigmatism evaluated by subjective manifest refraction
   3. A myopic shift (spherical equivalent) of 0.50 D on subjective manifest refraction
   4. A decrease ≥0.1 mm in the back optical zone radius in rigid contact lens wearers where other information was not available.

B. Some contracts do not cover refractive surgery. When refractive surgery is not covered, any service or supply provided or obtained relative to an excluded service is considered a general exclusion based on member contract.

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.

RATIONALE

This evidence review was created using with searches of the PubMed database. The most recent literature update was performed through December 26, 2025.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable

intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

CORNEAL COLLAGEN CROSS-LINKING FOR KERATOCONUS

Clinical Context and Therapy Purpose

Keratoconus is a bilateral dystrophy characterized by progressive ectasia (paracentral steepening and stromal thinning) that impairs visual acuity. While frequently diagnosed at a young age, the progression of keratoconus is variable. Results from a longitudinal study of over 900 patients with keratoconus showed that there was a decrease of 2 high- and 4 low-contrast letters in best-corrected visual acuity over 7-years follow-up.[3,4,] About 1 in 5 patients showed a decrease of 10 or more letters in high-contrast visual acuity and one-third of patients showed a decrease of 10 or more letters in low-contrast visual acuity.

The purpose of corneal collagen cross-linking using riboflavin and ultraviolet A irradiation in individuals with keratoconus is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with progressive keratoconus.

Intervention

The treatment being considered is corneal collagen cross-linking with riboflavin and ultraviolet A irradiation, which is performed by an ophthalmologist in an outpatient clinical setting.

Comparators

The comparators of interest are observation, rigid or specialty contact lens, intracorneal ring segments, or corneal transplant.

Outcomes

The outcomes of interest are change in disease status, functional outcomes, and treatment-related morbidity. Positive outcomes include slowing of disease progression and improvement in visual acuity and other ocular measurements. Negative outcomes include infection, adverse reactions, and need for alternative treatment, including corneal transplant.

Follow-up of at least 1 year is needed to assess outcomes.

Visual acuity definitions

Best spectacle-corrected visual acuity is the best vision correction that can be achieved with glasses as measured on the standard Snellen eye chart.

Best corrected visual acuity is the best vision correction that can be achieved with *any* visual correction (eg, glasses, contact lenses, keratonomy) as measured on the standard Snellen eye chart.

Uncorrected visual acuity is the vision correction without visual correction as measured on the standard Snellen eye chart.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
4. Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

EPITHELIUM-ON CORNEAL COLLAGEN CROSS-LINKING

Randomized Controlled Trials

The approval of Epioxa for epithelium-on corneal collagen cross-linking in patients with keratoconus was based on 2 sham-controlled RCTs (total N=592 eyes) that are summarized in the prescribing information but remain unpublished.[5,] The primary efficacy endpoint was assessed at 6 months and 12 months post-treatment in the first and second studies, respectively. In the first study, change from baseline to 6 months in maximum corneal curvature was significantly better with corneal cross-linking than sham treatment ($p<.01$). In the second study, change from baseline to 12 months in maximum corneal curvature was significantly better with corneal cross-linking than sham treatment ($p<.01$). Changes in visual acuity are not presented in the prescribing information.

EPITHELIUM-OFF CORNEAL COLLAGEN CROSS-LINKING

Systematic Reviews

A 2024 ophthalmic technology assessment from the American Academy of Ophthalmology reviewed the safety and efficacy of epithelium-off corneal collagen cross-linking for progressive corneal ectasia.[6,] The analysis included 6 RCTs: 5 on progressive keratoconus (including Hersh et al 2017 [summarized below]) and 1 on post-laser refractive surgery ectasia, with a mean follow-up of 2.4 years (range, 1 to 5 years). Although results were not statistically pooled, all studies reported reduced disease progression in treated patients versus controls and complications were rare. Treatment groups showed improvements in maximum keratometry (Kmax), corrected distance visual acuity, and uncorrected distance visual acuity. Corneal thickness decreased in both groups but was more pronounced in the treatment group. McAnena et al (2017) reported on the results of a systematic review and a meta-analysis assessing the efficacy of corneal collagen cross-linking treatment for keratoconus in pediatric patients.[7,] A total of 13 articles, published between May 2011 and December 2014, examining 490 eyes of 401 patients (mean age, 15.25 years), were included in the meta-analysis. Bias

