Corneal cross-linking

Clinical Policy ID: CCP.1415

Recent review date: 5/2026

Next review date: 9/2027

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

    - 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.
    - 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 consistently support corneal cross-linking as the preferred intervention for progressive keratoconus and corneal ectasia, particularly when used early. The American Academy of Ophthalmology's 2022 Preferred Practice Pattern states that corneal cross-linking reduces the risk of progression in early keratoconus, stabilizes the cornea across age groups, and may mitigate ectasia after refractive surgery, with closer follow-up every three to 6 months for younger individuals (American Academy of Ophthalmology, 2022). The Corneal Ectasia Preferred Practice Pattern further identifies progressive keratoconus as the clearest indication for treatment and lists important contraindications, including corneal thickness below 400 micrometers, prior herpes simplex virus keratitis, corneal scarring, severe ocular surface disease, and autoimmune disorders associated with corneal thinning (Jhanji, 2024).

European guidance and later updates from the American Academy of Ophthalmology also support the safety and efficacy of corneal cross-linking and continue to identify standard epithelium-off treatment as the best-supported approach for halting progression (Alio, 2015; Andreanos, 2017; American Academy of Ophthalmology, 2018, 2021; Cortina, 2024). A 2024 technology assessment of six randomized controlled trials with an average 2.4 years of follow-up found improvement in uncorrected distance visual acuity across all trials and improvement in corrected distance visual acuity in several, while reporting rare complications such as infectious keratitis in 0.6% of eyes, or two of 347 eyes, and loss of two or more lines of corrected distance visual acuity in 4.6% of eyes, or 16 of 347 eyes (Cortina, 2024). Overall, guideline-level evidence supports early treatment, careful patient selection, and ongoing follow-up, with particular relevance for children, adolescents, and other individuals at risk of rapid progression.

Systematic reviews

Systematic reviews support corneal cross-linking as an effective treatment for stabilizing keratoconus and show that outcomes are generally consistent across protocols, although not equivalent. A 2024 review of 27 studies with n = 1,399 found that both epithelium-off and epithelium-on treatment stabilized progression, but epithelium-off treatment produced better uncorrected distance visual acuity outcomes (Borchert, 2024). Another recent review of 29 studies with n = 2,866 eyes found no significant difference between pulsed and continuous protocols, suggesting some flexibility in energy delivery methods without clear evidence of reduced effectiveness (Qureshi, 2025).

Taken together, systematic reviews support the effectiveness of corneal cross-linking while indicating that standard epithelium-off treatment remains more consistently associated with favorable visual and topographic outcomes.

Meta-analyses

Meta-analyses provide the strongest pooled comparative evidence and generally show that standard epithelium-off corneal cross-linking is more effective than modified approaches in halting progression. A 2017 analysis of 24 studies found standard treatment more effective than modified protocols, such as transepithelial or accelerated treatment, in delaying deterioration in maximum keratometry, with P = .03, and in reducing spherical equivalent, with P < .00001 (Liu, 2017). A 2021 analysis of 12 studies with n = 966 and mean age 23.88 years, standard deviation 9.03, found that transepithelial treatment was inferior to epithelium-off treatment in change in maximum keratometry at 12 months, with P = .004, and at longest follow-up, with P < .001 (Nath, 2021). Despite fewer complications, with P = .020, transepithelial treatment had higher progression rates, with P = .022, while uncorrected distance visual acuity, with P = .386, and corrected distance visual acuity, with P = .732, were similar. A 2017 analysis of three randomized controlled trials with n = 244 eyes likewise found that standard treatment reduced maximum keratometry more effectively than transepithelial treatment at 12 months, although transepithelial treatment achieved greater improvement in corrected distance visual acuity and showed similar uncorrected distance visual acuity and safety profiles (Li, 2017).

Comparisons between accelerated and conventional treatment are more mixed, but the overall direction of evidence still favors conventional treatment for keratometric stability. A 2019 analysis of seven studies with n = 283 eyes reported that accelerated treatment reduced average keratometry more than standard treatment, with P < .01, while other outcomes showed no significant differences (Jiang, 2019). In contrast, a 2019 analysis of 22 studies with n = 1,158 eyes found that standard treatment outperformed accelerated treatment in minimum keratometry, with P < .00001, and demarcation line depth, with P < .00001, while accelerated treatment was better for minimum corneal thickness, with P = .0005 (Shajari, 2019). A 2018 analysis of 11 studies found better reduction in maximum keratometry with epithelium-off and transepithelial treatment, while accelerated treatment improved central corneal thickness and endothelial cell density (Wen, 2018). A 2024 analysis of 14 randomized controlled trials with n = 614 eyes found that conventional treatment achieved greater flattening in maximum keratometry than accelerated treatment, with standardized mean difference (SMD) 0.302, while visual acuity and endothelial cell counts were similar (Yeh, 2025). A 2023 analysis of four studies with n = 329 eyes found that a 10-minute accelerated protocol outperformed a 5-minute protocol in keratometry, with P < .00001, corneal high-order aberration, with P = .0002, and corneal coma, with P = .00001 (Karam, 2023). A 2022 analysis of oxygen-enhanced epithelium-on treatment that included five studies reported a 1.2-diopter reduction in maximum keratometry, with 95% confidence interval (CI) 0.2 to 2.3 and P = .02, and improvement in corrected distance visual acuity of 0.08 logarithm of the minimum angle of resolution, with 95% CI 0.02 to 0.13 and P = .01, after six months, with no serious adverse events (Borchert, 2022).

