Corneal cross-linking

Clinical Policy ID: CCP.1415

Recent review date: 5/2025

Next review date: 9/2026

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

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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 the following criteria are met (Cortina, 2024; Jhanji, 2024; U.S. Food and Drug Administration, 2016).

- To treat documented progressive keratoconus or corneal ectasia after refractive surgery (Cortina, 2024).
- Progressive disease must be documented by serial measurements over time demonstrating worsening based on at least two of the following within the prior 12 months (Cortina, 2024; Jhanji, 2024)
  - Increase in maximum keratometry (Kmax) ≥ 1.0 Diopter (D);
  - Increase in posterior corneal elevation ≥ 15 µm;
  - Reduction in minimum pachymetry ≥ 10 µm;
  - Increase in manifest cylinder or spherical equivalent ≥ 1.0 D;
  - Steepening of the anterior corneal surface;
  - Steepening of the posterior corneal surface; or

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- o Corneal thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point.
- For members under 18, topography every three to 6 months is recommended. Because of rapid disease velocity in this group, corneal cross-linking should be initiated promptly at the first objective sign of progression (Cortina, 2024; Jhanji, 2024).
- After conservative interventions have failed.
  - o When rapid progression is present, corneal cross-linking may be performed without prior failure of conservative interventions when the treating clinician determines that conservative measures are unlikely to stop disease progression (such as documented progression exceeding an increase in maximum keratometry of 1.0 Diopter within 6 months).

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

Limitations

Relative contraindications to corneal cross-linking are (Jhanji, 2024):

- Corneal stromal thickness below 400 µm.
- Prior herpes simplex virus keratitis.
- Significant central corneal stromal scarring that would impede treatment effectiveness or visualization.
- Severe, uncontrolled ocular-surface disease.
- Active autoimmune disorders known to affect corneal healing or cause corneal thinning.

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 gas-permeable contact lenses to reshape the cornea (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 carry a higher risk of rejection and may yield poorer visual outcomes, 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 typically prescribed following the procedure; topical steroids may also be necessary in some cases. 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

Clinical Guidelines

Clinical guidelines establish corneal cross-linking (CXL) as a primary intervention for keratoconus and corneal ectasia, providing foundational recommendations for its application. The American Academy of Ophthalmology's 2022 Preferred Practice Pattern confirms that CXL reduces the risk of progressive ectasia in early-stage keratoconus, stabilizes the cornea without age restrictions, and mitigates post-keratorefractive surgery ectasia, recommending follow-up every three to 6 months, particularly for younger patients (American Academy of Ophthalmology, 2022). The 2023 Corneal Ectasia Preferred Practice Pattern reinforces CXL as the preferred treatment for progressive keratoconus, emphasizing early intervention to preserve visual acuity and listing contraindications such as corneal thickness below 400 μm, prior herpes simplex virus keratitis, corneal scarring, severe ocular surface disease, and autoimmune disorders associated with corneal thinning (Jhanji, 2024). It highlights that standard CXL effectively slows progression in pediatric patients, who face more aggressive disease.

European guidelines affirm CXL's safety and efficacy in improving visual acuity and topographic indices since its introduction in the 1990s (Alio, 2015; Andreanos, 2017). Additional guidance from the American Academy of Ophthalmology in 2018 and 2021, along with a 2024 technology assessment of six randomized controlled trials (average 2.4 years follow-up), confirms CXL's ability to halt progression, with improvements in uncorrected distance visual acuity (UDVA) across all trials and corrected distance visual acuity (CDVA) in several, noting rare complications such as infectious keratitis (0.6%, 2/347 eyes) and CDVA loss of two or more lines (4.6%, 16/347 eyes) (American Academy of Ophthalmology, 2018; American Academy of Ophthalmology, 2021; Cortina, 2024).

Systematic Reviews

Systematic reviews synthesize qualitative evidence on CXL's outcomes, focusing on protocol comparisons and procedural variations. A 2024 review of 27 studies (n = 1,399) confirmed that both epithelium-off and epithelium-on CXL stabilize keratoconus progression, with epithelium-off yielding superior UDVA outcomes (Borchert, 2024). Another 2024 review of 29 studies (n = 2,866 eyes) found no significant outcome differences between pulsed and continuous CXL protocols, suggesting flexibility in energy delivery methods (Qureshi, 2025). These reviews highlight the consistency of CXL's stabilizing effects across diverse protocols, though variations in visual outcomes depend on procedural specifics.

Meta-Analyses

Meta-analyses provide quantitative evidence by pooling data to compare corneal cross-linking (CXL) protocols, with standard epithelium-off CXL often outperforming modified approaches. A 2017 analysis of 24 studies found standard CXL more effective than modified protocols, such as transepithelial or accelerated CXL, in delaying maximum keratometry (Kmax) deterioration (P = .03) (Liu, 2017). It also reported a significant reduction in spherical equivalent (P < .00001). A 2021 analysis of 12 studies (n = 966, mean age 23.88 years, SD 9.03) showed transepithelial CXL was inferior to epithelium-off CXL in Kmax change at 12 months (P = .004) and longest follow-up (P < .001) (Nath, 2021). Despite fewer complications (P = .020), transepithelial CXL had higher progression rates (P = .022), with similar UDVA (P = .386) and CDVA (P = .732) outcomes. A 2017 analysis of three randomized controlled trials (n = 244 eyes) confirmed standard CXL reduced Kmax more effectively than transepithelial CXL at 12 months (Li, 2017). Transepithelial CXL achieved greater CDVA improvement, but UDVA and safety profiles were similar. A 2019 analysis of seven studies (n = 283 eyes) reported accelerated CXL reduced average keratometry more than standard CXL (P < .01) (Jiang, 2019).