assessment of individual studies was not included. Reviewers reported a significant improvement in best-corrected visual acuity at 6 months (standardized mean difference [SMD], -0.66; 95% confidence interval [CI], -1.22 to -0.11; p=.02), which was maintained at 1 year (SMD, -0.69; 95% CI, -1.15 to -0.22; p<.01). Two-year data were available for 3 studies (N=131 eyes) and the improvement in best-corrected visual acuity remained significant (SMD, -1.03; 95% CI, -2 to -0.06; p=.04).

Randomized Controlled Trials

Hersh et al (2017) reported combined results from 2 open-label trials which informed FDA approval of Photrexa for epithelium-off corneal collagen cross-linking for treatment of keratoconus.[8,] The studies randomized 205 patients to corneal collagen cross-linking (n=102) or a sham procedure (n=103). At 1 year follow-up, those in the treatment group had a significant decrease in maximum corneal curvature score (-1.6) compared with baseline, while the control group saw an increase in maximum corneal curvature (1.0); the between-group difference in maximum corneal curvature change was 2.6 D (p<.001). Mean corrected distance visual acuity improved significantly more in the treatment group (5.7 Logarithm of the Minimum Angle of Resolution [logMAR]) than in the control group (2.2 logMAR; between-group difference, 3.5 logMAR; p<.01). A similar finding, though statistically insignificant, was observed for mean uncorrected distance visual acuity, with the treatment group improving by 4.4 logMAR, compared with the control group (2.6 logMAR; between-group difference, 1.8 logMAR). Endothelial cell count did not change significantly from baseline to 1 year in either group. Symptom and quality of life measures that were significantly improved from baseline at 1-year follow-up included reductions in difficulty driving, difficulty reading, double vision, vision fluctuations, glare and foreign body sensations in the corneal collagen cross-linking group; outcomes for the sham group were not reported. The trial was limited in that patients in the control group were allowed to switch to corneal collagen cross-linking treatment after 3 months; thus, their data were imputed based on the last observation carried forward method. Also, in the control group, patients did not undergo removal of their epithelium.

Nonrandomized Studies

Longer-term follow-up ranging from 2 to 10 years has been reported in cohort studies and case series conducted in Europe, where corneal collagen cross-linking has been performed for a greater number of years. Indications for treatment typically include progression of steepening (increase in maximum corneal curvature by at least 1 D in 1 year), deteriorating visual acuity, or the need to be fitted for new contact lenses more than once in 2 years. The largest and longest series to date are described next.

Toprak et al (2017) retrospectively analyzed 29 eyes from pediatric patients (age range, 10 to 17 years) whose progressive keratoconus was treated with unilateral corneal collagen cross-linking treatment.[9,] From baseline to 2-year follow-up, there was a significant decrease in mean corrected distance visual acuity (0.34 to 0.13 logMAR; p<.001). Maximum keratometry measures decreased from baseline 54.65 to 53.25 at 2 years (p=.034), while anterior chamber parameters, corneal thickness, and corneal volume were not significantly affected by corneal collagen cross-linking after 2 years (p>.05). Several parameters of the Scheimpflug imaging system were improved following corneal collagen cross-linking treatment: index of surface variance decreased from 69.75 at baseline to 62.95 at 2 years (p=.004); keratoconus index decreased from 1.16 to 1.14 (p=.001); center keratoconus index decreased from 1.05 to 1.04 (p=.004); and index of height decentration decreased from 0.056 to 0.042 (p=.001). The radius

of minimum curvature increased significantly from baseline to 2 years (6.21 to 6.36; p=.007), although 2 other indices (indices of height and vertical asymmetry) did not change significantly. The authors noted that follow-up beyond 2 years is required to make long-term assessments of corneal collagen cross-linking as a treatment for keratoconus, but concluded that their results seemed favorable for postoperative outcomes.

