Collagen Cross-Linking in Individuals With Keratoconus

Health Technology Assessment

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Glossary

AAO	American Academy of Ophthalmology
CHIP	Children's Health Insurance Program
CI	confidence interval
CoE	certainty of evidence
corneal ectasia	a condition that affects the clear, outermost layer of the eye that gradually changes the shape of the cornea (i.e., thins and bulges outward)
corneal hydrops	an uncommon complication in advanced keratoconus with sudden onset of corneal swelling from a rupture in the Descemet membrane that can cause impaired vision and pain
corneal tomography	imaging technique that evaluates the anterior and posterior surfaces of the cornea, and corneal thickness
corneal topography	imaging technique that evaluates the anterior surface of the cornea
CDVA	corrected distance visual acuity, measured with high accuracy and consistency using the logarithm of the minimal angle of resolution (logMAR)
CXL	collagen cross-linking
epithelium	a protective layer of tissue. In this report, we refer to the epithelium on the eye, and the standard procedure of the intervention of interest includes removing part of the epithelium in order to deliver the riboflavin solution; the removed area of the epithelium regenerates postprocedure
FDA	US Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HCPCS	Healthcare Common Procedure Coding System
ICER	incremental cost-effectiveness ratio
keratitis	inflammation of the cornea, which can cause moderate to intense pain and impaired eyesight
keratometry	the measurement of the corneal curvature. This is measured in diopters, which are calculated from the radii of curvature; meaningful change in maximal keratometry includes a reduction of 1.5 diopters or more
keratoplasty	a type of corneal transplant that includes the surgical excision of diseased or scarred corneal tissue and its replacement by a cornea from a human donor. Penetrating keratoplasty is a corneal transplant procedure involving

	replacement of the full thickness of the cornea with a donor cornea of equivalent thickness
logMAR	the logarithm of the minimum angle of resolution. A value of zero indicates standard vision, a negative value indicates good vision, and a positive value indicates poor vision. Low vision is defined as best-corrected visual acuity of 0.5 logMAR, and legal blindness in the US is defined as 1.0 logMAR or worse in the better eye
N	number
NCT	US National Clinical Trial
NICE	National Institute for Health and Care Excellence
NR	not reported
OR	odds ratio
pachymetry	measurement of corneal thickness
PiXL	photorefractive intrastromal crosslinking
QALY	quality-adjusted life year
RCT	randomized controlled trial
SD	standard deviation
UCVA	uncorrected visual acuity, measured with high accuracy and consistency using the logarithm of the minimal angle of resolution (logMAR)
UK	United Kingdom
US	United States
UVA	ultraviolet A (light)

Executive Summary

Background

Keratoconus is a progressive disease where thinning of the cornea leads to increased corneal curvature and decreased visual acuity that is not easily corrected with standard glasses or contact lenses.[1,2] Due to the high likelihood of disease progression and its negative impacts on visual acuity, it is important to diagnose and treat keratoconus as early as possible.[2-5] Prevalence estimates vary, but they suggest that about 0.04% of Medicaid and Children's Health Insurance Program participants may be diagnosed with keratoconus by the end of adolescence.[6] Recent developments in diagnostic tools have improved the ability to diagnose early keratoconus and to monitor for signs of progression during childhood and adolescence.[7] Standard care for individuals with keratoconus may include correcting visual acuity with rigid gas-permeable lenses or glasses in the early stages, and more invasive interventions in later stages of progression such as collagen cross-linking (CXL), penetrating keratoplasty (a type of corneal transplant), and regrafting for eyes that continue to need treatment.[8,9] The CXL procedure with ultraviolet A (UVA) light and riboflavin (vitamin B_2) is intended to slow or halt the progression of the disease.[10,11] The UVA light device and riboflavin eye drops for the standard CXL protocol were approved in 2016 by the US Food and Drug Administration.[12,13]

Key Questions

KQ1. What is the clinical effectiveness of CXL for individuals with keratoconus?

KQ2. What are the harms of CXL for individuals with keratoconus?

KQ3. What are the results of relevant cost analysis studies related to providing CXL for individuals with keratoconus?

KQ4. What are clinical practice guideline recommendations for the use of CXL in individuals with keratoconus?

KQ5. What are relevant Medicaid program coverage policies and private payer policies for individuals with keratoconus?

Methods

Researchers from the Center for Evidence-based Policy (Center) searched Ovid MEDLINE and other clinical evidence sources for randomized controlled trials (RCTs), registry studies, cost and cost-effectiveness studies, and clinical practice guidelines. Using a priori criteria, we conducted dual independent title and abstract screening and full-text article review for articles published in the English language. Detailed inclusion and exclusion criteria are listed in Appendix B. Two researchers assessed the included RCTs for risk of bias, using standard forms. A third researcher settled discrepancies as needed. Where sufficient data were available, we estimated pooled effect measures with meta-analyses of data abstracted from the included studies and reported the findings with figures, tables, and text. We applied the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to rate the certainty of evidence for each outcome.

We searched 10 state Medicaid program websites, 9 private payer websites, and the Centers for Medicare & Medicaid Services website for local and national coverage determinations of CXL for keratoconus.

Summary of Clinical Evidence and Recommendations Findings

We identified 7 publications from 5 eligible trials that compared standard CXL with no treatment, sham surgery, or standard care,[14-20] 1 publication from a registry study for safety outcomes,[21] 1 publication of a cost analysis study,[22] and 2 clinical practice guidelines.[23,24] Table 1 presents a summary of findings for standard CXL versus no treatment, sham surgery, or standard care; and for additional trials that reported serious adverse events. It is followed by a summary of a cost-effectiveness study and summary of the 2 clinical practice guidelines.

Table 1. Summary of Findings (GRADE):
Standard CXL vs. No Treatment, Sham Surgery, or Standard Care

Outcome Number of Studies Participant N	Certainty of Evidence (CoE)	Relationship	Rationale for CoE Rating
Corrected distance visual acuity (CDVA) 5 RCTs[14,15,17,18,20] Total, N = 265 • Standard CXL, N = 136 • Control group, N = 129	●○○○ Very Low	Standard CXL was associated with: • Significantly greater improvement in CDVA at 12 months (total N = 141; mean difference in logMAR, −0.07; 95% CI, −0.08 to −0.06; *P* < .001; based on a meta-analysis of 2 RCTs)[a] • No significant difference between groups at 36 months (total N = 120; mean difference in logMAR, −0.10; 95% CI, −0.22 to 0.01; *P* = .08; based on a meta-analysis of 2 RCTs)[a] • Overall, the results of the meta-analyses were mixed over time, and similar mixed results were reported in data from trials at additional time points for CDVA	Downgraded 1 level for risk of bias, 1 level for imprecision (i.e., small sample sizes), and 1 level for inconsistency
Uncorrected visual acuity (UCVA) 4 RCTs[15,17,18,20] Total, N = 239 • Standard CXL, N = 122 • Control group, N = 117	●○○○ Very Low	Standard CXL was associated with: • Significantly greater improvement in UCVA at 12 months (total N = 70; mean difference in logMAR, −0.20; 95% CI, −0.21 to −0.19; *P* < .001; based on a meta-analysis of 2 RCTs)[a] • Overall, the data from all 4 trials that reported UCVA indicated inconsistent effects across time points	Downgraded 1 level for risk of bias, 1 level for imprecision (i.e., small sample sizes), and 1 level for inconsistency

Outcome Number of Studies Participant N	Certainty of Evidence (CoE)	Relationship	Rationale for CoE Rating
Maximal keratometry 4 RCTs[14,15,17,20] Total, N = 219 • Standard CXL, N = 115 • Control group, N = 104	●○○○ Very Low	Standard CXL was associated with: • Significantly greater improvement in maximal keratometry at 12 months (total N = 141; mean difference in diopters, −1.92; 95% CI, −2.01 to −1.83; *P* < .001; based on a meta-analysis of 2 RCTs). The estimated mean difference between the groups exceeded the threshold for the minimum clinically important difference for maximal keratometry, which is a change of 1.5 diopters • No statistically significant mean difference between the 2 groups at 36 months (N = 120; mean difference in diopters, −1.63; 95% CI, −3.90 to 0.64; *P* = .16) • Overall, the results of the meta-analyses and data from other reported time points not included in the meta-analyses were mixed over time	Downgraded 1 level for risk of bias, 1 level for imprecision (i.e., small sample sizes), and 1 level for inconsistency
Patient-reported visual function 1 RCT[15] Total, N = 54 • Standard CXL, N = 29 • Control group, N = 25	●○○○ Very Low	No significant differences between the groups, as measured by 2 validated instruments	Downgraded[b] 1 level for risk of bias and 2 levels for imprecision (i.e., small sample sizes)
Serious adverse events 12 RCTs[14,15,17-20,25-32] Total eyes, N = 418 • Standard CXL, N = 297 • Control groups, N = 121 1 registry study[21] • Total eyes (all CXL), N = 976	●○○○ Very Low	Some RCTs reported rare serious adverse events associated with CXL. Where they did occur, they were scarring, infiltrates, or microbial keratitis. No serious adverse events were reported in the control groups. Of the 976 eyes in the registry study, 13 eyes underwent a second CXL operation within 5 years; 6 eyes developed microbial keratitis; 5 eyes had recurrent erosion; 3 eyes had sterile infiltrates; and 28 had scarring by the 1-year follow-up.	Downgraded 1 level for risk of bias and 2 levels for imprecision (very low rate of events)

Notes. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.* [b] *Unable to rate for inconsistency. For methods and interpretation of GRADE ratings, see Appendix F.*

Abbreviations. CI: confidence interval; CXL: collagen cross-linking; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; logMAR: logarithm of the minimum angle of resolution; N: number of participants; RCT: randomized controlled trial.

Cost and Cost-Effectiveness

We identified 1 cost-effectiveness study with a high risk of bias that used data from a US-based trial comparing standard CXL against a control group that crossed over to standard CXL treatment at 3 months after baseline.[22] Cost model results suggested that beginning treatment with standard CXL, instead of penetrating keratoplasty after lenses and glasses ceased to adequately address vision concerns, was associated with a reduction in direct medical costs (lifetime cost for CXL group, $30,944; lifetime cost for no-CXL group, $39,671) and more quality-adjusted life years (QALYs; CXL group QALYs, 21.8; no-CXL group QALYs, 19.93; mean difference, 1.88; no between-group test for significance reported).[22] The authors reported that the incremental cost-effectiveness ratio was cost-effective at $1,526 per QALY gained against a maximum willingness-to-pay of $150,000 per QALY gained.[22] In relation to the treatment pathway assumptions, the model estimated that the group of individuals that received CXL was 25.9% less likely to have penetrating keratoplasty and was likely to spend 27.9 fewer years in advanced disease stages.[22]

Clinical Practice Recommendations

A fair-methodological-quality preferred practice pattern guideline published in 2018 by the American Academy of Ophthalmology concluded that standard CXL stabilizes the cornea and reduces risk for progression in individuals with keratoconus.[23] This document also emphasized the importance of early diagnosis and treatment.[23]

A fair-methodological-quality interventional procedure guidance written for the National Institute for Health and Care Excellence (NICE) published in 2013 found low- and very-low-quality research to support the safety and efficacy of standard CXL for individuals with keratoconus.[24] This document was the basis for a NICE guidance recommendation that stated the evidence was sufficient in quantity and quality for the safety and efficacy of CXL for keratoconus.[33]

Key Policy Findings

We identified relevant coverage policies related to CXL from Aetna, Anthem Blue Cross and Blue Shield (formerly Empire BlueCross BlueShield), Capital District Physicians' Health Plan, Cigna, Highmark BlueShield of Northeastern New York, Tufts Health Plan, UnitedHealthcare, and from the Medicaid programs in California, Oregon and Washington state:

- 8 policies required that the keratoconus be documented as progressive[34-41]
- 2 policies required that the individual fail conservative treatment (i.e., spectacle correction, rigid contact lens ceased to adequately correct visual acuity) before being considered a candidate for CXL[35,36]
- Ineligibility criteria included individuals with active or a history of herpes simplex virus keratitis, thin corneas, corneal hydrops, visual disturbance from a significant central corneal opacity or other eye disease (e.g., neurotrophic keratopathy), or history of corneal or systemic disease that would interfere with healing after the procedure such as chemical injury or delayed epithelial healing in the past[34,35,37]
- 5 policies noted that individuals must be 14 years or older,[34,35,37,42] and 3 of these policies limited the maximum age to 64 or 65 years of age[34,37,42]

Conclusions

Based on the evidence in this report, we concluded that there is very low certainty of evidence that CXL improved visual acuity, maximal keratometry, or patient-reported visual function, or that CXL was associated with rare serious adverse events for individuals with progressive keratoconus. The limited number of trials, short length of follow-up, small sample sizes, high clinical and methodological heterogeneity, insufficient reporting of methods and results, and moderate to high risk of bias of included trials should be considered when drawing conclusions about the certainty of evidence for standard CXL for keratoconus. It is likely that new research will change our understanding of the effectiveness of CXL for keratoconus.

Meta-analysis results were mixed: 3 of the 5 meta-analyses favored standard CXL and included visual acuity and maximal keratometry measures. All 3 of these meta-analyses included data from 12-month time points, and the other 2 meta-analyses that did not favor either condition included data from later time points, which could indicate that there was an early benefit to CXL that faded over time. Very little information about patient-reported visual function was reported in the included studies. Most individuals who underwent standard CXL did not report any serious adverse events. Infrequent serious adverse events for standard CXL included keratitis, sterile infiltrates, and scarring that affected the vision of some individuals but not others.

It is not clear how durable improvements in visual acuity and maximal keratometry are for individuals with keratoconus. There were no analyses that directly reported on the relationship between participant characteristics (e.g., age at receipt of CXL, severity of disease progression) and vision outcomes. However, several insurance providers and 2 state Medicaid programs currently cover CXL for individuals with keratoconus, and both clinical guidance documents we identified from American Academy of Ophthalmology (AAO) and NICE supported the use of CXL for individuals with keratoconus.

Overall, we have very low certainty in these results and new research is likely to change our understanding of CXL for keratoconus in the future.

Background

Keratoconus is a progressive disease that increases corneal curvature, decreasing visual acuity. Collagen cross-linking (CXL) with riboflavin (vitamin B_2) ophthalmic solution and ultraviolet A (UVA) light is a procedure intended to slow or halt the progression of the disease. The following sections describe the CXL intervention and condition of keratoconus in detail and address the following contextual questions:

- What is the epidemiology of keratoconus?
- What are the barriers to diagnosis of keratoconus?
- Where is the place of CXL in the clinical care pathway for individuals diagnosed with keratoconus?
- What are the health equity considerations for providing CXL for individuals with keratoconus?

Description of the Condition

Keratoconus, from the Greek words *kerato* (cornea) and *konos* (cone), is a progressive disorder characterized by progressive corneal thinning and steepening.[1,2] Corneal ectasias are a group of conditions that cause the cornea to thin and bulge outward. In keratoconus, the central or paracentral cornea thins, which leads to corneal steepening and cone-like protrusion.[43,44] These changes contribute to regular, then irregular, astigmatism, loss of visual acuity, corneal scarring, and rarely, corneal hydrops (acute onset corneal swelling due to aqueous humor entering the stroma).[44] Keratoconus is considered a bilateral condition, although it may be asymmetric.[45]

Etiology

The etiology of keratoconus remains unknown.[1,4,43] The pathophysiology of keratoconus is likely a combination of genetic, environmental, biomechanical, and biochemical factors.[1] Although the majority of keratoconus cases are sporadic, autosomal dominant with incomplete penetrance and autosomal recessive modes of inheritance have been described.[2,46] Genome-wide association studies have identified multiple loci associated with keratoconus.[47-49] First-degree relatives of individuals with keratoconus have a higher risk of developing the condition than the general population.[2,46] In a meta-analysis of risk factors for keratoconus, individuals with a family history of keratoconus had a higher risk of developing the disease (odds ratio [OR], 6.42; 95% confidence interval [CI], 2.59 to 10.24).[50]

Keratoconus is associated with several systemic and ocular conditions, including Down syndrome, connective tissue disorders (e.g., Ehlers-Danlos syndrome, Marfan syndrome), Leber congenital amaurosis, retinitis pigmentosa, and corneal dystrophies (e.g., Fuchs endothelial dystrophy, posterior polymorphous corneal dystrophy).[1,2,10,46,51] Diabetes has been suggested to have a protective role against the development and progression of keratoconus, possibly due to glycosylation of corneal fibers and a subsequent auto crosslinking effect.[51-54] Results of studies evaluating the effect of diabetes on keratoconus have been mixed, and the association between the two, if one exists, has yet to be defined.[51]

Eye rubbing has consistently been identified as a risk factor for keratoconus,[1,2,50,51,55,56] which has been confirmed by 2 meta-analyses.[50,57] The mechanisms by which eye rubbing contributes to the development of keratoconus are complex and multifactorial, but likely include mechanical trauma, increased corneal temperature, increased tissue pressure, and abnormal enzyme

activity.[2,56] Triggers of excessive eye rubbing—such as atopic conditions like allergic rhinitis, ocular allergy, and atopic dermatitis[1,51]; dust in the working environment[55]; and dry environmental conditions[58]—have also been associated with keratoconus. It is unclear whether atopy alone is also a risk factor for keratoconus, or whether it is the behaviors related to atopy, in particular eye rubbing, that are the risk factors.[51] Globally, the prevalence of keratoconus has typically been higher in the Middle East,[50,58-61] Asia,[62,63] and Australia[64,65] than in the US[6,66,67] and Europe.[68,69] Environmental factors, in particular dry conditions and high annual sunshine hours, may contribute to the high prevalence of keratoconus in these regions.[58] Such conditions may lead to frequent eye rubbing and prolonged exposure to UV light, a source of oxidative stress for the eye.[58]

Prevalence

Prevalence estimates of keratoconus vary widely. This variation has been attributed to the genetic variability among populations, increased sensitivity of diagnostic devices over time, differences in diagnostic criteria, and differences in study design (in particular population selection).[58,68,70,71] A recent study of patients enrolled in Medicaid and the Children's Health Insurance Program (CHIP) reported a national prevalence of keratoconus of 0.04% in 2019.[6] Other estimates of keratoconus prevalence in the US have ranged from 0.175 per 1,000 individuals[67] in a national sample of Medicare beneficiaries (individuals 65 years of age or older) from 1999 to 2003, to 5.45 per 1,000 individuals[66] among residents of Olmsted County, Minnesota, from 1935 through 1982. Studies of keratoconus typically report a higher prevalence in males than females,[54,66] although a few studies have reported a higher prevalence in females,[6,72] or no gender difference in prevalence.[50,67]

Individuals with Down syndrome have a higher risk of keratoconus. A literature review on the prevalence of keratoconus in individuals with Down syndrome included 19 studies with prevalence ranging from 0% to 71%.[73] The 4 studies that reported a prevalence of 0% only included pediatric patients aged 18 years or younger (aged 14 years or younger, in 2 studies) and were published before 2008, before the widespread availability and use of advanced imaging technologies that allow earlier detection of keratoconus.[73] Data from the Norway Patient Registry from 2010 to 2019 showed a prevalence of keratoconus of 5.5% among individuals with Down syndrome.[74]

Diagnosis

Clinical Presentation

Keratoconus usually becomes apparent in early adolescence, although clinical signs and symptoms may develop earlier or later, and progresses into the 20s and 30s.[2,4] Progression of keratoconus is variable for each patient and eye, but the condition rarely progresses beyond 40 years of age as the cornea stiffens roughly linearly with age.[3,4,10,75] Some authors have reported that younger age at presentation is associated with more severe disease and with higher rate and speed of progression, necessitating early diagnosis and intervention to prevent severe visual impairment.[3,5]

Ocular symptoms of keratoconus vary depending on the severity of the disease. Patients in the incipient stage typically have no symptoms.[2] Patients with keratoconus often present with a history of frequent changes in eyeglasses prescription that do not adequately correct vision, or

progression from soft contact lenses to rigid gas-permeable lenses.[4] Patients with keratoconus may also describe blurred or distorted vision, glare, and photophobia.[10] Patients presenting with acute corneal hydrops describe sudden pain and loss of vision.[10]

Ophthalmic Examination

Clinical signs of keratoconus detectable on ophthalmic examination often do not appear until later in the course of the disease.[76] An early (and sensitive) sign of keratoconus on retinoscopy is the scissoring reflex, in which the light reflex is split into separate bands that move back and forth like the blades on a pair of scissors.[2,4,10,77,78] Another sign of keratoconus on retinoscopy is an annular dark shadow, also known as the Charleaux or oil droplet sign, which is distinguished by a bright reflex at the conical apex with a surrounding dark circular shadow.[78,79] Later signs of keratoconus, observed on external examination in advanced stages of the disease, are Munson sign and Rizzuti sign.[2,4,10] Munson sign is a V-shaped deformation of the lower eyelid caused by the cone when the eye is in the downward position.[2,10] Rizzuti sign is a conical reflection on the nasal sclera when light is directed on the cornea from the temporal side.[2,4,10]