Meta-analyses also suggest that combined procedures may improve refractive and visual outcomes in selected individuals. A 2018 analysis of 17 studies found no difference in corrected distance visual acuity or cylindrical refractive error after 12 months among groups treated with intracorneal ring segments and corneal cross-linking

on the same day, intracorneal ring segments first, or corneal cross-linking first (Hashemi, 2018). A 2019 analysis of 95 studies with n = 4,560 found that combined intracorneal ring segments, corneal cross-linking, and photorefractive keratectomy outperformed intracorneal ring segments alone in all measures except spherical equivalent correction (Benoist d'Azy, 2019). A 2025 analysis of eight nonrandomized studies with n = 731 eyes found that combined customized photorefractive keratectomy and corneal cross-linking improved uncorrected distance visual acuity, corrected distance visual acuity, refractive cylinder, and higher-order aberrations compared with corneal cross-linking alone, with similar progression rates over 6 to 44 months (Zhang, 2025). In children and adolescents, a 2022 analysis of 37 studies with n = 2,078 eyes found a 9.9% progression risk after standard treatment, with 95% CI 6.1% to 14.6% and P < .0001, based on increases in maximum keratometry, mean keratometry, or steep keratometry of at least 1.0 diopter (Achiron, 2022). Another 2022 analysis of 11 studies with n = 888 eyes found that standard treatment improved corrected distance visual acuity more than accelerated treatment at 24 months, with P = .03, with higher adverse effects but otherwise comparable outcomes (Li, 2022). A 2024 analysis of 15 studies with n = 421 confirmed effectiveness in ectasia after refractive surgery, improving corrected distance visual acuity, with SMD 0.33, and maximum keratometry, with SMD 0.15 (Amaral, 2024).

Meta-analytic evidence also supports the posterior segment safety of corneal cross-linking. A 2025 systematic review and meta-analysis of 10 studies involving 233 eyes from 215 participants found no clinically meaningful retinal or choroidal changes after treatment. The pooled analysis found no significant change in central macular thickness at one month, with Hedges g = -0.15, 95% CI -0.44 to 0.13, and P = .30, or at six months, with Hedges g = -0.12, 95% CI -0.47 to 0.22, and P = .48. It also found no significant change in subfoveal choroidal thickness at one month, with Hedges g = -0.14, 95% CI -0.45 to 0.17, and P = .37 (Bayat, 2025). Reported abnormalities were generally transient and more consistent with postoperative inflammation or medication effects than phototoxic injury. Overall, pooled evidence supports standard epithelium-off corneal cross-linking as the best-supported approach for stabilizing progression, while modified or combined protocols may offer advantages in selected circumstances.

Other evidence

Observational studies provide important long-term and real-world evidence on durability and nonresponse. A retrospective case series of 131 eyes, with 44 eyes followed for 10 years, found that corneal cross-linking slowed or halted progression and improved corrected distance visual acuity, although nonresponse increased from 16% at five years to 33% at 10 years. Risk factors for nonresponse included younger age, high astigmatism greater than 4.3 diopters, corneal thickness below 480 micrometers, poor initial corrected distance visual acuity of at least 0.3 logarithm of the minimum angle of resolution, and atopic dermatitis (Seifert, 2022). A multinational registry study reported significant improvement in corrected distance visual acuity from baseline at year one in 976 eyes, with 3.7 logarithm of the minimum angle of resolution letters and P < .001, and at year five in 162 eyes, with 6.9 letters and P < .001. Keratometry stabilized after year one, although 4.1% of individuals had reduced corrected distance visual acuity and 5.9% to 7.5% showed poor keratometric response (Ferdi, 2023).

Other supporting evidence aligns with these findings and supports the reliability of the broader evidence base for policy development (Ng, 2021; Saldanha, 2019). Overall, the evidence base is substantial and is anchored by clinical guidelines, multiple systematic reviews and meta-analyses, and longer-term observational follow-up. The general findings support standard epithelium-off corneal cross-linking, particularly the Dresden protocol, as an effective treatment for mild to moderate progressive keratoconus and corneal ectasia across age groups. Modified protocols may improve tolerability or convenience, but they are generally less effective at halting progression. Important knowledge gaps remain for treatment optimization in children and adolescents, corneas thinner than 400 micrometers, long-term retreatment risk, and the best use of combined surgical approaches.

In 2026, we added a systematic review and meta-analysis on retinal and choroidal changes following corneal collagen cross-linking, which found no clinically meaningful retinal or choroidal changes after treatment (Bayat, 2025).

References

On April 11, 2026, 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.
5/2025: Policy references updated.
5/2026: Policy references updated.

Related codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1415 This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code description
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