Badawi et al (2017) published a prospective nonrandomized observational study of accelerated corneal collagen cross-linking to treat pediatric patients with keratoconus.[10,] Of the 25 patients (33 eyes) enrolled, 80% were male, and most patients (n=17) received unilateral corneal collagen cross-linking, administered with VibeX Rapid solution and Vega CBM X-Linker. The group's mean unaided and aided visual acuity were significantly improved at all time points (3, 6, and 12 months). At 12-month follow-up, the mean unaided visual acuity score was 0.34, which was a significant decrease compared with the preoperative mean score (0.54; p<.001). For aided visual acuity, there was a similar decrease from preoperative (0.36) to 12-month (0.17) time points (p<.001). Mean corneal astigmatism values also decreased significantly (preoperative 2.4 D decreased to 2.01 D at 12 months; p<.001). The mean maximum corneal curvature showed an average flattening of 1.2 D in 1 year (49.12 D decreasing to 47.9 D; p<.001); the authors reported significant improvements in other measures such as central pachymetry, maximum anterior elevation, average progression indices, and Q values. A limitation of the study was the slight increase observed in posterior surface elevation, which, contrary to other study measures, showed no significant positive effect 12 months after accelerated corneal collagen cross-linking (p=.9). Advising further study of the procedure, the authors noted that the unusual result might be accounted for by the choice of Pentacam as a corneal analysis tool because there might have been corneal artifacts present during the evaluation.

Knutsson et al (2018) published a prospective cohort study of 43 patients (52 eyes) between the ages of 12 and 17 years who underwent corneal collagen cross-linking as a treatment for keratoconus in one or both eyes.[11,] Two-year outcomes were reported for all patients, although longer-term (up to 7 years) follow-up was available for 21 eyes. At 2 years, overall mean maximum corneal curvature decreased from 59.30±7.08 to 57.07±6.46 (p<.001), and overall mean uncorrected visual acuity and Best spectacle-corrected visual acuity decreased, although not significantly. Additional analyses were conducted of patients whose eyes had maximum corneal curvature values of 60 D or greater (n=25), compared with those whose keratometry was less severe (<60 D). As with the overall findings, mean maximum corneal curvature were significantly decreased for both cohorts, while neither uncorrected visual acuity nor best spectacle-corrected visual acuity measures changed significantly at 1 or 2 years. In patients with advanced keratoconus, mean maximum corneal curvature decreased from 64.94 (95% CI, 62.94 to 66.94) to 62.25 (95% CI, 60.55 to 63.95) at 2 years (p<.001); for the less-advanced cohort, mean maximum corneal curvature decreased from 53.88 (95% CI, 52.48 to 55.28) at baseline to 52.08 (95% CI, 50.68 to 53.48) at 2 years (p<.001). While most findings were favorable for the efficacy of corneal collagen cross-linking in treating even severe keratometry, the authors noted that the study was limited by the use of 2 pachymetric measurement techniques (optical coherence tomography and ultrasound) rather than a single technique across the study. Further, the lack of full long-term data for all patients limited the study to reporting only 2-year outcomes.

Papaioannou et al (2016) retrospectively analyzed 377 eyes of 336 patients (mean age, 15 years) who underwent corneal collagen cross-linking for progressive keratoconus.[12,] There was a significant improvement in mean best spectacle-corrected visual acuity from 0.33 to 0.27 logMAR ($p<.05$). The authors found that the benefits of corneal collagen cross-linking in stabilizing keratoconus were maintained for more than 2 years in most pediatric eyes. Padmanabhan et al (2017) published follow-up results from the retrospective study previously mentioned of 377 eyes in 336 pediatric patients.[13,] Of 59 eyes for which investigators had longer-term follow-up data (4 to 6.7 years), 30.9% showed worsening corrected distance visual acuity, and 24% showed corneal steepening of greater than 1 D (maximum corneal curvature). These results showed the majority of patients still experienced improvements or stabilization of keratoconus-related outcomes after corneal collagen cross-linking, but suggested that long-term there may be less efficacy.