Other outcomes showed no significant differences. Another 2019 analysis of 22 studies (n = 1,158 eyes) showed standard CXL outperformed accelerated CXL in minimum keratometry (P < .00001) and demarcation line depth (P < .00001) (Shajari, 2019). Accelerated CXL was better for minimum corneal thickness (P = .0005). A 2018 analysis of 11 studies found epithelium-off and transepithelial CXL superior in Kmax reduction, while accelerated CXL improved central corneal thickness and endothelial cell density (Wen, 2018). A 2024 analysis of 14 randomized controlled trials (n = 614 eyes) found conventional CXL achieved greater Kmax flattening (SMD 0.302) than accelerated CXL (Yeh, 2025). Visual acuity and endothelial cell counts were similar. A 2023 analysis of four studies (n = 329 eyes) showed a 10-minute accelerated CXL protocol outperformed a 5-minute protocol in keratometry (P < .00001), corneal high-order aberration (P = .0002), and corneal coma (P = .00001) (Karam, 2023). A 2022 analysis of oxygen-enhanced epithelium-on CXL, analyzing five of six studies (n unspecified), reported a 1.2-Diopter Kmax reduction (95% CI 0.2 to 2.3, P = .02) and CDVA improvement (0.08 logMAR, 95% CI 0.02 to 0.13, P = .01) after six months, with no serious adverse events (Borchert, 2022

Meta-analyses also evaluate CXL combined with other procedures, demonstrating enhanced outcomes. A 2018 analysis of 17 studies found no differences in CDVA or cylindrical refractive error after 12 months among groups combining intracorneal ring segments (ICRS) and CXL on the same day, ICRS first, or CXL first (Hashemi, 2018). A 2019 analysis of 95 studies (n = 4,560) showed combined ICRS, CXL, and photorefractive keratectomy (PRK) outperformed ICRS alone in all measures except spherical equivalent correction, supporting its use in young patients (Benoist d'Azy, 2019). A 2025 analysis of eight non-randomized studies (n = 731 eyes) found combined customized PRK and CXL improved UDVA, CDVA, refractive cylinder, and higher-order aberrations compared to CXL alone, with similar progression rates over 6–44 months (Zhang, 2025).

Specific populations, such as pediatric patients and those with post-refractive surgery ectasia, benefit from CXL, as shown in targeted meta-analyses. A 2022 analysis in pediatric patients (37 studies, n = 2,078 eyes) calculated a 9.9% progression risk after standard CXL (95% CI 6.1% to 14.6%, P < .0001) based on Kmax, Kmean, or Ksteep increases ≥ 1.0 Diopter (Achiron, 2022). Another 2022 pediatric analysis (11 studies, n = 888 eyes) found standard CXL improved CDVA more than accelerated CXL at 24 months (P = .03), with higher adverse effects

but comparable other outcomes (Li, 2022). A 2024 analysis of 15 studies (n = 421) confirmed CXL's efficacy in post-refractive surgery ectasia, improving CDVA (SMD 0.33) and Kmax (SMD 0.15) (Amaral, 2024).).

Other Evidence

Observational studies and other evidence provide critical long-term data on CXL's effectiveness and limitations. A 2022 retrospective case series (n = 131 eyes, 44 followed for 10 years) confirmed CXL slows or halts keratoconus progression and improves CDVA, but non-response rates increased from 16% at 5 years to 33% at 10 years, with risk factors including young age, high astigmatism (> 4.3 D), thin cornea (< 480 μm), poor initial CDVA (≥ 0.3 D), and atopic dermatitis (Seifert, 2022). A 2023 multinational registry study (n = 976 eyes at year 1, 162 at year 5) reported significant CDVA improvements from baseline at year 1 (3.7 logMAR letters, P < .001) and year 5 (6.9 logMAR letters, P < .001), with keratometry stabilizing after year 1, though 4.1% of patients had reduced CDVA and 5.9% to 7.5% showed poor keratometric responses (Ferdi, 2023). A 2021 Cochrane review reinforced CXL's efficacy and safety, aligning with prior findings (Ng, 2021).

A quality assessment of systematic reviews for corneal disease treatments validated the reliability of the synthesized evidence, supporting its use in policy development (Saldanha, 2019). Standard epithelium-off CXL, using the Dresden protocol, effectively halts mild to moderate keratoconus progression across age groups, improving CDVA, UDVA, and Kmax, particularly benefiting younger patients by delaying corneal transplantation. Modified protocols, such as transepithelial and accelerated CXL, show comparable visual outcomes but are less effective at halting progression, though transepithelial CXL reduces complications like postoperative pain, subepithelial haze, sterile infiltration, and infectious keratitis. Further research is needed to optimize protocols for pediatric patients, corneas thinner than 400 μm, and combinations with other surgical procedures.

In 2025, we reorganized the findings section and added five new systematic reviews and meta-analyses on corneal collagen crosslinking for ectasia after refractive surgery (Amaral, 2024), epithelium-on versus epithelium-off corneal collagen crosslinking (Borchert, 2024), pulsed corneal collagen crosslinking (Qureshi, 2025), accelerated versus conventional corneal collagen crosslinking (Yeh, 2025), and customized photorefractive keratectomy combined with corneal collagen crosslinking (Zhang, 2025)—as well as updated guidance from the American Academy of Ophthalmology (Cortina et al., 2024; Jhanji et al., 2024). Policy changes were made as the result of new guidelines.

References

On April 8, 2025, 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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