Slit lamp examination may reveal the Fleischer ring, a yellow or brown ring around the base of the cone, caused by deposition of hemosiderin (iron deposits) from the tear film onto the cornea due to changes in the corneal curvature and normal epithelial slide process.[2,10] Other findings on slit lamp examination include Vogt striae, corneal thinning, and visualization of the corneal nerves.[2,4,10] Vogt striae are vertical lines running from the posterior to anterior stroma, which disappear when pressure is applied to the cornea.[2,4,80] Vogt striae can occur in individuals with healthy eyes, but they tend to be few, short, and oblique, while in eyes with keratoconus, striae are numerous and vertical.[80]

Advanced Diagnostics

Modern corneal imaging devices allow for improved characterization of the cornea.[7] These devices can broadly be divided into 2 categories: anatomic imaging devices (which include corneal topography and corneal tomography) and biomechanical imaging devices.[7] Corneal topography provides qualitative and quantitative information about the anterior surface of the cornea.[10,81,82] The most commonly used systems in corneal topography are Placido disk–based videokeratoscopes.[7,82] These systems use photographs of Placido disk reflections off the tear film of the anterior surface of the cornea to generate color-coded curvature maps using computational technology.[82,83] Placido disk–based corneal topography can detect ectatic disease (i.e., conditions that cause a cornea to thin and bulge outward) in individuals with relatively normal corrected distance visual acuity, and before slit lamp findings develop.[83] However, corneal topography does not detect all individuals with subclinical keratoconus.[82]

Corneal topography only images the anterior surface of the cornea. Corneal tomography allows for 3-dimensional visualization of the anterior and posterior surfaces of the cornea, along with assessment of corneal thickness (pachymetry).[10,45] Abnormalities, such as stromal thinning and elevation changes, can be seen on the posterior cornea before topographic changes on the anterior surface, making tomography a reliable method for detecting early keratoconus.[10] The 2015 Global Consensus on Keratoconus and Ectatic Diseases panel concluded that tomography "is currently the best and most widely available test to diagnose early keratoconus."[1(p363)] The panel noted that posterior corneal elevation changes must be present to detect mild or

subclinical keratoconus.[1] Some corneal tomography devices also incorporate corneal wavefront technology, which models the passage of light through the cornea.[7] An irregularly shaped cornea will distort the passage of light.[7]

Biomechanical imaging devices characterize and predict changes in corneal structure over time.[45] These devices measure dynamic changes to the cornea after an air impulse and use this information to determine corneal biomechanical properties.[7] Minor changes in the shape of the cornea can lead to clinically significant changes in biomechanical parameters.[45]

In 2023, the American Academy of Ophthalmology (AAO) published an Ophthalmic Technology Assessment on the use of corneal tomography and functional biomechanical imaging in the diagnosis of keratoconus.[7] This assessment found that all anatomic locations (anterior cornea, posterior cornea, pachymetry) and devices were effective (i.e., high sensitivity, specificity and area under the curve) for detecting frank keratoconus.[7] The authors of this assessment concluded that while corneal topography, which was reviewed in an earlier AAO Ophthalmic Technology Assessment published in 1999,[81] remains a valuable diagnostic modality, newer technologies add to the diagnostic armamentarium by providing information beyond anterior surface curvature as well as combined metrics to predict the likelihood of keratoconus.[7] These newer devices and their calculated parameters were not as adept at detecting keratoconus suspects as they were at detecting frank keratoconus.[7] The authors observed that the suspect keratoconus population remains a diagnostic challenge.[7]

Potential barriers to CXL are discussed in the health equity considerations section of this report, but a relevant consideration for advanced diagnostics is whether the Medicaid program in New York covers these diagnostic procedures. The fee for Current Procedural Terminology (CPT) code 92132 (scanning computerized ophthalmic diagnostic imaging, anterior segment, with interpretation and report, unilateral or bilateral) was listed as $27.80 for non-facility global fee and $17.36 for facility global fee, and the fee for CPT code 92025 (computerized corneal topography, unilateral or bilateral, with interpretation and report) was listed as $31.97 for non-facility global fee, $24.87 for facility global fee, and $14.61 for professional component fee.[84,85]

Staging

While several staging systems for keratoconus exist, there is no single widely accepted system. Older classification systems, such as the Amsler-Krumeich system, fail to incorporate current information and technological advances, while newer systems, such as the Belin ABCD classification system, may depend on the use of specific devices and software.[1,86-88] Contributing to the difficulty of developing a unified classification system for keratoconus is a lack of consensus definitions for different stages of the disease.[7,89] For example, the terms forme fruste, suspect, and subclinical are all used to describe eyes that do not have frank keratoconus.[7] Among the studies included in a systematic review of forme fruste and subclinical keratoconus, the most common definition for forme fruste keratoconus was an eye with normal slit lamp examination and topographic findings, and keratoconus in the other eye.[89] The most common definition for subclinical keratoconus was an eye with normal slit lamp examination, abnormal or suspicious topographic findings, and keratoconus in the other eye.[89]

Progression and Monitoring

Defining progression and determining the appropriate interval for follow-up in patients with keratoconus has also been challenging.[90] In 2024, Koppen and colleagues observed that "there is no consensus whatsoever on how to define [keratoconus] progression."[90(p2)] These authors concluded that a one-size-fits-all definition for progression may not be appropriate for keratoconus.[90] Clinical trials evaluating CXL efficacy have used various combinations of parameters to define and measure progression.[90]

Challenges in defining progression include difficulty distinguishing normal variability in the diagnostic device from meaningful change, sometimes confusing longitudinal trends in the disease, and in some cases, worsening repeatability of measures with increasing severity of disease.[90] The 2015 Global Consensus on Keratoconus and Ectatic Diseases panel defined ectasia progression as consistent change in at least 2 of the following parameters: steepening of the anterior corneal surface; steepening of the posterior corneal surface; or thinning or increase in the rate of corneal thickness change from the periphery to the thinnest point.[1] The panel agreed that examination intervals should be shorter for younger patients, although a specific age recommendation was not provided.[1] A 2019 systematic review and meta-analysis explored the natural progression of keratoconus in patients who had not been treated for the condition and were followed for at least 6 months.[91] The authors of this study recommended that patients with keratoconus who are under the age of 17 years and who have steeper than normal baseline maximum keratometry be monitored closely and have a lower threshold for CXL.[91]

The AAO Preferred Practice Pattern guideline on corneal ectasias, including keratoconus, recommends that patients be rechecked every 3 to 6 months for progression, with younger patients (age not specified) possibly requiring more frequent evaluation.[23] The AAO noted that annual follow-up used to be recommended for patients with corneal ectasias, but the potential for early intervention with CXL warrants more frequent follow-up.[23]

Treatment

Treatment of keratoconus depends on the severity of the disease and patient characteristics, such as age and the presence of comorbidities.[10,45] Treatment approaches focus on controlling precipitating risk factors, restoration of vision, and correction or restoration of corneal integrity.[92] Patients with keratoconus are advised to avoid eye rubbing.[93] Topical mast cell stabilizers, antihistamines, or combination products may be prescribed to control ocular pruritus (itch), while topical lubricants are prescribed to alleviate dry eye symptoms.[93]

In patients with early keratoconus, eyeglasses may be used to improve vision associated with astigmatism.[8] Often, vision cannot be adequately corrected with eyeglasses due to factors associated with the disease, including high irregular astigmatism and anisometropia (difference in refractive power between the 2 eyes).[8] If eyeglasses cannot sufficiently manage the astigmatism, then contacts lenses are used.[8] The type of lens depends on the patient and the stage of keratoconus, with soft or soft toric lenses used early in the disease and rigid gas-permeable or specialized lenses, such as scleral lenses, used as the disease progresses.[8,10]

As keratoconus progresses, other treatment modalities are used either alone or in combination with one another. Intrastromal corneal ring segments (e.g., Intacs corneal implants) are medical

devices implanted into the corneal stroma to alter the morphology and refractive power of the cornea by reshaping its curvature.[8,45] Intrastromal corneal ring segments can improve vision and enhance the integrity of the cornea.[92] The segments are typically made of a synthetic material, such as polymethylmethacrylate.[45] A procedure using allogenic human donor cornea stromal segments for the implant material has been described.[9,94] Intrastromal corneal ring segments can be implanted at the same time as CXL, or the 2 procedures may be staggered.[95-106] Another procedure that may be combined with CXL in patients who are intolerant to contact lenses and have poor visual acuity is photorefractive or phototherapeutic keratectomy.[9,107-124] Photorefractive and phototherapeutic keratectomies are excimer laser-based procedures to correct refractive errors and manage anterior corneal pathologies.[125,126]

When less-invasive treatment strategies are not effective, patients with keratoconus may require corneal transplantation (keratoplasty).[10] Patients may undergo penetrating (full-thickness) keratoplasty or deep anterior lamellar keratoplasty.[8,10] In penetrating keratoplasty, the patient's cornea is completely removed and replaced with a donor cornea.[8,10] Deep anterior lamellar keratoplasty is a partial-thickness corneal transplant in which only the anterior portion of the cornea is replaced, leaving Descemet's membrane and the endothelium in place.[10,127]

Intervention of Interest

The CXL procedure with UVA light and riboflavin is designed to slow the progression of keratoconus.[45,128] In this procedure, riboflavin eye drops serve as a photosensitizer and UVA light is used to induce the formation of chemical bonds between fibers in the cornea, thereby improving the biomechanical strength of the cornea.[45] Wollensak and colleagues first described the use of CXL in individuals with keratoconus in a 2003 pilot study.[11] In their method, which came to be known as the Dresden protocol, the central corneal epithelium was removed, riboflavin solution was applied to the eye before and throughout irradiance, and UVA light was administered to the eye at 3 mW/cm^2 for 30 minutes.[11]

Since CXL was first described, several modifications to the original epithelium-off (or "epi-off," so named because the central corneal epithelium is removed during the procedure) method have been investigated in an attempt to reduce procedure times and minimize side effects. These modifications include using higher UVA intensities for shorter time periods in accelerated CXL and leaving the corneal epithelium intact in epithelium-on ("epi-on") or transepithelial cross-linking.[129-133] Several manufacturers are currently developing systems for use in epithelium-on[134-138] or pharmacologic[45,139] CXL.

The US Food and Drug Administration (FDA) approved iLink (Glaukos Corporation, Aliso Viejo, California), a CXL procedure that uses riboflavin ophthalmic solutions (Photrexa and Photrexa Viscous) and a UVA light source (the KXL System), for treatment of progressive keratoconus and post–refractive surgery corneal ectasia in 2016.[140,141] Photrexa and Photrexa Viscous, in combination with the KXL System, are approved for use in patients 14 years and older.[13,140,141] Patients younger than 14 years were not eligible for the clinical trials on which FDA approval was based (see Appendix E for further discussion of these trials),[12,142] although CXL has been performed in patients younger than this age.[143-145] The CXL procedure should not be performed on women who are pregnant.[13] Progressive keratoconus is not defined in either the FDA summary reviews for regulatory action[140,141] on Photrexa, Photrexa Viscous, and the KXL System

or the prescribing information[13] for Photrexa and Photrexa Viscous. In the clinical trials on which FDA approval was based, progressive keratoconus was defined as change in 1 or more of the following parameters over 24 months: increase of 1 diopter or more in steepest keratometry measurement, increase of 1 diopter or more in manifest cylinder, increase of 0.5 diopter or more in manifest refraction spherical equivalent.[12,146]

The iLink procedure uses the Dresden protocol methodology, which requires a minimal corneal thickness of 400 micrometers.[75,147] The CXL procedure may be performed in cases where corneal thickness is less than 400 µm (micrometers), with modifications to the procedure.[75,148] One such modification is the use of a hypoosmolar riboflavin solution, such as Photrexa, to swell the cornea to 400 µm before application of the UVA light.[13,75] Photrexa and Photrexa Viscous are supplied as single-use 3 mL glass syringes containing 1.46 mg/mL riboflavin 5'-phosphate ophthalmic solution and 1.56 mg/mL riboflavin 5'-phosphate in 20% dextran ophthalmic solution, respectively.[13]

Collagen cross-linking is typically performed as an outpatient procedure with topical anesthesia in an office setting. Some patients (e.g., children, patients with special needs) may require general anesthesia in a hospital setting, as the procedure requires the patient to remain still for a period of time.[148-150] The total procedure time for the FDA-approved iLink procedure is typically 1 hour or more.[148] After the procedure, a bandage contact lens is placed over the eye and left in place until corneal re-epithelialization is complete.[27,125,151-154]

Health Equity Considerations

Researchers have recently begun to probe the relationship between keratoconus and socioeconomic factors. In 2016, Woodward and colleagues published a study of patients with keratoconus, and their age-, sex-, and overall health–matched controls, from a nationwide US managed care network for the years 2001 through 2012.[54] In this study, neither education level nor personal income was associated with keratoconus.[54] Individuals residing in large rural communities had lower odds of keratoconus than those residing in urban communities; a similar trend was noted for small rural populations.[54] The authors hypothesized that the lower odds of keratoconus in rural populations may indicate failure to detect individuals with mild or subclinical disease due to lack of access to corneal specialists.[54] The authors also proposed that the lower odds of keratoconus in individuals residing in rural communities may be due to less exposure to environmental pollutants that exacerbate eye rubbing.[54]

In 2023, Ahmad and colleagues published a retrospective review examining the social determinants of health for patients with keratoconus at the University of California San Francisco.[52] Among the 725 included patients, the majority were male (65%), were non-White (55%), identified English as their primary language (94%), and were either employed or retired (65%).[52] Twenty percent of patients were insured by Medicaid, 17% were insured by Medicare, and the remainder were insured by private payers (63%).[52] In multivariate analysis, patients who were insured by Medicaid were significantly more likely to be diagnosed with severe keratoconus at presentation than patients who had private insurance (OR, 1.94; 95% CI, 1.12 to 3.35; $P = 0.017$).[52] Patients insured by Medicaid or Medicare were significantly more likely to require corneal transplantation than those who had private insurance.[52] This association was explored further in a post-hoc analysis, which revealed that patients insured by Medicaid were

significantly more likely to receive CXL and less likely to receive rigid gas-permeable or scleral lenses than patients with private insurance.[52] One likely explanation for this finding is that at the time the study was conducted, CXL was covered by Medicaid in California, while rigid gas-permeable and scleral lenses were not.[52] It is also possible that Medicaid patients presented with more severe disease, necessitating intervention with CXL.[52] The authors of this study noted that "socioeconomic factors were more consistent predictors of keratoconus severity on presentation, progression, and corneal transplantation compared with clinical factors that have received relatively greater attention in the keratoconus literature."[52(p62)]

Another recent retrospective study at a university-based ophthalmology practice also sought to unravel the relationship between race, socioeconomic status, and severity of keratoconus.[155] This study included patients with untreated keratoconus who were seen at 10 community-based and tertiary care sites associated with the Johns Hopkins Wilmer Eye Institute in Baltimore, Maryland.[155] Race was self-reported as Asian, Black, Native Alaskan, Native American, Pacific Islander, White, other, or unknown (individuals who identified as Native American, Native Alaskan, or Pacific Islander were combined with those who identified as other for the analysis).[155] The primary outcome was visual impairment.[155] Among the included patients, Black individuals had the highest median national area deprivation index (a multifactorial measure of social advantage and disadvantage), with a higher score correlating to more social disadvantage.[155] The proportion of individuals insured by Medicaid was highest among Black patients (18.2% insured by Medicaid), followed by other (12.6%), unknown (12.6%), White patients (4.1%), and Asian patients (3.6%).[155] Among patients who had corneal tomography within 6 months of presentation, Black patients had the highest mean maximum keratometry and lowest mean thinnest pachymetry, followed by those who identified as other or unknown race.[155] This finding suggested that Black patients with keratoconus presented with more severe disease.[155] Black patients were more likely than White patients to have visual impairment at presentation.[155] Patients insured by Medicaid or Medicare were also more likely than those with private insurance to have visual impairment at presentation.[155] The authors of this study suggested that their findings indicate a need for targeted screening programs that allow for early detection of, and intervention for, keratoconus in certain populations.[155]

In addition to exploring the relationship between socioeconomic factors and keratoconus severity and progression, several recent studies have examined disease knowledge in patients (and parents of patients) with keratoconus.[156-158] Patient knowledge of ophthalmic disease might help patients recognize and seek care in a timely way to avoid increased loss of visual acuity[159,160]; low patient knowledge may be a barrier to timely intervention. Studies of patient knowledge of keratoconus in Switzerland, the US, and the UK have shown consistently low disease knowledge, even among patients with university degrees, medical backgrounds, and long time since diagnosis,[157,158] and it is likely worse for socioeconomically disadvantaged families.[156] The low disease knowledge demonstrates a need for improved awareness of, and education about, keratoconus for individuals with and at risk for developing the condition.[158] The overall lack of knowledge about keratoconus in patients with this condition may make shared decision-making between patients and physicians difficult, leading to inefficient delivery of, and misunderstandings about, care.[157] The low disease knowledge also suggests a need for improvement in interdisciplinary patient care and sharing of information among health care providers such as contact lens specialists, ophthalmologists, and corneal specialists.[158]

Key Questions

The following key questions are addressed in the clinical evidence review and payer policies sections:

KQ1. What is the clinical effectiveness of CXL for individuals with keratoconus?

   a. Does clinical effectiveness vary by patient characteristics (e.g., age, sex), disease characteristics (e.g., pediatric vs. adult diagnosis, early vs. progressive disease), method (e.g., epithelium-off vs. epithelium-on protocols, standard vs. accelerated), provider characteristics, or setting?

KQ2. What are the harms of CXL for individuals with keratoconus?

   a. Do the harms vary by patient characteristics (e.g., age, sex), disease characteristics (e.g., pediatric vs. adult diagnosis, early vs. progressive disease), method (e.g., epithelium-off vs. epithelium-on protocols, standard vs. accelerated), provider characteristics, or setting?

KQ3. What are the results of relevant cost analysis studies related to providing CXL for individuals with keratoconus?

KQ4. What are clinical practice guideline recommendations for the use of CXL in individuals with keratoconus?

KQ5. What are relevant Medicaid program coverage policies and private payer policies for individuals with keratoconus?

Contextual Questions

Information that we identified to answer the following contextual questions is summarized in the Background section:

CQ1. What is the epidemiology of keratoconus?

CQ2. What are the barriers to diagnosis of keratoconus?

CQ3. Where is the place of CXL in the clinical care pathway for individuals diagnosed with keratoconus?

CQ4. What are the health equity considerations for providing CXL for individuals with keratoconus?

PICO (for KQ1 and KQ2)

Populations

Individuals with keratoconus

Interventions

CXL with UVA and riboflavin, including the Dresden protocol and any modified protocols

Comparators

No treatment; standard care; head-to-head comparisons of epithelium-off versus epithelium-on protocols for CXL; treatments to promote visual rehabilitation without adjunctive CXL (e.g.,

scleral contact lens, intracorneal ring segments, toric intraocular collamer lens, deep anterior lamellar keratoplasty, and laser-based treatments)

Outcomes

Keratometry (critical outcome); corrected or uncorrected distance visual acuity (critical outcome); patient-reported subjective visual function parameters (important outcome); serious adverse events, including corneal perforation and infection (important outcome)

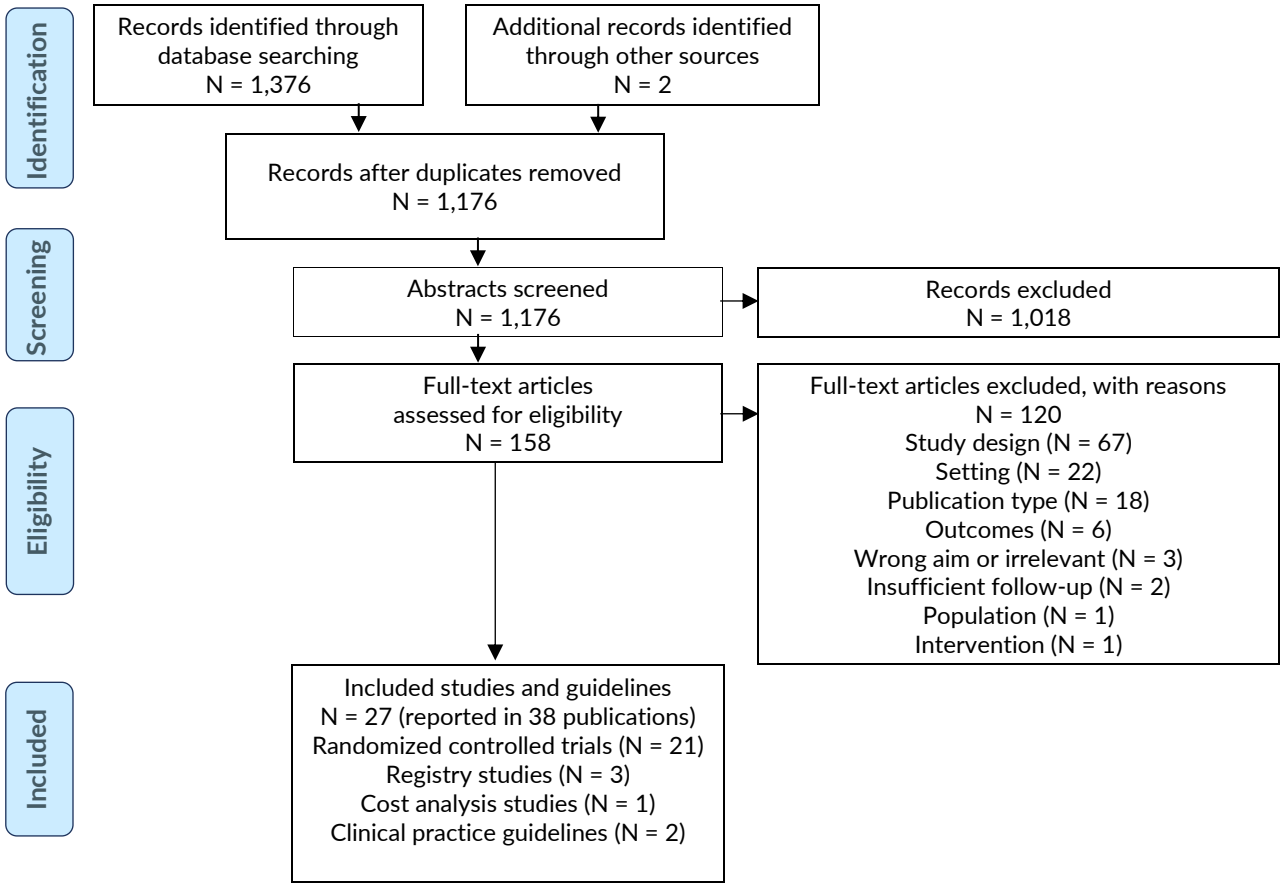
Methods

Evidence and Policy Searches

Researchers from the Center for Evidence-based Policy (Center) searched 10 state Medicaid program websites, 9 private payer websites, and the Centers for Medicare & Medicaid Services for local and national coverage determinations of CXL for keratoconus, and identified 10 relevant coverage policies. Appendix A lists search terms we used to identify relevant policies, and all sources searched.