Raiskup-Wolf et al (2008) reported on outcomes of 241 eyes (272 patients) treated with corneal collagen cross-linking, with a minimum of 6 months of follow-up.[14,] Follow-up examinations were performed at 1, 6, and 12 months, and then annually. Mean follow-up was 26 months, with a range of 12 months (n=142) to 6 years (n=5). In the first year (n=142), steepening (maximum corneal curvature) improved or remained stable in 86% of eyes, and best-corrected visual acuity improved by at least 1 line in 53% of the eyes. Three years after treatment (n=33), maximum corneal curvature improved by a mean of 2.57 D in 67% of eyes while best-corrected visual acuity improved by at least 1 line in 58% of eyes. In 2015, the same group published a 10-year follow-up of corneal collagen cross-linking treatment in 34 eyes (24 patients) with progressive keratoconus.[15,] Mean patient age at the time of treatment was 28 years (range, 14 to 42 years). Corneal steepening improved slightly between baseline and 10-year follow-up ($p<.001$), while corrected distance visual acuity improved by 0.14 logMAR ($p=.002$). Two eyes had repeat corneal collagen cross-linking, one after 5 years and one after 10 years, without adverse sequelae. One of the 34 eyes treated developed a permanent corneal scar. These studies were limited by their retrospective designs and the small number of cases with extended follow-up.

A publication from the Siena Eye Cross Study (2010) reported on 52-month mean follow-up (range, 48 to 60 months) for 44 keratoconic eyes treated with corneal collagen cross-linking.[16,] Follow-up evaluations were performed at 1, 2, 3, 6, 12, 24, 36, 48, and 60 months after corneal collagen cross-linking. Topographic analysis showed the following mean K reading reductions: -1.96 D after 1 year, -2.12 D after 2 years, -2.24 D after 3 years, and -2.26 D after 4 years of follow-up. By comparison, in fellow eyes untreated for the first 24 months, the mean K value increased by 1.2 D at 1 year and 2.2 D at 2 years. In treated eyes, uncorrected visual acuity improved by a mean of 2.41 lines after 12 months, 2.75 lines after 24 months, 2.80 lines after 36 months, and 2.85 lines after 48 months. There was no significant decrease in endothelial cell density, central corneal thickness, or intraocular pressure over follow-up. Temporary adverse events included stromal edema in the first 30 days (70% of patients) and temporary haze (9.8% of patients). No persistent adverse events were observed.

Section Summary: Corneal Collagen Cross-Linking for Keratoconus

The evidence for epithelium-on corneal collagen cross-linking for keratoconus includes 2 RCTs. Both studies showed a significant difference between corneal cross-linking and sham treatment in maximum corneal curvature, but visual acuity results are lacking. The evidence for epithelium-off corneal collagen cross-linking for keratoconus includes RCTs, systematic reviews,

and nonrandomized studies. Overall results showed long-term reduction in corneal curvature and less significant improvements in visual acuity, although some studies found significant improvement in best spectacle-corrected visual acuity up to at least 2 years.

CORNEAL COLLAGEN CROSS-LINKING FOR ECTASIA

Clinical Context and Therapy Purpose

Ectasia (also known as keratectasia, iatrogenic keratoconus, or secondary keratoconus) is a serious long-term complication of laser in situ keratomileusis (LASIK) surgery and photorefractive keratectomy (PRK). It is similar to keratoconus but occurs postoperatively and primarily affects older populations. It may result from unrecognized preoperative keratoconus or, less frequently, from the surgery itself. Similar to keratoconus, it is characterized by progressive thinning and steepening of the cornea, resulting in corneal optical irregularities and loss of visual acuity.

The purpose of corneal collagen cross-linking using riboflavin and ultraviolet A irradiation in individuals with ectasia is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with corneal ectasia.

Intervention

The treatment being considered is corneal collagen cross-linking with riboflavin and ultraviolet A irradiation, which is performed by an ophthalmologist in an outpatient clinical setting.

Comparators

The comparators of interest are observation, rigid or specialty contact lens, intracorneal ring segments, or corneal transplant.

Outcomes

The outcomes of interest are change in disease status, functional outcomes, and treatment-related morbidity. Positive outcomes include slowing of disease progression and improvement in visual acuity and other ocular measurements. Negative outcomes include infection, adverse reactions, and need for alternative treatment, including corneal transplant.

Follow-up of at least 1 year is needed to assess outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

1. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
2. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
3. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

4. Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

The previously mentioned 2024 report from the American Academy of Ophthalmology reviewed the safety and efficacy of epithelium-off corneal collagen cross-linking for progressive corneal ectasia.[6,] The analysis included 6 RCTs: 5 on progressive keratoconus and one on post-laser refractive surgery ectasia (including Wittig-Silva et al [2014] and Hersh et al [2017], both summarized below), with a mean follow-up of 2.4 years (range, 1 to 5 years). Although results were not statistically pooled, all studies reported reduced disease progression in treated patients versus controls and complications were rare. Treatment groups showed improvements in maximum Kmax, corrected distance visual acuity, and uncorrected distance visual acuity. Corneal thickness decreased in both groups but was more pronounced in the treatment group.

An additional systematic review with meta-analysis by Amaral et al (2024) reviewed the safety and efficacy of corneal collagen cross-linking for managing post-laser corneal ectasia, including 15 studies (N=421; 4 RCTs and 11 nonrandomized cohorts).[17,] The follow up ranged from 3 to 60 months. Pooled results showed stable uncorrected visual acuity and significant improvements in corrected distance visual acuity (SMD, 0.09; 95% CI, -0.07 to 0.26). Significant reductions were observed in spherical equivalent (SMD, -0.09; 95% CI, -0.35 to -0.02), Kmax (SMD, 0.15; 95% CI, 0.01 to 0.28), and central corneal thickness (SMD, 0.24; 95% CI, 0.07 to 0.41).

Randomized Controlled Trials

A trial reported by Hersh et al (2017), used to inform FDA approval of Photrexa for epithelium-off corneal collagen cross-linking for the treatment of corneal ectasia, enrolled 179 patients treated for post-surgical corneal ectasia.[18,] The prospective, multicenter controlled trial randomized 91 patients to treatment with standard corneal collagen cross-linking and 88 patients to a sham procedure that administered riboflavin alone and did not require the removal of the epithelium. The primary endpoint was a 1-year change in maximum corneal curvature, which was a mean 0.7 D decrease in the corneal collagen cross-linking group and a 0.6 D increase in the control group (between-group difference, 1.3 D; p<.001). A significantly greater improvement in corrected distance visual acuity was observed for the corneal collagen cross-linking group (5.0 logMAR gained) than for the control group (0.3 logMAR lost; p<.001), as was the case with uncorrected distance visual acuity, for which the between-group difference was 4.6 letters (p<.001). There was no significant difference between treatment and control groups for either manifest refraction spherical equivalent myopia or endothelial cell density, and fewer than 5% of eyes had adverse events. Over half of patients (68%) reported corneal stromal haze or demarcation line. The trial was limited by the last observation carried forward analysis required for the control patients who elected to receive treatment after 3 months; also, because only 4 patients received photorefractive keratectomy surgery, comparison between types of surgery and effects of postsurgery corneal collagen cross-linking were precluded.

Wittig-Silva et al (2008) reported the first RCT of epithelium-off corneal collagen cross-linking.[19,] Three-year results were published in 2014.[20,] Recruitment for the trial was completed in 2009 with 50 eyes randomized to corneal collagen cross-linking treatment and 50 eyes to the untreated control. To be eligible for enrollment, clear evidence of progression of ectasia over

the preceding 6 to 12 months was required. Progression was confirmed if at least one of the following criteria was met: an increase of at least 1 D in the steepest simulated maximum corneal curvature; an increase in astigmatism determined by manifest subjective refraction of at least 1 D; an increase of 0.50 D in manifest refraction spherical equivalent; or a 0.1-mm or more decrease in back optic zone radius of the best-fitting contact lens. At the time of analysis for the 2008 report, 20 eyes had reached 1-year follow-up. The 3-year results included 46 corneal collagen cross-linking treated and 48 control eyes. Last observation carried forward was used for 26 eyes, including 17 eyes from the control group with a progressive disease that underwent compassionate-use corneal collagen cross-linking or corneal transplantation. In the corneal collagen cross-linking group, there was a flattening of maximum corneal curvature by -1.03 D, compared with a 1.75 increase in maximum corneal curvature in the control group. One eye in the corneal collagen cross-linking group progressed by more than 2 D, compared with 19 eyes in the control group. Uncorrected visual acuity and best-corrected visual acuity improved in the corneal collagen cross-linking treated eyes at 1, 2, and 3 years.