We searched Ovid MEDLINE, Cochrane Database of Systematic Reviews via the Cochrane Library, and other databases and information sources for randomized controlled trials (RCTs), registry studies, cost and cost-effectiveness studies, and clinical practice guidelines. We identified 1,378 potentially relevant publications for the Key Questions of clinical evidence and clinical practice guidelines (Figure 1). We also searched trial registries for relevant ongoing trials. A full list of sources searched and the search strategies are listed in Appendix A. We did not conduct systematic searches to identify publications to answer contextual questions.

Figure 1. PRISMA Diagram With Details



Screening and Inclusion

Two Center researchers used the systematic review software platform DistillerSR to screen publications identified in the searches using the detailed inclusion and exclusion criteria listed in Appendix B. Disagreement about inclusion was resolved through discussion. Appendix D lists included studies, and Appendix E lists studies excluded during full text screening along with the primary reason each study was excluded. Figure 1 shows the numbers of studies screened and included or excluded at each step.

Risk of Bias Assessment

Two Center researchers assessed each included RCT and cost analysis study for risk of bias using standard forms. Two researchers also assessed the methodological quality of each included clinical practice guideline. Appendix F has detailed tables with criteria considered for assessing risk of bias or methodological quality. Disagreement between the researchers was resolved through discussion.

Data Abstraction

One Center researcher used a standard form to extract all data presented in tables in this report and used for the meta-analyses, and a second researcher checked each data point against the information in the publication from which it was abstracted to ensure accuracy.

Synthesis

Where sufficient data were available (i.e., same collection time points and method of measuring the specified outcome), we estimated pooled effect measures with meta-analyses of data abstracted from the included studies and reported the findings with figures, tables, and text. We used RevMan[161] (Review Manager) version 5.4 software to conduct meta-analyses. Figures generated during these meta-analyses appear throughout the report. For the meta-analyses, we used random effects models due to the methodological diversity (e.g., interventions for comparison groups, varied equipment used for surgery and outcome measurement) and clinical diversity (e.g., keratoconus progression of participants) of included studies that contributed to high heterogeneity. Random effects models assume that the studies measured related, but different, effects of an intervention.[162,163] We noted the I^2 statistic in each estimated meta-analysis as an indicator of statistical heterogeneity, but we did not use it as a criteria for selecting random effects models over fixed effect models because the I^2 estimate can be biased in meta-analyses with 7 or fewer studies (i.e., likely underestimates the true statistical heterogeneity).[164] The I^2 estimate can be found in each meta-analysis figure in this report; 9 meta-analyses reported I^2 of 0%, 2 reported I^2 of 35% to 56%, and 5 reported I^2 of greater than 70%.

For outcomes without sufficiently similar data across multiple studies, we provide a qualitative synthesis and tables as necessary. We applied the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to rate the certainty of evidence for each outcome from the data we abstracted from the trials that compared standard CXL with no treatment, sham surgery, or standard care. We only applied GRADE to that category of trials because the standard CXL procedure is the only procedure used in nonresearch settings in the US.

Clinical Evidence Review

We identified 27 publications from 21 eligible trials with effectiveness and safety outcomes, 3 registry studies for safety outcomes, 1 publication of a cost analysis study, 2 clinical practice guidelines reported in 4 publications, and 13 relevant ongoing trials. The clinical evidence review is organized by key question, then by comparison group, and finally by outcome.

This review focuses on standard CXL compared with no treatment, sham, or standard care (5 trials)[14,15,17,18,20] because standard CXL is currently the only approved protocol that uses both the riboflavin solution and the UVA light device. The other CXL protocols are considered experimental, and we summarize findings from trials of those protocols by comparing them with standard CXL. Four RCTs[165-168] compared standard CXL with accelerated CXL, 10 trials compared standard epithelium-off protocols with epithelium-on protocols,[25,26,29-32,169-172] a single RCT compared 2 different accelerated protocols,[173] and a single RCT compared photorefractive intrastromal crosslinking (PiXL) with standard CXL.[28]

Table 2 presents the study characteristics of the 21 included trials. Nineteen trials limited inclusion to individuals with progressive keratoconus,[15,17,20,25,26,28-32,165-173] and 2 trials only included participants with early or moderate keratoconus.[14,18] Ages of included participants ranged from 10 to 51 years. Six trials included children or adolescents (2 with only pediatric participants),[15,17,28,31,167,173] and 19 trials included adults (14 with only adult participants).[14,17,18,20,25,26,28-32,165,166,168-173]

Ten trials had high risk of bias,[14,17,25,26,30,166,168-171] 10 trials had moderate risk of bias,[15,18,20,26,28,29,31,32,165,167,172] and 1 trial had low risk of bias.[173] Across trials, the frequent reasons for downgrading the risk of bias included lack of participant and assessor masking, incomplete reporting of analytic methods (e.g., intent-to-treat analysis not clearly conducted, number of eyes or participants analyzed at each time point, loss to follow-up), and declarations of conflicts of interest or lack of details about funding and potential conflicts of interest.

Included trials typically listed the following exclusion criteria:

- Minimal corneal thickness of less than 400 µm
- Inability to discontinue contact lens use before baseline and follow-up ophthalmologic exam (e.g., 3 to 4 weeks for rigid gas-permeable lenses and 1 to 2 weeks for soft lenses)
- Corneal scarring, nystagmus, or other condition that prevented a fixed gaze during examination
- History of keratitis, recurrent infections, corneal hydrops, prior corneal surgery, or other ocular disorders (e.g., cataract, glaucoma)
- Comorbid autoimmune disease
- Current pregnancy or breastfeeding

Table 2. Characteristics of Included RCTs

Primary Publication Author, Year Additional Publications Trial Identifier Total Follow-Up Study Location Funding Source	Population Description N Randomized Participants (Eyes) N Analyzed Participants (Eyes) Age	Risk of Bias Outcomes of Interest Reported
Standard CXL vs. no treatment, sham, or standard care		
Lang et al., 2015[14] NCT00626717 36 months Germany Peschke Meditrade GmbH	Adults with progressive keratoconus at an early stage (i.e., correction possible with lenses) Randomized N = 29 (29 eyes) Analyzed N = 29 (29 eyes) Age range, 19 to 38 years	High risk of bias Outcomes: • Visual acuity • Maximal keratometry • Serious adverse events
Larkin et al., 2021[15] Larkin et al., 2021b[16] KERALINK ISRCTN17303768 18 months UK National Institute for Health Research Efficacy and Mechanism Evaluation Programme	Pediatric patients between 10 and 16 years of age with progressive keratoconus Randomized N = 60 (60 eyes) Analyzed N = 53 (53 eyes) Mean age, 15.2 years (SD, 1.4)	Moderate risk of bias Outcomes: • Visual acuity • Maximal keratometry • Patient-reported visual function • Serious adverse events
Meyer et al., 2021[17] ACTRN12608000367347 60 months New Zealand Maurice and Phyllis Paykel Trust	Adults and adolescents aged 14 years or more with bilateral, progressive keratoconus Randomized N = 38 (74 eyes) Analyzed N = 21 (30 eyes) Mean age, 21.1 years (SD, 6.7)	High risk of bias Outcomes: • Visual acuity • Maximal keratometry • Serious adverse events

Primary Publication Author, Year Additional Publications Trial Identifier Total Follow-Up Study Location Funding Source	Population Description N Randomized Participants (Eyes) N Analyzed Participants (Eyes) Age	Risk of Bias Outcomes of Interest Reported
O'Brart et al., 2011[18] ISRCTN08013636 18 months UK No source of funding listed	Adults with early or moderate bilateral keratoconus with no recent progression Randomized N = 24 (48 eyes) Analyzed N = 22 (44 eyes) Age range, 21 to 42 years	Moderate risk of bias Outcomes: • Visual acuity • Serious adverse events
Wittig-Silva et al., 2008[20] Wittig-Silva et al., 2014[19] NR 36 months Australia Royal Victorian Eye and Ear Hospital Research Committee, Eye Research Australia Foundation, and Keratoconus Australia, with loan of device from Institute of Refractive and Ophthalmic Surgery	Adults between the ages of 16 and 50 years with progressive keratoconus Randomized N = 50 (100 eyes) Analyzed N = 47 (94 eyes) Age range, 19 to 31 years	Moderate risk of bias Outcomes: • Visual acuity • Maximal keratometry • Serious adverse events
Standard CXL versus accelerated CXL		
Burcel et al., 2022[166] NR 24 months Romania No funding source listed	Adults with progressive keratoconus Randomized N = 62 (79 eyes) Analyzed N = 62 (79 eyes) Age range, 18 to 30 years	High risk of bias Outcomes: • Visual acuity • Maximal keratometry
Eissa et al., 2019[167] NR 36 months Saudi Arabia No funding source listed	Pediatric patients of less than 16 years of age with bilateral, progressive keratoconus Randomized N = 34 (68 eyes) Analyzed N = NR Age range, 9 to 16 years	Moderate risk of bias Outcomes: • Visual acuity • Maximal keratometry
Hagem et al., 2017[168] Hagem et al., 2019[174] NCT02883478 24 months Norway No funding source listed	Adults with progressive keratoconus Randomized N = 40 (40 eyes) Analyzed N = 32 (32 eyes) Age range, NR	High risk of bias Outcomes: • Visual acuity • Maximal keratometry
Uçakhan and Yeşiltaş, 2020[165] NR 24 months Turkey No funding source listed	Adults with progressive keratoconus Randomized N = 64 (64 eyes) Analyzed N = 59 (59 eyes) Age range, 19 to 30 years	Moderate risk of bias Outcomes: • Visual acuity • Maximal keratometry

Primary Publication Author, Year Additional Publications Trial Identifier Total Follow-Up Study Location Funding Source	Population Description N Randomized Participants (Eyes) N Analyzed Participants (Eyes) Age	Risk of Bias Outcomes of Interest Reported
Standard epithelium-off CXL vs. protocols with epithelium-on CXL		
Bikbova and Bikbov, 2016[171] NCT02456961 24 months Russia State Academy of Science of Republic Bashkortostan	Adults with progressive keratoconus Randomized N = 119 (149 eyes) Analyzed N = NR Age range, 18 to 48 years	High risk of bias Outcome: • Visual acuity
Caruso et al., 2021[25] NCT05019768 24 months Italy No funding listed	Adults with progressive keratoconus Randomized N = 41 (54 eyes) Analyzed N = NR Age range, 18 to 35 years	High risk of bias Outcomes: • Visual acuity • Maximal keratometry • Serious adverse events
Cifariello et al., 2018[170] NCT01350323 24 months Italy No funding listed	Adults with progressive keratoconus Randomized N = 32 (40 eyes) Analyzed N = NR Age range, 15 to 44 years	High risk of bias Outcome: • Visual acuity
Lombardo et al., 2016[175] Lombardo et al., 2017[26] Lombardo et al., 2019[27] NCT02117999 24 months Italy Device loan from Sooft Italia SpA, and no other funding source listed	Adults with progressive keratoconus Randomized N = 25 (35 eyes) Analyzed N = 25 (35 eyes) Age range, 25 to 37 years	High risk of bias Outcomes: • Visual acuity • Maximal keratometry • Serious adverse events
Napolitano et al., 2022[169] NR 24 months Italy No funding source listed	Adults with progressive keratoconus Randomized N = 49 (64 eyes) Analyzed N = NR Mean age, 26 (SD, 4.2)	High risk of bias Outcomes: • Visual acuity • Maximal keratometry • Patient-reported visual function
Rossi et al., 2015[29] NR 12 months Italy No funding source listed	Adults with progressive keratoconus Randomized N = 20 (20 eyes) Analyzed N = 20 (20 eyes) Age range, 22 to 42 years	Moderate risk of bias Outcomes: • Visual acuity • Maximal keratometry • Serious adverse events
Rossi et al., 2018[30] NR 12 months	Adults with progressive keratoconus Randomized N = 30 (30 eyes)	High risk of bias Outcomes: • Visual acuity

Primary Publication Author, Year Additional Publications Trial Identifier Total Follow-Up Study Location Funding Source	Population Description N Randomized Participants (Eyes) N Analyzed Participants (Eyes) Age	Risk of Bias Outcomes of Interest Reported
Italy No funding source listed	Analyzed N = 30 (30 eyes) Age range, 21 to 33 years	• Serious adverse events
Rush and Rush, 2016[31] NCT01708538 24 months US No funding source listed	Adult or pediatric patients with progressive keratoconus, pellucid marginal degeneration, or post–refractive surgery ectasia Participants with keratoconus randomized N = 102 Participants with keratoconus analyzed = NR Age range, 11 to 58	Moderate risk of bias Outcomes: • Visual acuity • Serious adverse events
Soeters et al., 2015[32] Godefrooij et al., 2017[176] NCT02349165 12 months Netherlands Dr. F.P. Fischer Stichting Company and Stichting Nederlands Oogheelkundig Onderzoek	Adults with progressive keratoconus Randomized N = 61 (61 eyes) Analyzed N = 61 (61 eyes) Age range, 18 to 48 years	Moderate risk of bias Outcomes: • Visual acuity • Maximal keratometry • Serious adverse events
Stojanovic et al., 2014[172] NCT01181219 12 months Norway SynsLaser Surgery AS and Norwegian Research Council	Adults with bilateral, progressive keratoconus Randomized N = 20 (40 eyes) Analyzed N = NR Age range, 19 to 51 years	Moderate risk of bias Outcomes: • Visual acuity • Maximal keratometry
Standard CXL vs. PiXL		
Nordström et al., 2016[28] NCT02514200 12 months Sweden KMA Fund and Ögonfonden	Adolescents and adults with progressive keratoconus Randomized N = 37 (50 eyes) Analyzed N = 35 (48 eyes) Age range, 16 to 50 years	Moderate risk of bias Outcomes: • Visual acuity • Maximal keratometry • Serious adverse events
Accelerated protocol vs. accelerated protocol		
Kirgiz et al., 2019[173] NR 12 months Turkey No funding source listed	Pediatric and adult patients with progressive keratoconus Randomized N = 66 (66 eyes) Analyzed N = NR Age range, 14 to 38 years	Low risk of bias Outcomes: • Visual acuity • Maximal keratometry

Abbreviations. CXL: collagen cross-linking; N: number; NR: not reported; PiXL: photorefractive intrastromal crosslinking; RCT: randomized controlled trial; SD: standard deviation; UK: United Kingdom; US: United States of America; vs.: versus.

GRADE Summary of Effectiveness and Safety of Standard CXL vs. Control

Table 3 presents a summary of the effectiveness and safety outcomes from the 5 trials that compared standard CXL with no treatment, sham surgery, or standard care; and for the other trials that reported serious adverse events. Detailed findings from those trials are described in the Effectiveness and Safety sections of this report.

Table 3. Summary of Findings (GRADE): Standard CXL vs. No Treatment, Sham Surgery, or Standard Care

Outcome Number of Studies Participant N	Certainty of Evidence (CoE)	Relationship	Rationale for CoE Rating
Corrected distance visual acuity (CDVA) 5 RCTs[14,15,17,18,20] Total N from all 5 studies reporting this outcome = 265 • Standard CXL N = 136 • Control group N = 129	●○○○ Very Low	Standard CXL was associated with: • Significantly greater improvement in CDVA at 12 months (total N = 141; mean difference in logMAR, −0.07; 95% CI, −0.08 to −0.06; *P* < .001; based on a meta-analysis of 2 RCTs)[a] • No significant difference between groups at 36 months (total N = 120; mean difference in logMAR, −0.10; 95% CI, −0.22 to 0.01; *P* = .08; based on a meta-analysis of 2 RCTs)[a] • Overall, the results of the meta-analyses were mixed over time, and similar mixed results were reported in data from trials at additional time points for CDVA	Downgraded 1 level for risk of bias, 1 level for imprecision (i.e., small sample sizes), and 1 level for inconsistency
Uncorrected visual acuity (UCVA) 4 RCTs[15,17,18,20] Total N from all 4 studies reporting this outcome = 239 • Standard CXL N = 122 • Control group N = 117	●○○○ Very Low	Standard CXL was associated with: • Significantly greater improvement in UCVA at 12 months (total N = 70; mean difference in logMAR, −0.20; 95% CI, −0.21 to −0.19; *P* < .001; based on a meta-analysis with 2 RCTs)[a] • Overall, the data from all 4 trials that reported UCVA indicated inconsistent effects across time points	Downgraded 1 level for risk of bias, 1 level for imprecision (i.e., small sample sizes), and 1 level for inconsistency

Outcome Number of Studies Participant N	Certainty of Evidence (CoE)	Relationship	Rationale for CoE Rating
Maximal keratometry 4 RCTs[14,15,17,20] Total N from all 4 studies reporting this outcome = 219 • Standard CXL N = 115 • Control group N = 104	●○○○ Very Low	Standard CXL was associated with: • Significantly greater improvement in maximal keratometry at 12 months (total N = 141; mean difference in diopters, −1.92; 95% CI, −2.01 to −1.83; *P* < .001; based on a meta-analysis with 2 RCTs). The estimated mean difference between the groups exceeded the threshold for the minimum clinically important difference for maximal keratometry, which is a change of 1.5 diopters. • No statistically significant mean difference between the 2 groups at 36 months (N = 120; mean difference in diopters, −1.63; 95% CI, −3.90 to 0.64; *P* = .16) • Overall, the results of the meta-analyses and data from other reported time points not included in the meta-analyses were mixed over time	Downgraded 1 level for risk of bias, 1 level for imprecision (i.e., small sample sizes), and 1 level for inconsistency
Patient-reported visual function 1 RCT[15] Total N = 54 • Standard CXL N = 29 • Control group N = 25	●○○○ Very Low	No significant differences between the groups, as measured by 2 validated instruments	Downgraded[b] 1 level for risk of bias and 2 levels for imprecision (i.e., small sample sizes)
Serious adverse events • 12 RCTs[14,15,17-20,25-32] with 297 eyes treated with standard CXL from any trial included in this report compared with 121 eyes in no treatment, sham, or standard care groups (total N = 418) • 1 registry study[21] with 976 eyes treated with CXL	●○○○ Very Low	Some RCTs reported rare serious adverse events associated with CXL. When they did occur, they were scarring, infiltrates, or microbial keratitis. No serious adverse events were reported in the control groups. Of the 976 eyes in the registry study, 13 eyes underwent a second CXL operation within 5 years, 6 eyes developed microbial keratitis, 5 eyes had recurrent erosion, 3 eyes had sterile infiltrates, and 28 had scarring by the 1-year follow-up.	Downgraded 1 level for risk of bias and 2 levels for imprecision (very low rate of events)

Notes. [a] Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision. [b] Unable to rate for inconsistency. For methods and interpretation of GRADE ratings, see Appendix F.

Abbreviations. CI: confidence interval; CXL: collagen cross-linking; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach; logMAR: logarithm of the minimum angle of resolution; N: number of participants; RCT: randomized controlled trial; vs.: versus.

Effectiveness

We identified 21 RCTs that reported effectiveness outcomes.[14-20,25-32,165-176] This section of the report is organized by comparison, then by outcome.

Standard CXL vs. No Treatment, Sham, or Standard Care

Corrected Distance Visual Acuity

Five RCTs reported change in corrected distance visual acuity (CDVA) 12 to 60 months after baseline (Table 4),[14-20] and 3 of these RCTs[14,17,19] contributed data for the meta-analyses of standard care versus no treatment, sham, or standard care control groups (Figures 2 and 3). Overall, there were mixed directions of effect across studies, and only 1 RCT reported a statistically significant greater improvement in CDVA for the standard CXL group than the standard care group (18 months after baseline).[15] The CDVA is measured in the logarithm of the minimum angle of resolution (logMAR; see Glossary); a value of zero on the logMAR indicates standard vision, a negative value indicates good vision, and a positive value indicates poor vision.

- At 12 months, a random-effects meta-analysis of change in CDVA with 2 RCTs favored standard CXL (N = 141; mean difference, −0.07; 95% CI, −0.08 to −0.06; *P* < .001). See Figure 2 for more details.
- At 36 months, a random-effects meta-analysis indicated no significant difference between groups (N = 120; mean difference, −0.10; 95% CI, −0.22 to 0.01; *P* = .08). See Figure 3 for more details.

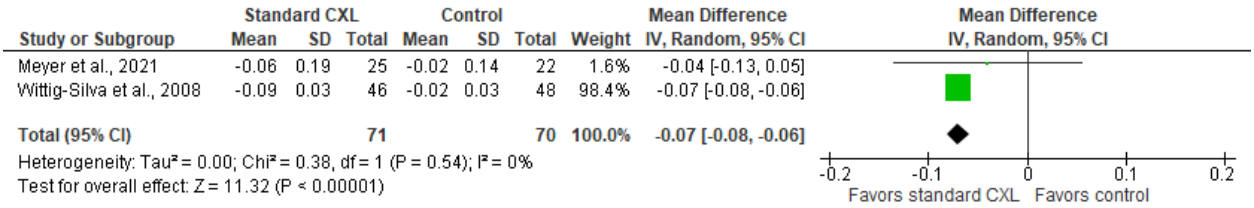
Table 4. Standard CXL vs. Control: Mean Change in CDVA (logMAR[a])

Author, Year Risk of Bias	Standard CXL Group N Mean, SD	Control Group N Mean, SD	Test for Between-Group Difference
12 months after baseline			
Meyer et al., 2021[17] High risk of bias	N = 25 Mean, −0.06; SD, 0.19	N = 22 Mean, −0.02; SD, 0.14	NR, *P* = .43
Wittig-Silva et al., 2008[20] Moderate risk of bias	N = 46 Mean, −0.09; SD, 0.03	N = 48 Mean, −0.02; SD, 0.03	NR, *P* = .094
18 months after baseline			
Larkin et al., 2021[15] Moderate risk of bias	N = 29 Mean, 0.4; SD, 0.4	N = 25 Mean, 0.6; SD, 0.6	Adjusted mean difference, −0.51; 95% CI, −1.37 to 0.35; *P* = .002
O'Brart et al., 2011[18] Moderate risk of bias	N = 22 Mean, 0.12; SD, NR[b]	N = 22 Mean, 0.13; SD, NR[b]	Mean difference, −0.1; SD, NR; *P* = .98
24 months after baseline			
Wittig-Silva et al., 2008[20] Moderate risk of bias	N = 46 Mean, −0.09; SD, 0.03	N = 48 Mean, −0.04; SD, 0.03	NR, *P* = .224
36 months after baseline			
Lang et al., 2015[14] High risk of bias	N = 14 Mean, 0.22; SD, 0.14	N = 12 Mean, 0.23; SD, 0.27	NR, *P* = .61

Author, Year Risk of Bias	Standard CXL Group N Mean, SD	Control Group N Mean, SD	Test for Between-Group Difference
Wittig-Silva et al., 2008[20] Moderate risk of bias	N = 46 Mean, −0.09; SD, 0.03	N = 48 Mean, 0.05; SD, 0.03	NR, *P* = .347
60 months after baseline			
Meyer et al., 2021[17] High risk of bias	N = 21 Mean, −0.04; SD, 0.23	N = 9 Mean, −0.02; SD, 0.20	NR, *P* = .76

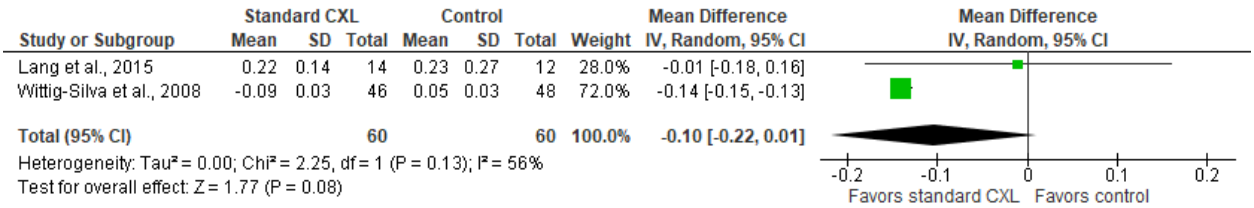
Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.* [b] *Because the O'Brart study did not report SDs, we were not able to use those data to pool with the Larkin study's 18-month data to conduct a meta-analysis.*
Abbreviations. CI: confidence interval; CVDA: corrected distance visual acuity; CXL: collagen cross-linking; logMAR: logarithm of the minimum angle of resolution; N: number; NR: not reported; SD: standard deviation; vs.: versus.

Figure 2. Standard CXL vs. No Treatment, Sham, or Standard Care: CDVA at 12 Months (logMAR[a])



Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; CVDA: corrected distance visual acuity; CXL: collagen cross-linking; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; vs.: versus.

Figure 3. Standard CXL vs. No Treatment, Sham, or Standard Care: CDVA at 36 Months (logMAR[a])



Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; CVDA: corrected distance visual acuity; CXL: collagen cross-linking; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; vs.: versus.

Uncorrected Visual Acuity (UCVA)

Four RCTs compared change in uncorrected visual acuity (UCVA) between standard CXL groups and control groups (Table 5),[15,17-20] and there were sufficient data to include 2 of these RCTs[17,19,20] in a meta-analysis of change in UCVA at 12 months (Figure 4). Overall, the direction of effect across studies and time points favored standard CXL (Table 5). The UCVA is measured in the logMaR; a value of zero logMAR indicates standard vision, a negative value indicates good vision, and a positive value indicates poor vision.

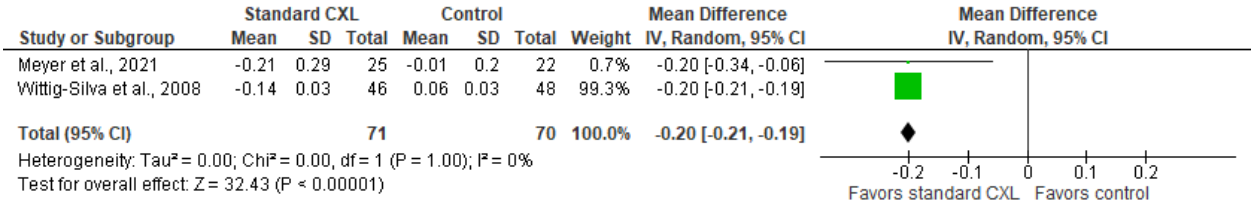
- At 12 months after baseline, a random effects meta-analysis with 2 RCTs[17,19] favored standard CXL (N = 141; mean difference, −0.20; 95% CI, −0.21 to −0.19; *P* < .001); see Figure 4 for more details.

Table 5. Standard CXL vs. Control: Mean Change in UCVA (logMAR[a])

Author, Year Risk of Bias	Standard CXL Group N Mean, SD	Control Group N Mean, SD	Test for Between-Group Difference
12 months after baseline			
Meyer et al., 2021[17] High risk of bias	N = 25 Mean, −0.21; SD, 0.29	N = 22 Mean, −0.01; SD, 0.20	NR; *P* < .01
Wittig-Silva et al., 2008[20] Moderate risk of bias	N = 46 Mean, −0.14; SD, 0.03	N = 48 Mean, 0.06; SD, 0.03	NR; *P* = .001
18 months after baseline			
Larkin et al., 2021[15] Moderate risk of bias	N = 29 Mean, 0.5; SD, 0.3	N = 25 Mean, 0.8; SD, 0.6	Adjusted mean difference, −0.31; 95% CI, −0.50 to −0.11; *P* = .002
O'Brart et al., 2011[18] Moderate risk of bias	N = 22 Mean, 0.06; SD, NR[b]	N = 22 Mean,- 0.01; SD, NR[b]	Mean difference, 0.07; SD, NR; *P* = .2
24 months after baseline			
Wittig-Silva et al., 2008[20] Moderate risk of bias	N = 46 Mean, 0.07; SD, 0.04	N = 48 Mean, −0.13; SD, 0.05	NR, *P* = .003
36 months after baseline			
Wittig-Silva et al., 2008[20] Moderate risk of bias	N = 46 Mean, −0.15; SD, 0.06	N = 48 Mean, 0.10; SD, 0.04	NR, *P* = .001
60 months after baseline			
Meyer et al., 2021[17] High risk of bias	N = 21 Mean, −0.13; SD, 0.31	N = 9 Mean, 0.02; SD, 0.29	NR, *P* = .06

Note. [a] Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision. [b] Because the O'Brart study did not report standard deviations, we were not able to use those data to pool with the Larkin study's 18-month data to conduct a meta-analysis.
Abbreviations. CI: confidence interval; logMAR: logarithm of the minimum angle of resolution; N: number; NR: not reported; SD: standard deviation; UCVA: uncorrected visual acuity; vs.: versus.

Figure 4. Standard CXL vs. No Treatment, Sham, or Standard Care: UCVA at 12 Months (logMAR[a])



Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; CXL: collagen cross-linking; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; UCVA: uncorrected visual acuity; vs.: versus.

Maximal Keratometry

Four RCTs compared change in maximal keratometry between standard CXL groups and no treatment, sham, or standard care groups.[14,15,19,20,175] Two of these RCTs[17,19,20] contributed data to a meta-analysis of change in maximal keratometry 12 months after baseline, and 2 RCTs[14,19] contributed data to a meta-analysis of change in maximal keratometry 18 months after baseline. Overall, the direction of effect across studies and time points favored standard CXL (Table 6).

- At 12 months, a random effects meta-analysis with 2 RCTs favored standard CXL (N = 141; mean difference, -1.92; 95% CI, -2.01 to -1.83; *P* < .001)[17,19]; see Figure 5 for more details. The estimate of the mean difference between the groups exceeded the threshold for the minimum clinically important difference for maximal keratometry, which is a change of 1.5 diopters.[15]
- At 36 months, a random effects meta-analysis with 2 RCTs did not find a statistically significant mean difference between the 2 groups (N = 120; mean difference, -1.63; 95% CI, -3.90 to 0.64; *P* = .16)[14,19]; see Figure 6 for more details.

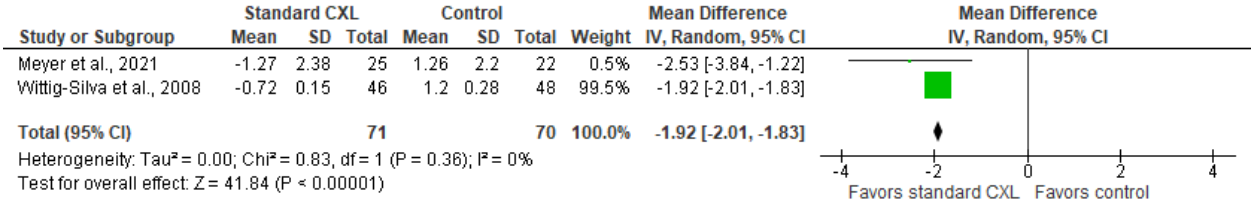
Table 6. Standard CXL vs. Control: Mean Change in Maximal Keratometry (Diopters)

Author, Year Risk of Bias	Standard CXL Group N Mean, SD	Control Group N Mean, SD	Between-Group Difference
12 months after baseline			
Meyer et al., 2021[17] High risk of bias	N = 25 Mean, −1.27; SD, 2.38	N = 22 Mean, 1.26; SD, 2.20	NR, *P* < .001
Wittig-Silva et al., 2008[20] Moderate risk of bias	N = 46 Mean, −0.72; SD, 0.15	N = 48 Mean, 1.20; SD, 0.28	NR, *P* < .001
18 months after baseline			
Larkin et al., 2021[15] Moderate risk of bias	N = 30 Mean, 57.0[a]; SD, 6.2	N = 22 Mean, 60.3; SD, 7.7	Adjusted mean difference, −2.11; 95% CI, −4.81 to 0.60; *P* = .13
24 months after baseline			
Wittig-Silva et al., 2008[20] Moderate risk of bias	N = 46 Mean, −0.96; SD, 0.16	N = 48 Mean, 1.70; SD, 0.36	NR, *P* < .001

Author, Year Risk of Bias	Standard CXL Group N Mean, SD	Control Group N Mean, SD	Between-Group Difference
36 months after baseline			
Lang et al., 2015[14] High risk of bias	N = 14 Mean, −0.35; SD, 0.58	N = 12 Mean, 0.11; SD, 0.61	NR, *P* = .02
Wittig-Silva et al., 2008[20] Moderate risk of bias	N = 46 Mean, −1.03; SD, 0.19	N = 48 Mean, 1.75; SD, 0.38	NR, *P* < .001
60 months after baseline			
Meyer et al., 2021[17] High risk of bias	N = 25 Mean, −1.45; SD, 2.25	N = 22 Mean, 1.71; SD, 2.46	NR, *P* < .001

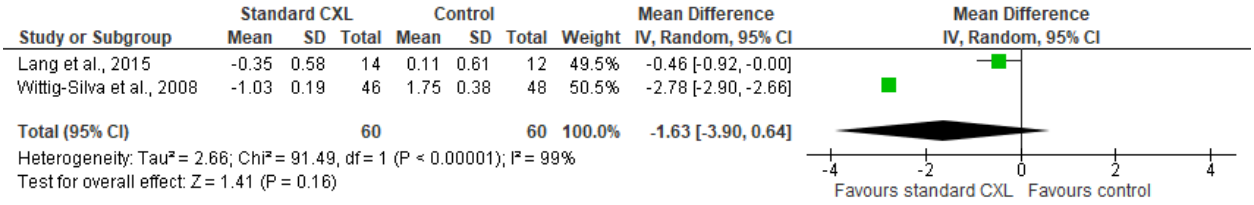
Note. [a] *The Larkin study reported maximal keratometry in mean diopters at 18 months after baseline, instead of mean change in diopters between 18 months and baseline.*
Abbreviations. CI: confidence interval; N: number; NR: not reported; SD: standard deviation; vs.: versus.

Figure 5. Standard CXL vs. No Treatment, Sham, or Standard Care: Maximal Keratometry at 12 Months (Diopters)



Abbreviations. CI: confidence interval; CXL: collagen cross-linking; IV: inverse variance; SD: standard deviation; vs.: versus.

Figure 6. Standard CXL vs. No Treatment, Sham, or Standard Care: Maximal Keratometry at 36 Months (Diopters)



Abbreviations. CI: confidence interval; CXL: collagen cross-linking; IV: inverse variance; SD: standard deviation; vs.: versus.

Patient-Reported Visual Function

We identified 1 RCT that included measures of patient-reported visual function. Larkin and colleagues' publication of results from an RCT compared standard CXL with standard care, and collected patient-reported visual function at 18 months postsurgery with the Cardiff Visual Ability Questionnaire for Children and the Child Health Utility 9D assessment.[15] Results indicated that neither group had statistically significantly better visual function as measured by the Cardiff Visual Ability Questionnaire for Children (standard CXL mean, −1.2; standard

deviation [SD], 0.8; standard care mean, −1.1; SD, 0.9; *P* = .22) and by the Child Health Utility 9D (standard CXL mean, 1.0; SD, 0.1; standard care mean, 0.9; SD, 0.1; *P* = .14).[15]

Protocols Other Than Standard CXL

The standard (i.e., Dresden) CXL protocol was used in the trial that provided safety and effectiveness data for the FDA approval of the riboflavin solution and UVA device used for CXL. The other protocols presented in the remainder of the clinical evidence review have not been approved for use outside of a research setting as of February 2024. The following sections include a summary of the results from trials that compared these protocols; detailed data tables and figures to support the summaries are in Appendix C.

Standard CXL vs. Accelerated CXL

CDVA

Four RCTs that compared standard CXL with accelerated CXL reported CDVA outcomes (Table C1).[165-168,174] Two RCTs contributed data to a meta-analysis of mean change in CDVA at 12 months (Figure C1),[167,168,174] 4 RCTs contributed data to a meta-analysis of mean change in CDVA at 24 months (Figure C2),[165-168,174] and 1 RCT reported mean change in CDVA at 36 months (Table C1).[167] None of the RCTs reported statistically significant differences in CDVA between the standard CXL and accelerated CXL groups at any time point, and the meta-analyses did not favor either standard CXL or accelerated CXL (Figures C1 and C2).

UCVA

Three RCTs that compared standard CXL with accelerated CXL reported UCVA outcomes (Table C2).[165,167,168,174] Two of these RCTs contributed data for a meta-analysis of mean change in UCVA 12 months after baseline (Figure C3),[167,168,174] 2 RCTs contributed data for a meta-analysis of mean change in UCVA 24 months after baseline (Figure C4),[165,167] and 1 RCT reported a mean change in UCVA 36 months after baseline (Table C2).[167] The RCTs reported no statistically significant difference between the standard CXL and accelerated CXL groups (Table C2), and the meta-analyses did not favor either group (Figures C3 and C4).

Maximal Keratometry

Four RCTs that compared standard CXL with accelerated CXL reported mean change in maximal keratometry between 12 and 36 months (Table C3).[165-168,174] Two of these RCTs[167,168,174] contributed data to a meta-analysis of change in maximal keratometry 12 months after baseline (Figure C5), 4 RCTs[165-168,174] contributed data to a meta-analysis of change in maximal keratometry 24 months after baseline (Figure C6), and 1 RCT[167] reported change in maximal keratometry 36 months after baseline (Table C3). Overall, the meta-analyses did not favor either standard CXL or accelerated CXL, and there was no clear difference between the groups at any time point (Figures C5 and C6).

Patient-Reported Visual Function

None of the RCTs comparing standard CXL with accelerated CXL included patient-reported visual function.

Standard Epithelium-Off vs. Epithelium-On Protocols

CDVA

Ten RCTs that compared epithelium-off protocols with epithelium-on protocols reported CDVA outcomes (Table C4).[18,25-32,169-172] The meta-analysis of CDVA 12 months after baseline included 7 RCTs[26,27,29,30,169,171,172] and favored epithelium-on protocols (N = 368; mean difference, 0.05; 95% CI, 0.02 to 0.07; *P* = .0005; Figure C7). The meta-analysis of CDVA 24 months after baseline included 6 RCTs[25,26,31,169-171] and did not favor either group (Figure C8).

UCVA

Six RCTs that compared epithelium-off protocols with epithelium-on protocols reported UCVA outcomes (Table C5).[26,27,29,30,32,171,172] All 6 of these RCTs contributed data to a meta-analysis of mean change in UCVA 12 months after baseline, but the results did not favor either group (Figure C9). Two of these RCTs contributed data to a meta-analysis of mean change in UCVA 24 months after baseline, but the results did not favor either group (Figure C10).[27,171]

Maximal Keratometry

Six RCTs that compared epithelium-off versus epithelium-on protocols reported change in maximal keratometry at 12 months (Table C6).[25,26,29,32,169,172] All 6 of these RCTs contributed data for a meta-analysis of mean change in maximal keratometry 12 months after baseline (Figure C11),[25,26,29,32,169,172] and 3 RCTs contributed data for a meta-analysis of mean change in maximal keratometry 24 months after baseline (Figure C12).[25,26,169] The meta-analyses did not favor either epithelium-off or epithelium-on protocols (Figures C11 and C12).

Patient-Reported Visual Function

The Napolitano and colleagues publication reported results from an RCT that compared standard epithelium-off CXL with epithelium-on iontophoresis corneal CXL, results of which included patient-reported visual function within 24 months postsurgery with the Ocular Surface Disease Index.[169] The results indicated that the epithelium-off group experienced a statistically significantly greater amount of ocular discomfort (mean, 13.65; SD, 2.15) than the epithelium-on group (mean, 11.62; SD, 2.12; *P* = .02).

Standard CXL vs. PiXL

CDVA

A single RCT reported greater improvement in CDVA 12 months after baseline for the group that received individualized PiXL (N = 25; mean, −0.16; SD, 0.24) compared with the group that received standard CXL (N = 23; mean, 0.01; SD, 0.29; between-group test for difference not reported; *P* = .03).[28]

UCVA

A single RCT reported greater improvement in UCVA 12 months after baseline for the group that received individualized PiXL (N = 25; mean, −0.31; SD, 0.40) compared with the group that received standard CXL (N = 23; mean, −0.07; SD, 0.16; between-group test for difference not reported; *P* = .02).[28]

Maximal Keratometry

A single RCT reported greater improvement in maximal keratometry between their baseline measures and 12 months after baseline for the group that received individualized PiXL (N = 25; mean, −1.31; SD, 1.52) compared with the group that received standard CXL (N = 23; mean, 0.30; SD, 1.33; between-group test for difference not reported; $P < .01$).[28]

Patient-Reported Visual Function

The RCT that compared standard CXL with PiXL did not include patient-reported visual function.