Nonrandomized Studies

Margines et al (2023) reported on outcomes of 82 eyes (54 patients) treated with epithelium-off corneal collagen cross-linking for corneal ectasia following LASIK.[21,] Participants were followed prospectively with examinations performed on day 1, week 1, 1 month, 3 months, 6 months, 12 months, and then annually through 5 years. The mean follow-up was 39 months, ranging from 12 months (n=48) to 5 years (n=19). Patients had a mean age of 42.8 years and underwent corneal cross-linkage after an average of 11.4±4.65 years following LASIK surgery with an average spherical equivalent fraction of -2.08. After treatment, the spherical equivalent did not change significantly. From pre-corneal cross-linkage values to 5 years follow-up, logMAR uncorrected visual acuity improved from 0.78±0.35 to 0.63±0.32 (p>.05), and logMAR corrected distance visual acuity improved from 0.29±0.17 to 0.25±0.26 (p>.05). Steep keratometry improved significantly from pre-operation (49.0±4.3 D) to one year post-operatively (45.5±1.9 D; p<.0125) and remained stable through 5 year follow-up (47.2±3.0 D; p<.0125). The authors reported no surgical complications, and no patient underwent additional treatment. Post-operative corneal haze was reported as occurring occasionally, but the number of eyes was not reported. This study was limited by a lack of experimental design and the small number of cases with extended follow-up.

Section Summary: Corneal Collagen Cross-Linking for Ectasia

Evidence for epithelium-off corneal collagen cross-linking for corneal ectasia includes 2 systematic reviews, 2 RCTs, and one prospective, single-arm cohort study. Results showed improvement in uncorrected distance visual acuity, corrected distance visual acuity, best spectacle-corrected visual acuity, and maximum corneal curvature compared to sham after at least 12 months. In addition, a higher proportion of participants in the corneal collagen cross-linking group had a ≥15-letter improvement with best spectacle-corrected visual acuity than in the sham group. Five-year follow-up in a prospective cohort study found sustained improvement in uncorrected and corrected distance visual acuity scores as well as steep keratometry from baseline levels with no significant change in spherical equivalent.

Adverse Events

A safety analysis conducted by the FDA included 512 eyes (293 eyes with keratoconus, 219 eyes with corneal ectasia) in 364 patients who received epithelium-off corneal collagen cross-linking treatment.[22,] As described earlier, the procedure involves removing the corneal

epithelium to enhance the riboflavin solution's penetration. As a result, patients may develop a range of ocular adverse reactions, including corneal opacity (haze), corneal epithelial defects, punctate keratitis, corneal striae, eye pain, reduced visual acuity, blurred vision, dry eye, and photophobia among others. Most adverse events resolved in the first month, while others took up to 12 months to resolve. However, in 1% to 6% of patients, these adverse events could continue beyond 12 months.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Institute for Health and Care Excellence

In 2013, the NICE issued guidance on corneal collagen cross-linking using riboflavin and ultraviolet A, updating its guidance based on a 2009 systematic review of primarily low-quality evidence; review authors declared no financial conflicts of interest.[23,] The 2013 guidance stratified recommendations for corneal collagen cross-linking as follows:

"Most of the published evidence on photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A (UVA) for keratoconus and keratectasia relates to the technique known as 'epithelium-off corneal collagen cross-linking'. 'Epithelium-on (transepithelial) corneal collagen cross-linking' is a more recent technique and less evidence is available on its safety and efficacy. Either procedure (epithelium-off or epithelium-on corneal collagen cross-linking) can be combined with other interventions, and the evidence base for these combination procedures (known as 'corneal collagen cross-linking plus') is also limited. Therefore, different recommendations apply to the variants of this procedure, as follows.

1.1 Current evidence on the safety and efficacy of epithelium-off corneal collagen cross-linking for keratoconus and keratectasia is adequate in quality and quantity. Therefore, this procedure can be used provided that normal arrangements are in place for clinical governance, consent and audit.