Two Accelerated Protocols Head-to-Head

CDVA

A single RCT compared accelerated CXL including 5 minutes of UVA light (N = 37) with accelerated CXL including 10 minutes of UVA light (N = 29).[173] The authors reported no statistically significant difference between groups for improvement in CDVA (5-minute group mean, 0.10; 5-minute group SD, 0.13; 10-minute group mean, 0.14; 10-minute group SD, 0.15; $P = .137$).[173]

UCVA

A single RCT compared accelerated CXL including 5 minutes of UVA light (N = 37) to accelerated CXL including 10 minutes of UVA light (N = 29).[173] The authors reported no statistically significant difference between groups for improvement in UCVA (5-minute group mean, 0.13; 5-minute group SD, 0.22; 10-minute group mean, 0.09; 10-minute group SD, 0.21; $P = .51$).[173]

Maximal Keratometry

A single RCT compared accelerated CXL including 5 minutes of UVA light (N = 37) to accelerated CXL including 10 minutes of UVA light (N = 29).[173] The authors reported that the 10-minute group had significantly greater improvement in maximal keratometry 12 months after baseline (5-minute group mean, 0.79; 5-minute group SD, 1.59; 10-minute group mean, 1.85; 10-minute group SD, 1.58; $P = .003$).[173]

Patient-Reported Visual Function

The RCT that compared 2 accelerated CXL protocols did not include patient-reported visual function.

Safety

We identified 12 RCTs that reported serious adverse events.[14,15,17,18,20,25,26,28-32,176] Table 7 presents the reported serious adverse events from these RCTs. We also identified 3 publications from the Save Sight Keratoconus Registry Study that reported adverse events at 1-year[177] and 5-year[21,178] follow-up periods.

Standard CXL vs. No Treatment, Sham, or Standard Care

Five RCTs that compared standard CXL with no treatment or sham reported serious adverse events as an outcome.[14,15,17-20] Detailed information about serious adverse events is in Table 7. Overall, serious adverse events for the standard CXL group were rare, but included microbial keratitis within a week of the operation and scarring that impacted visual acuity (see Table 7).

A publication of data from the Save Sight Keratoconus Registry reported on adverse events at 1 to 5 years after surgery for the 975 eyes treated with standard CXL.[21] Similarly, serious adverse events were rare, but included a second CXL operation on the same eye within 5 years, microbial keratitis, recurrent erosion, sterile infiltrates, and scarring.[21] Information at the 2-year, 3-year, 4-year, and 5-year follow-up times reported decreasing numbers of eyes and frequencies with any of these complications.[21]

Standard CXL vs. Accelerated CXL

None of the RCTs that compared standard CXL with accelerated CXL reported serious adverse events as an outcome collected.

One publication from the Save Sight Keratoconus Registry analyzed 1-year follow-up information from 266 eyes (228 individuals) treated with standard CXL and 418 eyes (327 individuals) treated with accelerated CXL.[177] Serious adverse events were rare; they included microbial keratitis within a few weeks of surgery for eyes in both treatment groups and mild scarring that negatively impacted visual acuity (unclear which protocol this eye was treated with).[177] At the 12-month follow-up, 21 eyes (7.9%) in the standard CXL group and 23 eyes (5.5%) in the accelerated CXL group had scarring, stromal edema, or recurrent erosion (P = .21).[177]

A second publication from the Save Sight Keratoconus Registry analyzed 5-year follow-up information from 100 eyes (75 individuals) treated with standard CXL compared with 76 eyes (66 individuals) treated with accelerated CXL.[178] Serious adverse events were rare; they included microbial keratitis with a decrease in visual acuity and maximal keratometry in that eye, scarring, sterile infiltrates, epithelial defect, stromal edema, and recurrent corneal erosion.[178]

Standard Epithelium-Off vs. Epithelium-On Protocols

Six RCTs that compared epithelium-on protocols with epithelium-off protocols reported serious adverse events as an outcome collected. Serious adverse events were rare, and they included scarring, infiltrates, or microbial keratitis. None of the individuals in the epithelium-on groups reported serious adverse events.

Standard CXL vs. PiXL

The single RCT that compared PiXL to standard CXL reported serious adverse events as an outcome collected, and it reported no serious adverse events in either group (standard CXL N = 25; PiXL N = 25).[28]

Two Accelerated Protocols Head-to-Head

The RCT that compared 2 accelerated CXL protocols did not report serious adverse events.

Table 7. Reported Serious Adverse Events From Included RCTs

Author, Year Additional Publications Total Follow-Up Risk of Bias	N Randomized Participants (eyes) N Analyzed Participants (eyes)	Serious Adverse Events
Standard CXL vs. no treatment or sham		
Lang et al., 2015[14] 36 months High risk of bias	Randomized N = 29 (29 eyes) Analyzed N = 29 (29 eyes)	• 0/15 eyes in CXL group had bacterial keratitis • 0/15 eyes in CXL group needed reoperation • 0/14 eyes in the no treatment group had serious adverse events
Larkin et al., 2021[15] Larkin et al., 2021b[16] KERALINK 18 months Moderate risk of bias	Randomized N = 60 (60 eyes) Analyzed N = 53 (53 eyes)	• 0/30 eyes in CXL group had serious adverse events reported • 0/23 adverse events reported for control group
Meyer et al., 2021[17] 60 months High risk of bias	Randomized N = 38 (74 eyes) Analyzed N = 21 (30 eyes)	• 1/21 eyes in CXL group was diagnosed with microbial keratitis (culture positive *Staphylococcus aureus*) diagnosed on postoperative day 3. Treated with antibiotics, but left an anterior stromal scar and had associated loss of corrected visual acuity. The scar was reduced through phototherapeutic keratectomy. • 4/21 eyes in the CXL group had visible stromal scarring, and 1 of the eyes had a loss of 2 lines of CDVA due to the haze. Two other eyes in the CXL group had lost 2 or more lines of CDVA, possibly from corneal remodeling. • 0/9 serious adverse events reported for control group
O'Brart et al., 2011[18] 18 months Moderate risk of bias	Randomized N = 24 (48 eyes) Analyzed N = 22 (44 eyes)	• 0/22 eyes in the CXL group had corneal infections • 0/22 eyes in the CXL group had scarring • 0/22 adverse events reported for control group
Wittig-Silva et al., 2008[20] Wittig-Silva et al., 2014[19] 36 months Moderate risk of bias	Randomized N = 50 (100 eyes) Analyzed N = 47 (94 eyes)	• 1/41 eyes in the CXL group had small paracentral infiltrate, possibly due to premature resumption of rigid contact lens wear • 1/41 eyes in the CXL group had possible microbial keratitis 2 days after operation • 1/41 eyes in the CXL group had peripheral corneal vascularization 3 years after CXL operation, but possibly unrelated to the CXL treatment • 0/53 eyes in the no treatment group had serious adverse events
Standard epithelium-off CXL vs. protocols with epithelium-on		
Caruso et al., 2021[25] 24 months High risk of bias	Randomized N = 41 (54 eyes) Analyzed N = NR	• 2/29 eyes in the epithelium-off group had late-onset deep stromal scarring, but the location of the scars did not affect visual acuity • 0/25 in the epithelium-on group had serious adverse events reported

Author, Year Additional Publications Total Follow-Up Risk of Bias	N Randomized Participants (eyes) N Analyzed Participants (eyes)	Serious Adverse Events
Lombardo et al., 2016[175] Lombardo et al., 2017[26] Lombardo et al., 2019[27] 24 months High risk of bias	Randomized N = 25 (35 eyes) Analyzed N = 25 (35 eyes)	• 1/12 eyes in the epithelium-off group had 2 small peripheral subepithelial infiltrates 3 days after operation, which resulted in 2 superior faint corneal scars but stable visual acuity • 0/22 eyes in the epithelium-on group had serious adverse events reported
Rossi et al., 2015[29] 12 months Moderate risk of bias	Randomized N = 20 (20 eyes) Analyzed N = 20 (20 eyes)	• 0/10 eyes in the epithelium-off group had ocular or systemic adverse events reported • 0/10 eyes in the epithelium-on group had ocular or systemic adverse events reported
Rossi et al., 2018[30] 12 months High risk of bias	Randomized N = 30 (30 eyes) Analyzed N = 30 (30 eyes)	• 0/10 eyes in the epithelium-off group had ocular or systemic adverse events reported • 0/20 eyes in either of the epithelium-on groups had ocular or systemic adverse events reported
Rush and Rush, 2016[31] 24 months Moderate risk of bias	Participants with keratoconus randomized N = 102 Participants with keratoconus analyzed = NR	• 1/56 eyes in the epithelium-off group developed postoperative bacterial conjunctivitis (*Haemophilus influenzae* on culture), with no long-term impact on visual acuity • 0/75 eyes in the epithelium-on group had serious adverse events reported
Soeters et al., 2015[32] Godefrooij et al., 2017[176] 12 months Moderate risk of bias	Randomized N = 61 (61 eyes) Analyzed N = 61 (61 eyes)	• 4/26 eyes in the epithelium-off group developed complications related to healing (e.g., sterile infiltrate, herpes keratitis, central haze, and stromal scar) • 0/35 eyes in the epithelium-on group had serious adverse events reported
Standard CXL vs. PiXL		
Nordström et al., 2016[28] 12 months Moderate risk of bias	Randomized N = 37 (50 eyes) Analyzed N = 35 (48 eyes)	• 0/25 eyes in the standard CXL group had serious adverse events • 0/25 eyes in the PiXL group had serious adverse events

Abbreviations. CXL: collagen cross-linking; N: number; NR: not reported; RCT: randomized controlled trial; PiXL: photorefractive intrastromal crosslinking; UK: United Kingdom; US: United States of America; vs.: versus.

Subpopulation Considerations for Effectiveness and Safety

The included RCTs of any of the protocols described above did not report subgroup analyses that answer the questions about effectiveness and safety considerations for any subpopulations of individuals with keratoconus.

Cost and Cost-Effectiveness

We identified 1 cost-effectiveness study published in 2021 that presented a lifetime economic model comparing standard CXL with no CXL for individuals with keratoconus in the US.[22] This cost study used data from a US-based trial that tested standard CXL against a control group that crossed over to standard CXL treatment at 3 months after baseline (see Basis for FDA Approval

subsection of the Background of this report for more details about this interventional trial). Primary concerns about risk of bias included unexplained missing data from the trial, funding and employment of investigators of the trial and cost study by the company that makes the riboflavin eye drops used in standard CXL, and weaknesses of the interventional trial study design.[179]

Cost-Model Building

The discrete-event microsimulation (estimated in Excel) cost model simulated treatments that individual eyes likely sequence through with the progression of keratoconus over the course of the individual person's lifetime, which the authors determined by consulting literature about the natural history of keratoconus and standard treatment pathways.[22] This lifetime model used a US payer perspective. This model assumed that keratoconus is first addressed with contact lenses or glasses, then standard CXL, followed by regular assessment for continued progression that would lead to penetrating keratoplasty for eyes that continue to progress, and regrafting or enucleation for eyes that continue to need treatment.[22]

Direct cost inputs for the model included[22]:

- Penetrating keratoplasty ($22,165)
- CXL procedure ($1,780)
- Riboflavin solution ($2,850)
- Glasses ($356)
- Lenses ($400 to $800)
- Routine check-ups ($362)
- Increase in intraocular pressure ($46)
- Graft rejection ($604)
- Glaucoma ($3,629)
- Enucleation ($3,386)
- Treatment for other conditions (i.e., cataracts, infection, and other irritation; $862)

It was not clear whether this model accounted for continued evaluation, fitting, and use of contact lenses or glasses after the more intensive treatments of standard CXL, penetrating keratoplasty, or other treatments. The model did not account for indirect costs, such as lost productivity during intervention treatment and recovery. Quality-adjusted life years (QALYs) were discounted at 3% annually.

Because the cost effectiveness study was published 3 years ago and costs can change over time, we searched for current cost information. The riboflavin solutions are assigned the Healthcare Common Procedure Coding System (HCPCS) code J2787. The wholesale acquisition cost of the solution kit used for the procedure is currently $4,150.[180] The manufacturer has not signed a federal rebate agreement.[181]

Cost Model Results

The cost model assumed that individuals had bilateral progressive keratoconus, assumed a mean baseline age of 31, assumed a patient population that was 73.5% male, assumed that 80% of the patient population had slow-progressing keratoconus and 20% had fast-progressing keratoconus, used actuarial life tables for background mortality, and used the change in vision data from the US-based trial with 205 participants described above.[22] As a note, the proportion

of males was higher than what we found in other studies included in this report, and the mean age was higher than the mean age from most studies in this report.

The results suggested that beginning treatment with standard CXL instead of penetrating keratoplasty after lenses and glasses ceased to adequately address vision concerns was associated both with a reduction in direct medical costs (lifetime cost for CXL group, $30,944; lifetime cost for no-CXL group, $39,671), and with more QALYs (CXL group QALYs, 21.8; no-CXL group QALYs, 19.93; mean difference, 1.88; no between-group test for significance reported).[22] The authors reported an incremental cost-effectiveness ratio of $1,526 per QALY gained, which would be cost-effective with a maximum willingness-to-pay threshold of $150,000 per QALY gained.[22] In relation to the treatment pathway assumptions, the model estimated that the group that received CXL was 25.9% less likely to have penetrating keratoplasty and was likely to spend 27.9 fewer years in advanced disease stages.[22]

Clinical Practice Recommendations

We identified 2 publications of relevant clinical practice recommendations.

AAO Preferred Practice Pattern

The AAO published a preferred practice pattern guideline for corneal ectasia in 2018, and this document included a section specific to keratoconus.[23] The stated purpose of the AAO preferred practice pattern guidelines was to "describe the core criteria of quality eye care, based on the best available scientific data as interpreted by a panel of knowledgeable health professionals."[23(p175)] We assessed this guidance document as having fair methodological quality, primarily due to lack of reporting about the methods used to identify, assess risk of bias, and include or exclude studies used to generate the information and recommendations in the document. The panel that drafted the preferred practice guidelines included clinical experts, a representative of the Cornea Society, and a methodologist, and the final draft was reviewed by internal and external groups before publication.[23] It was not clear which published studies were used in the formulation of their key findings and recommendations, or what the quality of those studies were (e.g., design, risk of bias).

Key findings and recommendations related to the treatment of keratoconus included the following[23]:

- Recommendation to require the individual to stop wearing typically prescribed contact lenses for a period (amount of time not specified by the committee) before use of corneal topography and tomography to review evidence of irregular astigmatism or abnormalities suggestive of keratoconus or other forms of corneal ectasia[(p177)]
- Recommendation to strive for early diagnosis, given the typically early onset of the condition and the risk of vision loss with continued progression,[(p180)] including more frequent follow-up visits (i.e., every 3 to 6 months instead of annually) to watch for signs of progression[(p197)]
- "CXL reduces the risk of progressive ectasia in patients with keratoconus (particularly in its early stages) and stabilizes the cornea [*sic*]"[(p177)]
- An expectation that CXL be combined with eyeglasses and contact lenses to preserve visual acuity[(p180)]

The panel noted in the document that "complications of CXL may include punctate keratitis, corneal striae, photophobia, dry eye, eye pain, infectious keratitis, sterile infiltrates, corneal haze, corneal scarring, nonhealing epithelial defects, and corneal edema."[23(p193)]

National Institute for Health and Care Excellence (NICE)

The National Institute for Health and Care Excellence (NICE) published an interventional procedure guidance document with a systematic review on photochemical CXL using riboflavin and UVA for keratoconus in 2013.[24] This document was an update from guidance issued in 2009 that recommended that CXL should only be used with special arrangements, due to inadequate evidence.[24] Interventional procedure guidance reviews focus primarily on safety for novel procedures for which safety and efficacy is not known or is uncertain.[182] We assessed this guidance as having fair methodological quality, primarily due to an absence of clinical expert involvement and patient representatives, lack of a plan to update the guidance with findings from research published after the search strategies, and lack of a plan for assessing implementation and monitoring safety.

The authors of the review noted several limitations to their review of safety and efficacy of CXL for keratoconus, including differences in outcomes collected across studies (e.g., measures and time points), indications of high heterogeneity in the meta-analyses, lack of long-term studies (i.e., inability to understand the durability of the intervention), small numbers of participants in trials, and the fact that included studies were likely subject to selection bias and observer bias, and lacked appropriately matched comparators (i.e., most of the evidence was from case series or RCTs with fellow-eye comparators, or had an early crossover of control to treatment).[24]

With those limitations in mind, the authors concluded the following[24,33]:

- Current evidence on the safety and efficacy of epithelium-off CXL for keratoconus and keratectasia (a rare complication of corneal refractive surgery) 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.
- Current evidence on the safety and efficacy of epithelium-on (transepithelial) CXL and the combination (CXL-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.
- Patient selection for these procedures should include assessment of corneal thickness and consideration of the likelihood of disease progression.
- The procedures should only be carried out by ophthalmologists with expertise in managing corneal disease and specific training in the use of ultraviolet light or by appropriately trained staff under their supervision.
- NICE encourages further research into CXL using riboflavin and UVA for keratoconus and keratectasia, especially epithelium-on (transepithelial) CXL and the combination (CXL-plus) procedures. Details of the techniques used should be clearly described. Reported outcomes should include visual acuity, corneal topography, and quality of life. Data on long-term outcomes for all types of CXL using riboflavin and UVA for keratoconus and keratectasia would be useful, specifically data about prevention of progression to corneal transplantation and about repeat procedures and their efficacy.

Relevant Ongoing Trials

We identified 13 ongoing RCTs registered on ClinicalTrials.gov that fit the inclusion criteria for this review.[183-195] We did not identify any relevant ongoing trials in the ScanMedicine search, which is an international database of registered trials. We consider any registered trial that does not have published results to be ongoing. Trial characteristics are presented in Table 8.

Two trials compare standard CXL with no treatment or sham[183,189]; 1 trial compares standard CXL with customized CXL (i.e., standard protocol, except topography measurements guide corneal debridement that is limited to the most affected portions of the eye to provide more targeted treatment that leaves healthy areas intact)[192]; 8 trials compare epithelium-on CXL with standard epithelium-off CXL[184,186-188,191,193-195]; and 2 trials compare simultaneous CXL and placement of Intacs implants to standard CXL alone.[185,190] Estimated completion dates ranged from December 2011 to December 2025, and estimated enrollment numbers varied from 32 participants to 600 participants.

Table 8. Characteristics of Relevant Ongoing RCTs of Treatments of Keratoconus

Trial Identifier Intervention Location Estimated Completion Date Sponsor	Population Estimated N	Outcomes
Standard CXL		
NCT00841386[183] CXL US December 2011 University at Buffalo	Individuals aged 16 to 35 years with keratoconus N = 66	• Maximal keratometry at 24 months • CDVA at 24 months
NCT01604135[189] CXL Sweden April 2024 Sahlgrenska University Hospital	Individuals with keratoconus or corneal ectasia N = 36	• Maximal keratometry at 12 months • Change in CDVA and UCVA at 12 months
Customized CXL		
NCT04532788[192,196] Customized CXL Sweden June 2024 Maastricht University Medical Center	Individuals aged 16 and 45 years with progressive keratoconus N = 124	• Maximal keratometry at 12 months • Change in CDVA and UCVA at 12 months • Health-related quality of life as measured by HUI3 (Health Utility Index Mark 3) questionnaire at 12 months • Patient satisfaction and vision-specific quality of life as measured by NEI VFQ-25 at 12 months • Patient satisfaction and vision-specific quality of life as measured by Keratoconus Outcome Research Questionnaire (KORQ) at 12 months • Cost and budget outcomes

Trial Identifier Intervention Location Estimated Completion Date Sponsor	Population Estimated N	Outcomes
Epithelium-on CXL or PiXL		
NCT03598634[184] Transepithelial CXL Italy June 2015 University of Molise	Individuals with progressive keratoconus N = 32	• Change in CDVA and UCVA up to 48 months after baseline
NCT03442751[187] Transepithelial CXL US August 2020 Glaukos Corporation	Individuals aged 12 years and older with progressive keratoconus N = 279	• Maximal keratometry at 12 months
NCT03990506[191] Epithelium-on PiXL Sweden January 2023 Umeå University	Adults with bilateral keratoconus N = 32	• Maximal keratometry at 12 and 24 months • Change in CDVA and UCVA 12 and 24 months after baseline
NCT03858036[186] Epithelium-on CXL US December 2024 Center for Sight: LASIK Sacramento	Adolescents and adults with keratoconus or other corneal ectasia N = 550	• Maximal keratometry at 12 months • Change in CDVA and UCVA at 12 months
NCT06100939[195] (Apricity-A) Epithelium-on CXL US October 2025 Epion Therapeutics	Individuals aged 8 to 45 years with progressive keratoconus N = 400	• Change in CDVA 12 months after baseline, using ETDRS visual acuity testing charts • Vision-related quality of life as assessed by the NEI-VFQ-25 at 12 months
NCT06100952[194] (Apricity-B) Epithelium-on CXL US November 2025 Epion Therapeutics	Individuals aged 8 to 45 years of with progressive keratoconus N = 400	• Change in CDVA 12 months after baseline, using ETDRS visual acuity testing charts • Vision-related quality of life as assessed by the NEI-VFQ-25 at 12 months
NCT01464268[188] Transepithelial CXL US December 2025 Cornea and Laser Eye Institute	Adults with keratoconus or corneal ectasia N = 160	• Maximal keratometry at 12 months • Change in CDVA and UCVA at 12 months

Trial Identifier Intervention Location Estimated Completion Date Sponsor	Population Estimated N	Outcomes
NCT04905108[193] Transepithelial CXL US December 2025 Cornea and Laser Eye Institute	Individuals aged 12 years and older with keratoconus or other corneal ectasia N = 160	• Maximal keratometry at 12 months
CXL in combination with other interventions		
NCT01081561[185] CXL plus Intacs US June 2021 Cornea Genetic Eye Institute	Individuals with progressive keratoconus and ectasia after Lasik N = 600	• Maximal keratometry up to 10 years
NCT01112072[190] CXL plus Intacs US December 2025 Cornea and Laser Eye Institute	Individuals with keratoconus or corneal ectasia N = 50	• Maximal keratometry at 12 months • CDVA at 12 months

Abbreviations. CDVA: corrected distance visual acuity; CXL: collagen cross-linking; ETDRS: Early Treatment Diabetic Retinopathy Study; N: number; NEI-VFQ-25: National Eye Institute 25-Item Visual Function Questionnaire; PiXL: photorefractive intrastromal crosslinking; RCT: randomized controlled trial; UCVA: uncorrected visual acuity; US: United States of America.

Payer Policies

We identified relevant coverage policies related to CXL from Aetna, Anthem Blue Cross and Blue Shield ("Anthem"; formerly Empire BlueCross BlueShield), Capital District Physicians' Health Plan, Cigna, Highmark Blue Shield of Northeastern New York ("Highmark"), Tufts Health Plan, UnitedHealthcare, and from the Medicaid programs in California (Medi-Cal), Oregon (Oregon Health Plan), and Washington State (Apple Health).[34-42,197,198] These policies are described in Table 9. Appendix A lists search terms used to identify relevant coverage policies, along with all the policy sources searched.

Wording for medical necessity criteria and CXL coverage varied across policies:

- 8 policies required that the keratoconus be documented as progressive (Anthem, Capital District Physicians', Cigna, Highmark, UnitedHealthcare, Medi-Cal, Oregon Health Plan, Apple Health)[34-41]
- 2 policies required that the individual fail conservative treatment (i.e., spectacle correction, rigid contact lens ceased to adequately correct visual acuity) before being considered a candidate for CXL (Anthem, Highmark)[35,36]
- Ineligibility criteria included individuals with active or a history of herpes simplex virus keratitis, thin corneas, corneal hydrops, visual disturbance from a significant central corneal opacity or other eye disease (e.g., neurotrophic keratopathy), and history of corneal or

systemic disease that would interfere with healing after the procedure such as chemical injury or delayed epithelial healing in the past (Anthem, Cigna, Medi-Cal)[34,35,37]
- 5 policies noted that individuals must be aged 14 years or older (Anthem, Capital District Physicians', Cigna, Tufts Health Plan, Medi-Cal),[34,35,37,42] and 3 of these policies limited the maximum age to 64 or 65 years of age (Cigna, Tufts Health Plan, Medi-Cal)[34,37,42]

Some policies explicitly noted limits on the CXL procedure, other interventions covered for keratoconus, and specific interventions considered to be experimental or investigational:
- 5 policies included language limiting the CXL procedure to the standard epithelium-off protocol (Aetna, Capital District Physicians', Cigna, UnitedHealthcare, Oregon Health Plan)[34,39-41,197]
- Other covered interventions for keratoconus included lamellar keratoplasty (nonpenetrating keratoplasty), penetrating keratoplasty, intrastromal corneal ring segments, phototherapeutic keratectomy, and contact lenses
- Other interventions considered to be experimental or investigational included epithelium-on (transepithelial) CXL, automated lamellar keratoplasty, photochemical CXL, conductive keratoplasty, thermokeratoplasty, endothelial keratoplasty, crescent keratectomy, combined photorefractive keratectomy and corneal crosslinking, and polymorphism testing for predisposition (i.e., *ALDH3A1*, *LOX*, and *SPARC* genes)

Table 9. Overview of Coverage Criteria for CXL for Individuals With Keratoconus

Policy Author Last Review Date	Medical Necessity Criteria for CXL	CXL Coverage	Other Interventions Covered for Keratoconus	Considers Experimental or Investigational for Keratoconus
Private payers				
Aetna[197] March 19, 2024	Keratoconus or keratectasia	Epithelium-off photochemical collagen cross-linkage using riboflavin (Photrexa) and UVA	• Lamellar keratoplasty (non-penetrating keratoplasty) • Penetrating keratoplasty • Intrastromal corneal ring segments (not excluding Intacs) • Phototherapeutic keratectomy	• Epithelium-on (transepithelial) collagen cross-linkage • Photochemical collagen cross-linkage • Conductive keratoplasty • Thermokeratoplasty • Endothelial keratoplasty • Crescent keratectomy • *ALDH3A1*, *LOX*, and *SPARC* polymorphism testing for predisposition • Combined photorefractive keratectomy and corneal crosslinking
Anthem Blue Cross and Blue Shield (formerly Empire BlueCross BlueShield)[35,199,200] November 9, 2023	Corneal CXL is considered medically necessary as a treatment for progressive keratoconus when all the following conditions are met: • Diagnosis of keratoconus based on keratometry and corneal mapping; ***and*** • Any of the following changes have occurred within 24 months: ○ Increase of 1.00 D or more in the steepest	Corneal CXL	• Intrastromal corneal ring segments (e.g., Intacs)	• Endothelial keratoplasty

Policy Author Last Review Date	Medical Necessity Criteria for CXL	CXL Coverage	Other Interventions Covered for Keratoconus	Considers Experimental or Investigational for Keratoconus
	keratometry measurement; ***or*** ○ Increase of 1.00 D or more in manifest cylinder; ***or*** ○ Increase of 0.50 D or more in manifest refraction spherical equivalent (MRSE); ***and*** • Age 14 years or older; ***and*** • Corrected distance visual acuity (CDVA) worse than 20/20 with properly fitted spectacles or contact lenses; ***and*** • Corneal thickness 300 microns or more; ***and*** • No history of corneal or systemic disease that would interfere with healing after the procedure such as chemical injury or delayed epithelial healing in the past			
Capital District Physicians' Health Plan (K. Alshaer, MD, Medical Director Medicaid Managed Care Division of Health Plan Contracting and Oversight, written communication, February 8, 2024) May 1, 2023	Progressive keratoconus when the following criteria are met: • Any of the following changes have occurred within 24 months: ○ Increase of 1.00 D or more in the steepest keratometry measurement; ***or*** ○ Increase of 1.00 D or more in manifest cylinder; ***or*** ○ Increase of 0.50 D or more in manifest refraction	Prior authorization required. Requests for medically necessary corneal collagen crosslinking must be submitted in writing to include the following documentation: • All clinical notes to include medical history • Refractive stability Conventional CXL is considered experimental, investigational, or unproven for all indications other than those stated above.	• Phototherapeutic keratectomy • Intrastromal corneal ring segments • Lamellar keratoplasty (nonpenetrating keratoplasty)	• All other corneal collagen crosslinking procedures (e.g., epithelium-on/trans epithelial) are considered experimental, investigational, or unproven • Endothelial keratoplasty

Policy Author Last Review Date	Medical Necessity Criteria for CXL	CXL Coverage	Other Interventions Covered for Keratoconus	Considers Experimental or Investigational for Keratoconus
	spherical equivalent (MRSE) • Enrollee is 14 years of age or older • There is a progressive deterioration in vision and corrected distance visual acuity is worse than 20/20 • Corneal thickness is 300 µm or more • There is no history of corneal or systemic disease that would interfere with healing (i.e., chemical injury, delayed epithelial healing in the past)			
Cigna[34] October 15, 2023	Progressive keratoconus or corneal ectasia following refractive surgery, when all of the following criteria are met: • Aged 14 to 65 years • Progressive deterioration in vision • Absence of visual disturbance from a significant central corneal opacity or other eye disease (e.g., herpetic keratitis, neurotrophic keratopathy)	Conventional, epithelium-off, corneal CXL using an FDA-approved drug and device system (e.g., Photrexa Viscous or Photrexa with the KXL System); CPT Code 0402T; HCPCS Code J2787	• Intrastromal corneal ring segments (e.g., Intacs) • Lamellar keratoplasty • Penetrating keratoplasty	• Epithelium-on (transepithelial) CXL • Conductive keratoplasty • Photorefractive keratectomy • Laser thermokeratoplasty • Automated Lamellar keratoplasty
Highmark BlueShield of Northeastern New York[36] June 2023	Corneal CXL using riboflavin and UVA may be considered medically necessary in individuals who have failed conservative treatment (i.e., spectacle correction, rigid contact lens) when used for	Corneal surgery to correct refractive errors, phototherapeutic keratectomy, or corneal CXL is typically an outpatient procedure which is only eligible for coverage as an inpatient procedure in special circumstances, including, but not	• Phototherapeutic keratectomy • Intrastromal corneal ring segments • Contact lenses	• None listed

Policy Author Last Review Date	Medical Necessity Criteria for CXL	CXL Coverage	Other Interventions Covered for Keratoconus	Considers Experimental or Investigational for Keratoconus
	either of the following conditions: • Progressive keratoconus; ***or*** • Corneal ectasia after refractive surgery.	limited to, the presence of a co-morbid condition that would require monitoring in a more controlled environment such as the inpatient setting.		
Tufts Health Plan[42] March 20, 2024	CXL covered for: • Unstable keratoconus • Age 14 to 64 years	CXL of cornea, including removal of the corneal epithelium and intraoperative pachymetry (when performed) covered for ICD-10 diagnosis codes H18.621 thru H18.623 (unstable keratoconus, right eye, left eye, or bilateral). All others will deny, investigational	• None listed	• None listed
UnitedHealthcare March 1, 2024[40] April 1, 2024[39]	CXL using an epithelium-off approach, riboflavin (vitamin B_2), and UVA is proven and medically necessary for the treatment of the following indications: • Progressive keratoconus • Corneal ectasia resulting from refractive surgery in individuals who have failed conservative treatment (e.g., rigid contact lens, spectacle correction)	CXL using an epithelium-off approach, riboflavin (vitamin B_2), and UVA. CXL is unproven and not medically necessary for all indications other than progressive keratoconus and corneal ectasia resulting from refractive surgery or using any other methods due to insufficient evidence of efficacy.	• None listed	• None listed
State Medicaid agencies				
Medi-Cal[37] (California Medicaid program) November 2022	Patient must have a diagnosis made by patient history and clinical exam of one of the following: • Progressive keratoconus • Corneal ectasia following refractive surgery	Providers must submit clinical documentation of the following on the treatment authorization request: • HCPCS code J2787 must be used for FDA-approved indications and dosages	• Intrastromal corneal ring segments	• None listed

Policy Author Last Review Date	Medical Necessity Criteria for CXL	CXL Coverage	Other Interventions Covered for Keratoconus	Considers Experimental or Investigational for Keratoconus
	and • Patient must be between the ages of 14 and 65 • Patient does not have active or history of herpes simplex virus (HSV) keratitis, thin corneas, or corneal hydrops	• HCPCS code J2787 must be prescribed by an ophthalmologist • Patient must have a diagnosis of one of the following: ○ Progressive keratoconus ○ Corneal ectasia following refractive surgery • Diagnosis was made by patient history and clinical exam • HCPCS code J2787 is being used for corneal collagen cross-linkage in combination with ultraviolet light • Patient must be between the ages of 14 and 65 • Patient does not have active or history of herpes simplex virus (HSV) keratitis, thin corneas, or corneal hydrops The treatment authorization request is authorized for three months (one treatment). Treatment is limited to once in a lifetime. Reauthorization is not approvable. Providers must document one of the following ICD-10-CM diagnosis codes with HCPCS code J2787 to support medical necessity: • H18.601 thru H18.629 • H18.711 thru H18.719 Frequency of billing is once in a lifetime. Maximum billing units for HCPCS code J2787 equals 6 mL or		

Policy Author Last Review Date	Medical Necessity Criteria for CXL	CXL Coverage	Other Interventions Covered for Keratoconus	Considers Experimental or Investigational for Keratoconus
		2 units when performing the corneal cross-linking procedure. Cost for J2787 (riboflavin) listed as $2,075 per 3ml vial[201] (1 vial needed per eye treated)		
Oregon Health Plan[41] (Oregon Medicaid program) January 1, 2024	Only for treatment of: • Progressive keratoconus, or • Corneal ectasia following refractive surgery; and only when there is objective progressive deterioration in vision	Only for conventional epithelium-off corneal CXL	• Intrastromal corneal ring segments • Keratoplasty	• None listed
Apple Health[38] (Washington state Medicaid program) April 1, 2024	Corneal thickness at thinnest point is at minimum 350 microns, and documented progression of keratoconus as evidenced by one or more of the following: • Increase of 1 D or more in the steepest keratometry measurement in the last 12 months (if the client is < 26 years old, interval can be 3 months) • Increase of 1 D or more in astigmatism in the last 12 months • Myopic shift of 0.5 D on subjective manifest refraction	Prior authorization is required. The following is required from providers: • The servicing provider must be classified as board eligible or board-certified with the American Board of Ophthalmology. • Providers must submit a completed Corneal Cross-Linking Prior Authorization Form with the request. • Providers must submit in full any supporting clinical documentation • Reimbursement amount for procedure 0402T (CXL) not including riboflavin solution: $525.65[202]	• Specialty contact lens designs for clients age 20 and younger[203]	• None listed

Abbreviations. CPT: Current Procedural Terminology; CXL: collagen cross-linking; D: diopter; FDA: US Food and Drug Administration; HCPCS: Healthcare Common Procedure Coding System; ICD-10: 10th revision of the International Classification of Diseases; ICD-10-CM: ICD-10 Clinical Modification; UVA: ultraviolet A.

Discussion

Based on the evidence in this report, we concluded that there is very low certainty of evidence that CXL improved visual acuity, maximal keratometry, or patient-reported visual function; or that CXL was associated with rare serious adverse events for individuals with progressive keratoconus. The limited number of trials, short length of follow-up, small sample sizes, high clinical and methodological heterogeneity, insufficient reporting of methods and results, and moderate to high risk of bias of included trials should be considered when drawing conclusions about the certainty of evidence for standard CXL for keratoconus. It is likely that new research will change our understanding of the effectiveness of CXL for keratoconus.

Meta-analysis results were mixed: 3 of the 5 meta-analyses favored standard CXL compared with no treatment, sham surgery, or standard care. All 3 of these meta-analyses included data from 12-month time points; the other 2 meta-analyses that did not favor either condition included data from later time points, which could indicate that there was an early benefit to CXL that faded over time. It is not clear how durable improvements in visual acuity and maximal keratometry are for individuals with keratoconus. Very little information about patient-reported visual function was reported in the included studies. Most individuals who underwent standard CXL did not report any serious adverse events. Infrequent serious adverse events for standard CXL included keratitis, sterile infiltrates, and scarring that impacted the vision of some individuals but not others. Less serious adverse events included corneal haze that typically resolved within a few months.

Comparisons of standard CXL with other protocols with experimental elements (e.g., epithelium-off, accelerated) generally did not favor any protocol, except for greater improvement in CDVA for epithelium-on groups and greater improvement in maximal keratometry for individualized PiXL.

Some of the 13 ongoing trials may provide more insight into the safety and efficacy of CXL in the next few years. Glaukos, the current owner of the riboflavin solutions used in standard CXL, is conducting a phase 3 confirmatory trial for Epioxa, which is an epithelium-on CXL treatment.[135] Glaukos plans to submit an application for a new drug approval to the FDA within the next year.[135]

A single cost analysis for standard CXL suggested that the procedure is cost-effective,[22] but the high risk of bias of this cost study and concerns about the model building should encourage readers to be cautious in accepting the validity and generalizability of these findings. The cost of the CXL procedure was noted as $1,780 plus the cost of the riboflavin solution, which was reported as $2,850.[22] However, the current wholesale acquisition cost of the solution kit used for the procedure is currently $4,150,[180] and the manufacturer has not signed a federal rebate agreement.[181] The cost of the riboflavin solution kit may be a barrier to CXL for individuals paying out of pocket, and we did not find information about the manufacturer's participation in rebate programs.

Both the NICE (2013) and AAO (2019) guidance documents concluded that standard CXL is generally safe and may be an effective intervention for slowing or halting the progression of keratoconus.[23,24] The AAO preferred practice pattern also emphasized the importance of early

diagnosis and treatment, given the progressive nature of the disease and the typically early onset (i.e., childhood or adolescence).[23] The authors of these guidance documents noted similar limitations in the body of evidence for CXL for keratoconus to the limitations we describe above, including lack of long-term follow-up to understand the durability of benefits associated with CXL, study design limitations (e.g., many studies lacked a control group), and methodological and statistical heterogeneity.

The 10 coverage policies we identified and describe varied in their criteria for medical necessity, but most specified that there must be documented progression of the keratoconus, and 5 required that the individual must be at least 14 years of age (in line with the FDA approval's minimum age).

In summary, we concluded that based on the trials included in this report there is very low certainty of evidence that CXL improved visual acuity, maximal keratometry, or patient-reported visual function, or that CXL was associated with rare serious adverse events for individuals with progressive keratoconus.

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Appendix A. Search Methods

Clinical Evidence Sources and Search Strategies

We searched selected bibliographic databases and gray literature sources using key words such as *keratoconus*, *corneal ectasia*, *collagen cross link**, *collagen cross-link**, *collagen crosslink**, *Photrexa*, and *KXL System* to identify randomized controlled trials, registry studies, cost and cost-effectiveness studies, and clinical practice guidelines. We did not use date limits, but we did limit search results to publications available in English language. Systematic reviews were used for reference list searching and not as evidence sources. Searches were conducted on November 27 through 29, 2023, and December 21, 2023.

Bibliographic Database Sources

- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- Ovid MEDLINE

Evidence Synthesis Sources

- Agency for Healthcare Research and Quality (AHRQ)
- Canada's Drug and Health Technology Agency (CADTH)
- Epistemonikos
- Health Quality Ontario
- Institute for Clinical and Economic Review (ICER)
- Institute for Health Quality and Efficiency in Health Care
- International HTA Database
- National Institute for Health and Care Excellence (NICE)
- Oregon Health Evidence Review Commission (HERC)
- Veterans Administration Evidence Synthesis Program (ESP)
- Washington Health Technology Assessment

Clinical Practice Guideline Sources

- American Academy of Ophthalmology
- American Optometric Association
- Canadian Medical Association (CMA)
- Cornea Research Foundation of America
- Cornea Society
- Guidelines International Network (GIN) International Guidelines Library
- Keratoconus International Consortium
- Scottish Intercollegiate Guidelines Network (SIGN)
- US Preventive Services Task Force (USPSTF)
- Veterans Administration/Department of Defense Clinical Practice Guidelines

Clinical Trial Sources

- ClinicalTrials.gov
- ScanMedicine

Regulatory Body and Manufacturer Sources

- Glaukos
- US Food and Drug Administration Drugs@FDA Search
- US Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE)
- US Food and Drug Administration MedWatch

Ovid MEDLINE ALL Search Strategy

1	keratoconus/
2	keratocon*.ti,ab,kf.
3	kerat?ectas*.ti,ab,kf.
4	(conical adj2 cornea*).ti,ab,kf.
5	(cornea* adj2 ectas*).ti,ab,kf.
6	forme fruste.ti,ab,kf.
7	(pellucid marginal adj2 degenerat*).ti,ab,kf.
8	or/1-7
9	exp photochemotherapy/
10	cross-linking reagents/
11	photosensitizing agents/
12	exp collagen/re
13	exp riboflavin/
14	exp ultraviolet therapy/
15	ultraviolet rays/
16	(photochemical? or photo-chemical? or photo chemical?).ti,ab,kf.
17	(photochemotherap* or photo-chemotherap* or photo chemotherap*).ti,ab,kf.
18	(photodynam* or photo-dynam* or photo dynam*).ti,ab,kf.
19	(photoactivat* or photo-activat* or photo activat*).ti,ab,kf.
20	(photosensiti* or photo-sensiti* or photo sensiti*).ti,ab,kf.
21	(crosslink* or cross-link* or cross link*).ti,ab,kf.
22	cxl.ti,ab,kf.

23 ((athens or cretan or dresden or tel aviv) adj2 (method* or protocol*)).ti,ab,kf.

24 riboflavin*.ti,ab,kf.

25 (vitamin* b2 or vitamin* b-2 or vitamin* b 2).ti,ab,kf.

26 vitamin* g.ti,ab,kf.

27 beflavin*.ti,ab,kf.

28 lactoflavin*.ti,ab,kf.

29 ovoflavin*.ti,ab,kf.

30 photrexa.ti,ab,kf.

31 (ultraviolet* or ultra-violet* or ultra violet*).ti,ab,kf.

32 (uv adj2 (light* or ray* or source*)).ti,ab,kf.