1.2 Current evidence on the safety and efficacy of epithelium-on (transepithelial) corneal collagen cross-linking, and the combination (corneal collagen cross-linking plus) procedures for keratoconus and keratectasia is inadequate in quantity and quality. Therefore, these procedures should only be used with special arrangements for clinical governance, consent and audit or research."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT07135167	Compassionate Use Study of Epi-ON Corneal Collagen Crosslinking Performed Using UVA Exposure on Eyes With Ectatic Corneal Diseases for Subjects With Down Syndrome	225	Feb 2026
NCT01112072	Randomized Study of Safety and Efficacy of Corneal Collagen Crosslinking and Intacs for Treatment of Keratoconus and Corneal Ectasia	160	Dec 2025
NCT03319082[a]	A Phase IV Observational Registry to Assess the Durability of Effect of Corneal Collagen Cross-linking With Photrexa Viscous, Photrexa, and the KXL System in Patients With Corneal Ectasia Following Refractive Surgery	200	Feb 2026
NCT01604135	Collagen Crosslinking for Keratoconus - a Randomized Controlled Clinical Trial	36	April 2025
NCT03760432	Clinical Trial of Laser Custom Corneal Collagen Cross-Linking in Keratoconus	100	Dec 2027
NCT00560651	German Corneal Cross-Linking Registry	7500	Nov 2027
Unknown			
NCT01708538[a]	Phase III Study of Corneal Collagen Cross-linking Using Two Different Techniques	30	Oct 2024
Unpublished			
NCT04213885	Safety and Effectiveness of the PXL Platinum 330 System for Corneal Collagen Cross-Linking in Eyes With Corneal Thinning Position	12	Aug 2024
NCT03531047	A Prospective, Controlled Study of Refractive Corneal Cross-linking for Progressive Keratoconus	53	Nov 2021

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.
b Terminated to initiate FDA and IND-cleared study protocol.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
0402T	Collagen cross-linking of cornea, including removal of the corneal epithelium, when performed, and intraoperative pachymetry, when performed
J2787	Riboflavin 5'-phosphate, ophthalmic solution, up to 3 mL
J3490	Unclassified drugs

REVISIONS	
04-28-2017	Policy added to the bcbsks.com web site.
04-11-2018	Updated Description section.
	Updated Rationale section.
	Updated References section.
08-01-2018	In Policy section: ▪ Revised Policy Guidelines Item 1 c, removed "decrease in the" to read, "A myopic shift (spherical equivalent) of 0.50 D on subjective manifest refraction."
	Updated References section.
01-01-2019	In Coding section: ▪ Added new HCPCS code: J2787.
04-24-2019	Updated Description section.
	In Policy section: ▪ In Item A, removed "after" and added "resulting from" to read, "Corneal collagen cross-linking using riboflavin and ultraviolet A may be considered medically necessary as a treatment of progressive keratoconus or corneal ectasia resulting from refractive surgery in patients who have failed conservative treatment (e.g., spectacle correction, rigid contact lens) (see Policy Guidelines)."
	Updated Rationale section.
	Updated References section.
07-01-2019	In Coding section: ▪ Revised nomenclature to CPT code: 0402T.
05-05-2021	Updated Description section.
	Updated Rationale section.
	Updated References section.
05-04-2022	Updated Description Section
	Updated Policy Guidelines ▪ Section A updated to read: "The American Academy of Ophthalmology has not set forth definitive criteria defining progressive keratoconus but has suggested

REVISIONS	
	that signs of progression include changes in refraction, visual acuity and corneal shape (https://eyewiki.aao.org/Corneal_Collagen_Cross-Linking). In the trials leading to FDA approval of corneal collagen cross-linking, progressive keratoconus or corneal ectasia were defined as one or more of the following"
	Updated Rationale Section
	Updated Coding Section ▪ Converted ICD-10 codes to ranges
	Update References Section
07-01-2022	Updated Coding Section ▪ Updated nomenclature for 0402T
04-25-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed ICD-10 Codes
	Updated References Section
04-23-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section
04-23-2025	Updated Description Section
	Updated Rationale Section
	Updated References Section
Posted: 05-14-2026 Effective: 06-15-2026	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Added code J3490
	Updated References Section

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