33 (uva or uv-a or uv a).ti,ab,kf.

34 (actinotherap* or actino-therap* or actino therap*).ti,ab,kf.

35 actinic ray*.ti,ab,kf.

36 (ilink or i-link or i link).ti,ab,kf.

37 or/9-36

38 clinical trials as topic/

39 clinical trials, phase iii as topic/

40 clinical trials, phase iv as topic/

41 comparative effectiveness research/

42 controlled clinical trials as topic/

43 double-blind method/

44 multicenter studies as topic/

45 exp randomized controlled trials as topic/

46 clinical trial.pt.

47 clinical trial, phase iii.pt.

48 clinical trial, phase iv.pt.

49 controlled clinical trial.pt.

50	equivalence trial.pt.
51	pragmatic clinical trial.pt.
52	randomized controlled trial.pt.
53	random*.ti,ab,kf.
54	((clinical or controlled or equivalence or randomi#ed) adj3 trial*).ti,ab,kf.
55	((single* or double* or triple* or treb* or quad*) adj1 (blind* or mask*)).ti,ab,kf.
56	(2 arm* or two arm* or 3 arm* or three arm* or 4 arm* or four arm* or 5 arm* or five arm*).ti,ab,kf.
57	(phase 3* or phase iii* or phase 4* or phase iv*).ti,ab,kf.
58	(head to head or head-to-head).ti,ab,kf.
59	(compar* adj3 (effectiveness or efficacy)).ti,ab,kf.
60	quasi*.ti,ab,kf.
61	or/38-60
62	adverse effects.fs.
63	complications.fs.
64	long term adverse effects/
65	exp patient-reported outcome measures/
66	exp quality of life/
67	complication*.ti,ab,kf.
68	safe*.ti,ab,kf.
69	harm*.ti,ab,kf.
70	((adverse or negative or rare or serious) adj2 (effect* or event* or reaction?)).ti,ab,kf.
71	((procedure-associated or procedure associated or procedure-induced or procedure induced or procedure-related or procedure related or treatment-associated or treatment associated or treatment-induced or treatment induced or treatment-related or treatment related) adj2 (event* or reaction? or side effect*)).ti,ab,kf.
72	revision*.ti,ab,kf.
73	(quality-of-life or quality of life).ti,ab,kf.
74	hrqol.ti,ab,kf.

75 (patient-report* or patient report*).ti,ab,kf.

76 or/62-75

77 exp "costs and cost analysis"/

78 economics.fs.

79 medicaid/

80 dual medicaid medicare eligibility/

81 cost?.ti,ab,kf.

82 economic*.ti,ab,kf.

83 medicaid*.ti,ab,kf.

84 or/77-83

85 clinical decision rules/

86 exp clinical protocols/

87 consensus/

88 exp consensus development conferences as topic/

89 critical pathways/

90 decision making, shared/

91 exp guidelines as topic/

92 health planning guidelines/

93 consensus development conference.pt.

94 consensus development conference, NIH.pt.

95 guideline.pt.

96 practice guideline.pt.

97 consensus.ti,kf.

98 guideline?.ti,kf.

99 position*.ti,kf.

100 recommend*.ti,kf.

101 ((committee or executive) adj2 (statement or summary)).ti,kf.

102 ((joint or position) adj2 statement).ti,kf.

103 ((clinical or critical or practice) adj2 (path* or pathway or standard? or statement)).ti,kf.

104 or/85-103

105 exp meta-analysis as topic/

106 systematic reviews as topic/

107 technology assessment, biomedical/

108 meta-analysis.pt.

109 systematic review.pt.

110 (metaanaly* or meta-analy* or meta analy*).ti,ab,kf.

111 (systematic adj2 (overview? or review?)).ti,ab,kf.

112 (technology adj assessment?).ti,ab,kf.

113 cinahl.ab.

114 cochrane.ab.

115 embase.ab.

116 medline.ab.

117 (psychinfo or psycinfo).ab.

118 pubmed.ab.

119 scopus.ab.

120 web of science.ab.

121 or/105-120

122 and/8,37,61

123 and/8,37,76

124 and/8,37,84

125 and/8,104

126 limit 125 to yr="2018 -Current"

127 and/8,37,121

128 or/122-124,126-127

129	(exp animals/ not humans/) or (baboon? or bovine? or canine? or cat? or chimpanzee? or cow? or dog? or feline? or fish or goat? or hens or macque? or mice or monkey? or mouse or murine? or ovine or pig? or porcine or primate? or sheep or rabbit? or rat or rats or rattus or rhesus or rodent? or zebrafish).ti.
130	128 not 129
131	limit 130 to english language

Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library Search Strategy

1	[mh keratoconus]
2	(keratocon*):ti,ab,kw
3	(kerat?ectas*):ti,ab,kw
4	(conical NEAR/2 cornea*):ti,ab,kw
5	(cornea NEAR/2 ectas*):ti,ab,kw
6	("forme fruste"):ti,ab,kw
7	("pellucid marginal" NEAR/2 degenerat*):ti,ab,kw
8	{OR #1-#7}
9	[mh photochemotherapy]
10	[mh ^"cross-linking reagents"]
11	[mh "photosensitizing agents"]
12	[mh collagen/RE]
13	[mh riboflavin]
14	[mh "ultraviolet therapy"]
15	[mh "ultraviolet rays"]
16	(photochemical? OR photo-chemical? OR photo NEXT chemical?):ti,ab,kw
17	(photochemotherap* OR photo-chemotherap* OR photo NEXT chemotherap*):ti,ab,kw
18	(photodynam* OR photo-dynam* OR photo NEXT dynam*):ti,ab,kw
19	(photoactivat* OR photo-activat* OR photo NEXT activat*):ti,ab,kw
20	(photosensiti* OR photo-sensiti* OR photo NEXT sensiti*):ti,ab,kw
21	(crosslink* OR cross-link* OR cross NEXT link*):ti,ab,kw
22	(cxl):ti,ab,kw
23	((athens OR cretan OR dresden OR "tel aviv") NEAR/2 (method* OR protocol*)):ti,ab,kw
24	(riboflavin*):ti,ab,kw
25	(vitamin* b2 OR vitamin* b-2 OR "vitamin b 2"):ti,ab,kw
26	("vitamin g"):ti,ab,kw
27	(beflavin*):ti,ab,kw

28 (lactoflavin*):ti,ab,kw
29 (ovoflavin*):ti,ab,kw
30 (photrexa):ti,ab,kw
31 (ultraviolet* OR ultra-violet* OR ultra NEXT violet*):ti,ab,kw
32 (uv NEAR/2 (light* OR ray* OR source*)):ti,ab,kw
33 (uva OR uv-a OR "uv a"):ti,ab,kw
34 (actinotherap* OR actino-therap* OR actino NEXT therap*):ti,ab,kw
35 ("actinic ray"):ti,ab,kw
36 (ilink OR i-link OR "i link"):ti,ab,kw
37 {OR #9-#36}
38 {AND #8, #37} in Cochrane Reviews, Trials

Policy Sources and Search Terms

We searched websites for the state Medicaid programs and private payers listed below using terms such as *keratoconus*, *collagen cross-linking*, *CXL*, *040T*, *J2787*, *riboflavin*, *H18.6**, *cornea**, *ectasia*, *ophthamolo**, *vision*, *optic**, and *eye*.

State Medicaid Programs

- California Medicaid
- Florida Medicaid
- Massachusetts Medicaid
- New Jersey Medicaid
- New York Medicaid
- North Carolina Medicaid
- Oregon Medicaid and the Health Evidence Review Commission (HERC) coverage guidance (including topics under consideration)
- Pennsylvania Medicaid
- Texas Medicaid
- Washington Medicaid and the Washington Health Technology Assessment Program coverage determinations (including topics under consideration)

Private Payers

- Aetna
- Anthem Blue Cross and Blue Shield (formerly Empire BlueCross BlueShield)
- Highmark Blue Shield of Northeastern New York
- Capital District Physicians' Health Plan
- Cigna
- EmblemHealth
- Excellus BlueCross BlueShield
- Tufts Health Plan
- UnitedHealthcare

Appendix B. Detailed Inclusion and Exclusion Criteria

Table B. Detailed Inclusion and Exclusion Criteria

Study Component	Inclusion	Exclusion
Populations	• Individuals with keratoconus	• Individuals with other corneal ectasias, such post–refractive surgery progressive corneal ectasia
Interventions	• Any method of CXL that involves the use of riboflavin (vitamin B_2) eyedrops and UVA light to promote formation of new collagen bonds • Studies in which different adjunctive therapies were used in both treatment arms • Studies in which chemical enhancers or topical anesthetics were used to improve transepithelial stromal absorption of riboflavin	• Treatments without CXL
Comparators	• No treatment • Standard care to reduce precipitating factors • Head-to-head comparisons of different protocols for CXL • Treatments to promote visual rehabilitation without adjunctive CXL (e.g., scleral contact lens, intracorneal ring segments, toric intraocular collamer lens, deep anterior lamellar keratoplasty, and laser-based treatments)	• None listed
Outcomes	<u>Critical</u> • Maximal keratometry • Visual acuity <u>Important</u> • Patient-reported visual function parameters • Serious adverse events, including corneal perforation and infection	• Central corneal thickness, thinnest corneal point (pachymetry) • Refraction (spherical equivalent) • High order aberrations (e.g., spherical, coma, trefoil)
Timing and follow-up	• Minimum follow-up of 12 months	• Less than 12 months of follow-up
Setting	• In-office procedure • Ambulatory in-hospital procedure (e.g., for children or adults who may need sedation or anesthesia to tolerate the procedure)	• Studies conducted in countries not categorized as very high on the Human Development Index

Study Component	Inclusion	Exclusion
Study design	KQ1 and KQ2 • Randomized controlled trials for effectiveness and harms • Registry studies for harms KQ3 • Comparative studies and economic evaluations • Cost-effectiveness analyses • Economic simulation modeling studies KQ4 • Evidence-based clinical practice guidelines that provide specific recommendations	• Studies without a comparator • Proof-of-principle studies (e.g., procedure development or technique modification) • Studies without extractable data • Uncontrolled studies • Retrospective studies unless otherwise noted
Sample size	• No limit on number of eyes or participants included	• None listed
Publication type	• Peer-reviewed publication of primary study results • Published in the English language • Ancillary publications with additional comparative follow-up	• Abstracts, conference proceedings, posters, editorials, letters • Studies that have not been formally peer reviewed (i.e., preprint publications) • Studies published in languages other than English • Studies that cannot be found • Duplicate publications of the same study that do not report different outcomes or follow-up times, or single-site reports from published multicenter studies

Abbreviations. CXL: collagen cross-linking; KQ: key question; UVA: ultraviolet A.

Appendix C. Additional Evidence Tables and Figures

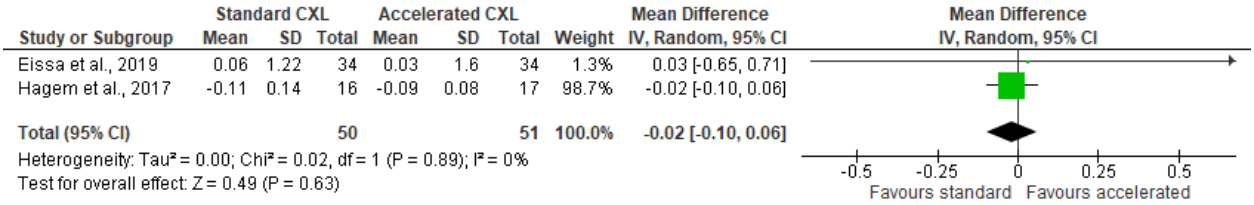
Standard CXL vs. Accelerated CXL: Tables and Figures

Table C1. Standard CXL vs. Accelerated CXL: Mean Change in CDVA (logMAR[a])

Author, Year Risk of Bias	Standard CXL Group N Mean, SD	Accelerated CXL Group N Mean, SD	Between-Group Difference
12 months after baseline			
Eissa et al., 2019[167] Moderate risk of bias	N = 34 Mean, 0.06; SD, 1.22	N = 34 Mean, 0.03; SD, 1.60	NR, NR
Hagem et al., 2017[168] High risk of bias	N = 16 Mean, −0.11; SD, 0.14	N = 17 Mean, −0.09; SD, 0.08	NR, *P* = .53
24 months after baseline			
Burcel et al., 2022[166] High risk of bias	N = 42 Mean, 0.09; SD, 0.22	N = 37 Mean, 0.16; SD, 0.23	NR, *P* = .117
Eissa et al., 2019[167] Moderate risk of bias	N = 34 Mean, 0.06; SD, 1.40	N = 34 Mean, 0.03; SD, 1.40	NR, NR
Hagem et al., 2017[168] High risk of bias	N = 16 Mean, −0.13; SD, 0.14	N = 17 Mean, −0.10; SD, 0.11	NR, *P* = .48
Uçakhan and Yeşiltaş, 2020[165] Moderate risk of bias	N = 32 Mean, 0.12; SD, 0.1	N = 27 Mean, 0.10; SD, 0.1	NR, *P* = .351
36 months after baseline			
Eissa et al., 2019[167] Moderate risk of bias	N = 34 Mean, 0.06; SD, 1.22	N = 34 Mean, 0.03; SD, 1.60	NR, NR

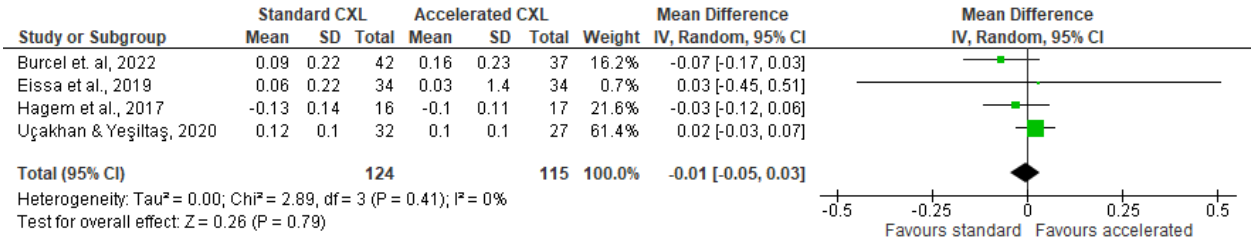
Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CVDA: corrected distance visual acuity; CXL: collagen cross-linking; logMAR: logarithm of the minimum angle of resolution; N: number; NR: not reported; SD: standard deviation.

Figure C1. Standard CXL vs. Accelerated CXL: Mean Change in CDVA at 12 Months (logMAR[a])



Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; CVDA: corrected distance visual acuity; CXL: collagen cross-linking; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; vs.: versus.

Figure C2. Standard CXL vs. Accelerated CXL: Mean Change in CDVA at 24 Months (logMAR[a])



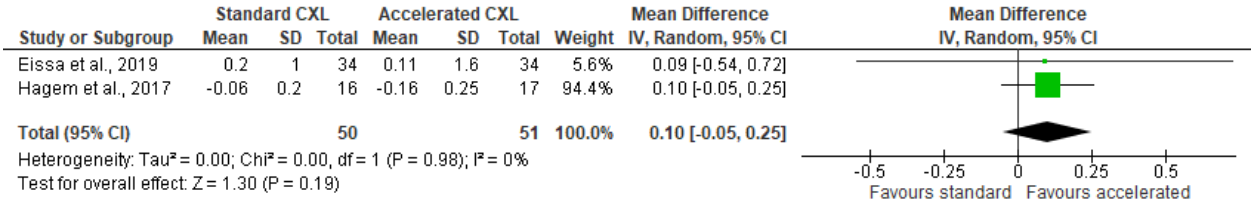
Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; CVDA: corrected distance visual acuity; CXL: collagen cross-linking; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; vs.: versus.

Table C2. Standard CXL vs. Accelerated CXL: Mean Change in UCVA (logMAR[a])

Author, Year Risk of Bias	Standard CXL Group N Mean, SD	Accelerated CXL Group N Mean, SD	Between-Group Difference
12 months after baseline			
Eissa et al., 2019[167] Moderate risk of bias	N = 34 Mean, 0.20; SD, 1.00	N = 34 Mean, 0.11; SD 1.60	NR, *P* < .05
Hagem et al., 2017[168] High risk of bias	N = 16 Mean, −0.06; SD, 0.20	N = 17 Mean, −0.16; SD, 0.25	NR, *P* = .22
24 months after baseline			
Eissa et al., 2019[167] Moderate risk of bias	N = 34 Mean, 0.20; SD, 0.92	N = 34 Mean, 0.11; SD, 1.52	NR, *P* < .05
Uçakhan and Yeşiltaş, 2020[165] Moderate risk of bias	N = 32 Mean, 0.46; SD, 0.4	N = 27 Mean, 0.43; SD, 0.5	NR, *P* = .082
36 months after baseline			
Eissa et al., 2019[167] Moderate risk of bias	N = 34 Mean, 0.20; SD, 1.0	N = 34 Mean, 0.11; SD, 1.60	NR, NR

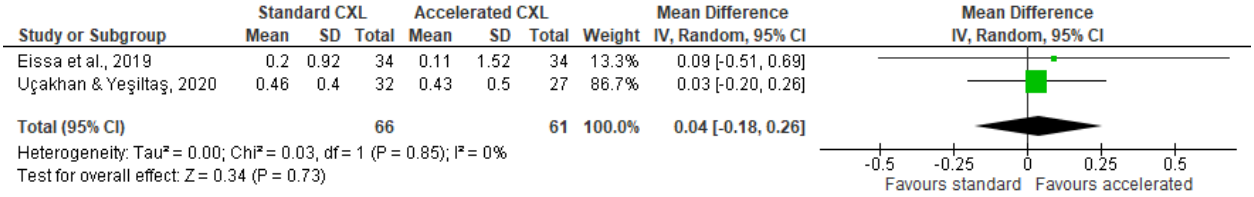
Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CXL: collagen cross-linking; logMAR: logarithm of the minimum angle of resolution; N: number; NR: not reported; SD: standard deviation; UCVA: uncorrected visual acuity.

Figure C3. Standard CXL vs. Accelerated CXL: Mean Change in UCVA at 12 Months (logMAR[a])



Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; CXL: collagen cross-linking; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; UCVA: uncorrected visual acuity; vs.: versus.

Figure C4. Standard CXL vs. Accelerated CXL: Mean Change in UCVA at 24 Months (logMAR[a])



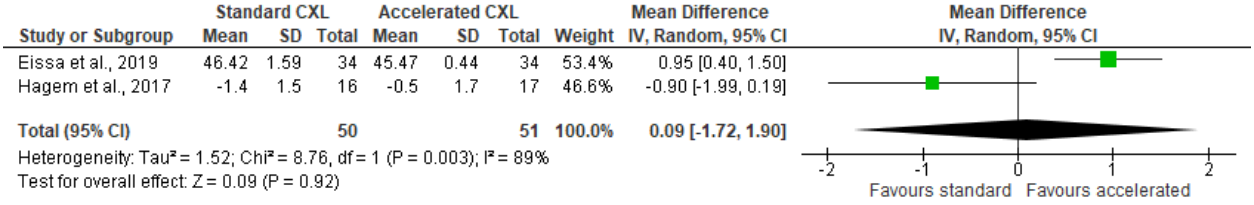
Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; CXL: collagen cross-linking; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; UCVA: uncorrected visual acuity; vs.: versus.

Table C3. Standard CXL vs. Accelerated CXL: Mean Change in Maximal Keratometry (Diopters)

Author, Year Risk of Bias	Standard CXL Group N Mean, SD	Accelerated CXL Group N Mean, SD	Between-Group Difference
12 months after baseline			
Eissa et al., 2019[167] Moderate risk of bias	N = 34 Mean, 46.41[a]; SD, 1.59	N = 34 Mean, 45.47; SD, 0.44	NR, NR
Hagem et al., 2017[168] High risk of bias	N = 16 Mean, -1.4; SD, 1.5	N = 17 Mean, −0.5; SD, 1.7	NR, *P* = .11
24 months after baseline			
Burcel et al., 2022[166] High risk of bias	N = 42 Mean, -1.13; SD, 1.22	N = 37 Mean, −0.96; SD, 1.09	NR, *P* = .52
Eissa et al., 2019[167] Moderate risk of bias	N = 34 Mean, 46.43[a]; SD, 1.43	N = 34 Mean, 45.48; SD, 0.44	NR, NR
Hagem et al., 2017[168] High risk of bias	N = 16 Mean, -1.6; SD, 2.1	N = 17 Mean, -1.0; SD, 1.3	NR, *P* = .28
Uçakhan and Yeşiltaş, 2020[165] Moderate risk of bias	N = 32 Mean, 53.8; SD, 7.2	N = 27 Mean, 55.6; SD, 5.4	NR, *P* = .49
36 months after baseline			
Eissa et al., 2019[167] Moderate risk of bias	N = 34 Mean, 46.45[a]; SD, 1.43	N = 34 Mean, 45.47; SD, 0.54	NR, NR

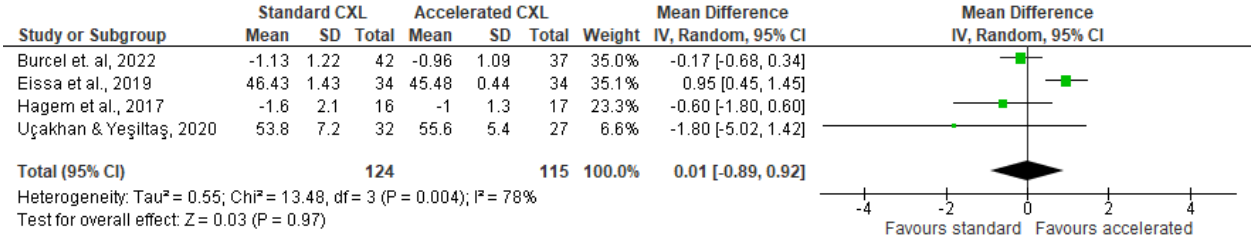
Note. [a] *The Eissa study reported maximal keratometry in mean diopters at 12, 18, and 36 months after baseline, instead of mean change in diopters.*
Abbreviations. CXL: collagen cross-linking; N: number; NR: not reported; SD: standard deviation.

Figure C5. Standard CXL vs. Accelerated CXL: Mean Change in Maximal Keratometry at 12 Months



Abbreviations. CI: confidence interval; CXL: collagen cross-linking; IV: inverse variance; SD: standard deviation; vs.: versus.

Figure C6. Standard CXL vs. Accelerated CXL: Mean Change in Maximal Keratometry at 24 Months (Diopters)



Abbreviations. CI: confidence interval; CXL: collagen cross-linking; IV: inverse variance; SD: standard deviation; vs.: versus.

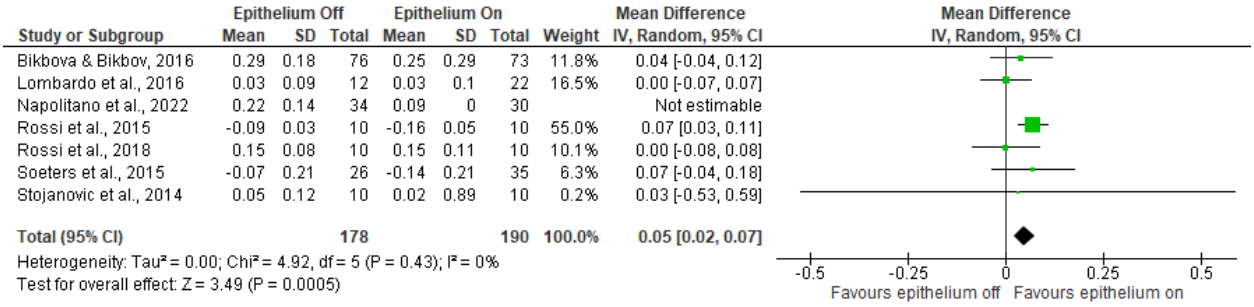
Epithelium-Off vs. Epithelium-On Protocols: Tables and Figures

Table C4. Epithelium-Off vs. Epithelium-On: Mean Change in CDVA (logMAR[a])

Author, Year Risk of Bias	Epithelium Off Group N Mean, SD	Epithelium On Group N Mean, SD	Between-Group Difference
12 months after baseline			
Bikbova and Bikbov, 2016[171] High risk of bias	N = 76 Mean, 0.29; SD, 0.18	N = 73 Mean, 0.25; SD, 0.29	NR, NR
Lombardo et al., 2016[175] High risk of bias	N = 12 Mean, 0.03; SD, 0.09	N = 22 Mean, 0.03; SD, 0.10	NR, *P* = .12
Napolitano et al., 2022[169] High risk of bias	N = 34 Mean, 0.22; SD, 0.14	N = 30 Mean, 0.09; SD, 0.0	NR, *P* = .90
Rossi et al., 2015[29] Moderate risk of bias	N = 10 Mean, −0.09; SD, 0.03	N = 10 Mean, −0.16; SD, 0.05	NR, *P* = .003
Rossi et al., 2018[30] High risk of bias	N = 10 Mean, 0.15; SD, 0.08	Iontophoresis N = 10 Iontophoresis mean, 0.15; SD, 0.11 Standard N = 10 Standard mean, 0.12; SD, 0.04	NR, NR
Soeters et al., 2015[32] Moderate risk of bias	N = 26 Mean, −0.07; SD, 0.21	N = 35 Mean, −0.14; SD, 0.21	NR, *P* = .023
Stojanovic et al., 2014[172] Moderate risk of bias	N = 10 Mean, 0.05; SD, 0.12	N = 10 Mean, 0.02; SD, 0.89	NR, *P* = .239
24 months after baseline			
Bikbova and Bikbov, 2016[171] High risk of bias	N = 76 Mean, 0.30; SD, 0.27	N = 73 Mean, 0.26; SD, 0.56	NR, *P* = .829
Caruso et al., 2021[25] High risk of bias	N = 29 Mean, −0.04; SD, 0.015	N = 25 Mean, −0.015; SD, 0.005	NR, NR
Cifariello et al., 2018[170] High risk of bias	N = 20 Mean, 0.27; SD, 0.19	N = 20 Mean, 0.22; SD, 0.17	NR, *P* = .01
Lombardo et al., 2016[175] High risk of bias	N = 12 Mean, 0.03; SD, 0.09	N = 22 Mean, 0.04; SD, 0.13	NR, *P* = .17
Napolitano et al., 2022[169] High risk of bias	N = 34 Mean, 0.22; SD, 0.14	N = 30 Mean, 0.09; SD, 0.01	NR, *P* = .90
Rush and Rush, 2016[31] Moderate risk of bias	N = 39 Mean, −0.20; 95% CI, −0.31 to −0.08	N = 63 Mean, −0.15; 95% CI, −0.25 to −0.05	NR, *P* = .54

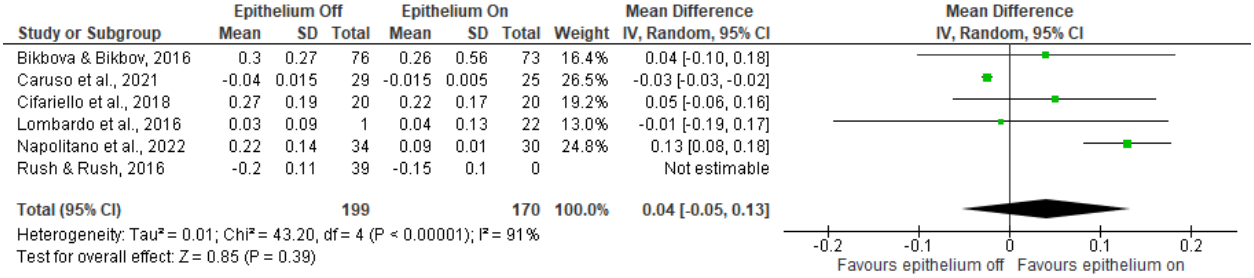
Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CVDA: corrected distance visual acuity; logMAR: logarithm of the minimum angle of resolution; N: number; NR: not reported; SD: standard deviation.

Figure C7. Epithelium-Off vs. Epithelium-On Protocols: Mean Change in CDVA at 12 Months (logMAR[a])



Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; CVDA: corrected distance visual acuity; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; vs.: versus.

Figure C8. Epithelium-Off vs. Epithelium-On Protocols: Mean Change in CDVA at 24 Months (logMAR)



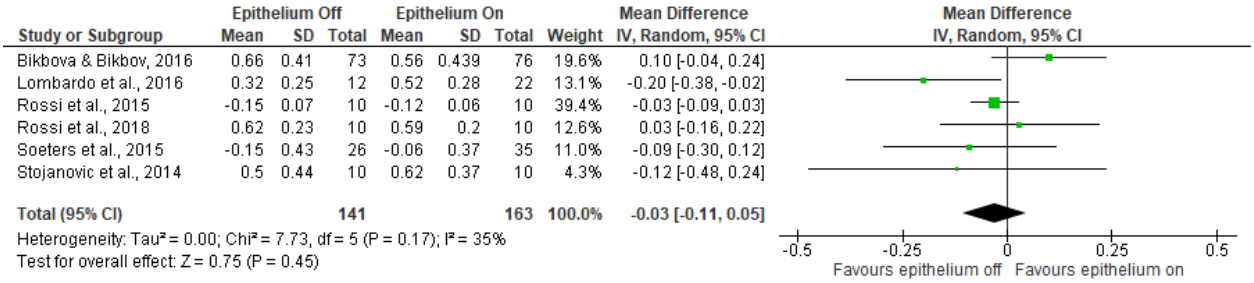
Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; CVDA: corrected distance visual acuity; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; vs.: versus.

Table C5. Epithelium-Off vs. Epithelium-On: Mean Change in UCVA (logMAR[a])

Author, Year Risk of Bias	Epithelium Off Group N Mean, SD	Epithelium On Group N Mean, SD	Between-Group Difference
12 months after baseline			
Bikbova and Bikbov, 2016[171] High risk of bias	N = 73 Mean, 0.66; SD, 0.41	N = 76 Mean, 0.56; SD, 0.439	NR, NR
Lombardo et al., 2016[175] High risk of bias	N = 12 Mean, 0.32; SD, 0.25	N = 22 Mean, 0.52; SD, 0.28	NR, *P* = .71
Rossi et al., 2015[29] Moderate risk of bias	N = 10 Mean, −0.15; SD, 0.07	N = 10 Mean, −0.12; SD, 0.06	NR, *P* = .38
Rossi et al., 2018[30] High risk of bias	N = 10 Mean, 0.62; SD, 0.23	Iontophoresis N = 10 Iontophoresis mean, 0.59; SD, 0.2 Standard N = 10 Standard mean, 0.6; SD, 0.17	NR, NR
Soeters et al., 2015[32] Moderate risk of bias	N = 26 Mean, −0.15; SD, 0.43	N = 35 Mean, −0.06; SD, 0.37	NR, *P* = .59
Stojanovic et al., 2014[172] Moderate risk of bias	N = 10 Mean, 0.50; SD, 0.44	N = 10 Mean, 0.62; SD, 0.37	NR, *P* = .289
24 months after baseline			
Bikbova and Bikbov, 2016[171] High risk of bias	N = 76 Mean, 0.68; SD, 0.56	N = 73 Mean, 0.53; SD, 0.42	NR, NR
Lombardo et al., 2016[175] High risk of bias	N = 12 Mean, 0.32; SD, 0.29	N = 22 Mean, 0.48; SD, 0.36	*P* = .78

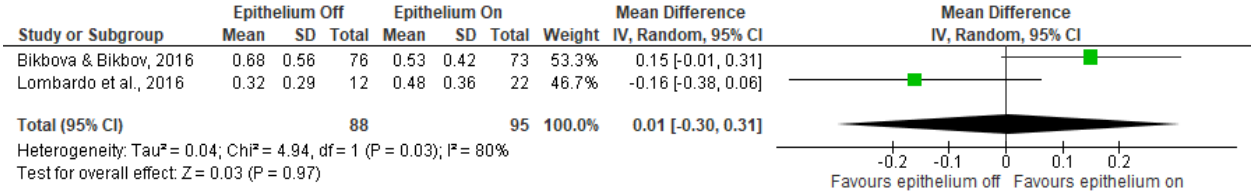
Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. logMAR: logarithm of the minimum angle of resolution; N: number; NR: not reported; SD: standard deviation; UCVA: uncorrected visual acuity.

Figure C9. Epithelium-Off vs. Epithelium-On Protocols: Mean Change in UCVA at 12 Months (logMAR[a])



Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; UCVA: uncorrected visual acuity; vs.: versus.

Figure C10. Epithelium-Off vs. Epithelium-On Protocols: Mean Change in UCVA at 24 Months (logMAR[a])



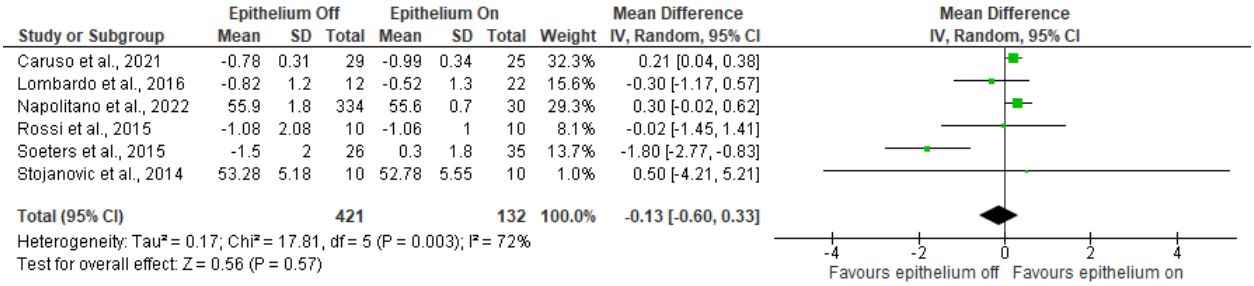
Note. [a] *Negative values for the logMAR indicate good vision, a value of zero indicates standard vision, and positive values indicate poor vision.*
Abbreviations. CI: confidence interval; IV: inverse variance; logMAR: logarithm of the minimum angle of resolution; SD: standard deviation; UCVA: uncorrected visual acuity; vs.: versus.

Table C6. Epithelium-Off vs. Epithelium-On: Mean Change in Maximal Keratometry (Diopters)

Author, Year Risk of Bias	Epithelium Off Group N Mean, SD	Epithelium On Group N Mean, SD	Between-Group Difference
12 months after baseline			
Caruso et al., 2021[25] High risk of bias	N = 29 Mean, −0.78; SD, 0.31	N = 25 Mean, −0.99; SD, 0.34	NR, NR
Lombardo et al., 2016[175] High risk of bias	N = 12 Mean, −0.82; SD, 1.20	N = 22 Mean, −0.52; SD, 1.30	NR, *P* = .53
Napolitano et al., 2022[169] High risk of bias	N = 34 Mean, 55.9[a]; SD, 1.8	N = 30 Mean, 55.6 [a]; SD, 0.7	NR, *P* = .96
Rossi et al., 2015[29] Moderate risk of bias	N = 10 Mean, -1.08; SD, 2.08	N = 10 Mean, -1.06; SD, 1.00	NR, *P* = .97
Soeters et al., 2015[32] Moderate risk of bias	N = 26 Mean, -1.5; SD, 2.0	N = 35 Mean, 0.3; SD, 1.8	NR, *P* = .022
Stojanovic et al., 2014[172] Moderate risk of bias	N = 10 Mean, 53.28[a]; SD, 5.18	N = 10 Mean, 52.78[a]; SD, 5.55	NR, *P* = .755
24 months after baseline			
Caruso et al., 2021[25] High risk of bias	N = 29 Mean, −0.97; SD, 0.35	N = 25 Mean, -1.1; SD, 0.38	NR, NR
Lombardo et al., 2016[175] High risk of bias	N = 12 Mean, 53.2[a]; SD, 4.9	N = 22 Mean, 53.7[a]; SD, 4.0	NR, *P* = .06
Napolitano et al., 2022[169] High risk of bias	N = 30 Mean, 56.2[a]; SD, 1.8	N = 34 Mean, 55.9[a]; SD, 0.7	NR, *P* = .96

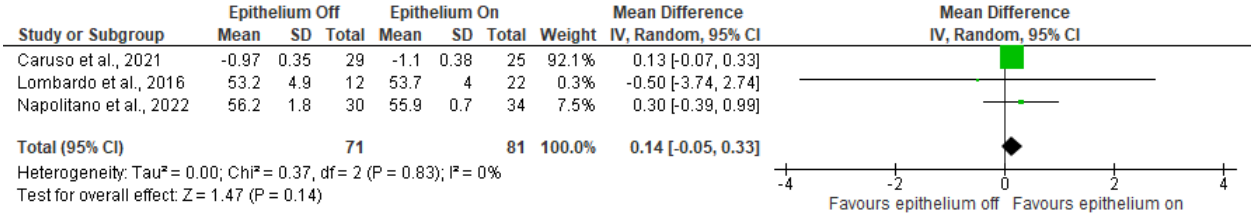
Note. [a] The Lombardo, Napolitano, and Stojanovic studies reported maximal keratometry in mean diopters, instead of mean change in diopters.
Abbreviations. N: number; NR: not reported; SD: standard deviation.

Figure C11. Epithelium-Off vs. Epithelium-On Protocols: Mean Change in Maximal Keratometry at 12 Months (Diopters)



Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation; vs.: versus.

Figure C12. Epithelium-Off vs. Epithelium-On Protocols: Mean Change in Maximal Keratometry at 24 Months (Diopters)



Abbreviations. CI: confidence interval; IV: inverse variance; SD: standard deviation; vs.: versus.

Appendix D. Included Studies

Table D. Studies Included in Clinical Evidence Review of Treatments for Keratoconus

Primary Publication from Included Trial	Publications Reporting Additional Results
Bikbova G, Bikbov M. Standard corneal collagen crosslinking versus transepithelial iontophoresis-assisted corneal crosslinking, 24 months follow-up: randomized control trial. *Acta Ophthalmol.* 2016;94(7):e600-e606. doi: 10.1111/aos.13032.	None identified
Burcel MG, Lacraru IC, Dascalescu DMC, Corbu MC, Potop V, Coviltir V. Assessment of two-year clinical outcomes after keratoconus treatment using two different crosslinking protocols. *Eur Rev Med Pharmacol Sci.* 2022;26(3):906-916. doi: 10.26355/eurrev_202202_28000.	None identified
Caruso C, Epstein RL, Troiano P, Napolitano F, Scarinci F, Costagliola C. Topo-pachimetric accelerated epi-on cross-linking compared to the Dresden protocol using riboflavin with vitamin E TPGS: results of a 2-year randomized study. *J Clin Med.* 2021;10(17):25. doi: 10.3390/jcm10173799.	None identified
Cifariello F, Minicucci M, Di Renzo F, et al. Epi-off versus epi-on corneal collagen cross-linking in keratoconus patients: a comparative study through 2-year follow-up. *J Ophthalmol.* 2018;2018:4947983. doi: 10.1155/2018/4947983.	None identified
Eissa SA, Yassin A. Prospective, randomized contralateral eye study of accelerated and conventional corneal cross-linking in pediatric keratoconus. *Int Ophthalmol.* 2019;39(5):971-979. doi: 10.1007/s10792–018–0898-y.	None identified
Ferdi AC, Kandel H, Nguyen V, et al. Five-year corneal cross-linking outcomes: a Save Sight Keratoconus Registry Study. *Clin Exp Ophthalmol.* 2023;51(1):9-18. doi: 10.1111/ceo.14177.	None identified
Hagem AM, Thorsrud A, Sandvik GF, Raen M, Drolsum L. Collagen crosslinking with conventional and accelerated ultraviolet-A irradiation using riboflavin with hydroxypropyl methylcellulose. *J Cataract Refract Surg.* 2017;43(4):511-517. doi: 10.1016/j.jcrs.2017.01.013.	Hagem AM, Thorsrud A, Sandvik GF, Drolsum L. Randomized study of collagen cross-linking with conventional versus accelerated UVA irradiation using riboflavin with hydroxypropyl methylcellulose: two-year results. *Cornea.* 2019;38(2):203-209. doi: 10.1097/ICO.0000000000001791.
Kandel H, Abbondanza M, Gupta A, et al. Comparison of standard versus accelerated corneal collagen cross-linking for keratoconus: 5-year outcomes from the Save Sight Keratoconus Registry. *Eye (Lond).* 2023;27:27. doi: 10.1038/s41433–023–02641-6.	None identified
Kandel H, Nguyen V, Ferdi AC, et al. Comparative efficacy and safety of standard versus accelerated corneal crosslinking for keratoconus: 1-year outcomes from the Save Sight Keratoconus Registry study. *Cornea.* 2021;40(12):1581-1589. doi: 10.1097/ICO.0000000000002747.	None identified

Primary Publication from Included Trial	Publications Reporting Additional Results
Kirgiz A, Eliacik M, Yildirim Y. Different accelerated corneal collagen cross-linking treatment modalities in progressive keratoconus. *Eye Vis (Lond).* 2019;6:16. doi: 10.1186/s40662−019−0141-6.	None identified
Lang SJ, Messmer EM, Geerling G, et al. Prospective, randomized, double-blind trial to investigate the efficacy and safety of corneal cross-linking to halt the progression of keratoconus. *BMC Ophthalmol.* 2015;15:78. doi: 10.1186/s12886−015−0070-7.	None identified
Larkin DFP, Chowdhury K, Burr JM, et al. Effect of corneal cross-linking versus standard care on keratoconus progression in young patients: the KERALINK randomized controlled trial. *Ophthalmology.* 2021;128(11):1516-1526. doi: 10.1016/j.ophtha.2021.04.019.	Larkin DFP, Chowdhury K, Dore CJ, et al. Epithelium-off corneal cross-linking surgery compared with standard care in 10- to 16-year-olds with progressive keratoconus: the KERALINK RCT. *Efficacy and Mechanism Evaluation.* 2021;8(15). doi: 10.3310/eme08150.
Lindstrom RL, Berdahl JP, Donnenfeld ED, et al. Corneal cross-linking versus conventional management for keratoconus: a lifetime economic model. *J Med Econ.* 2021;24(1):410-420. doi: 10.1080/13696998.2020.1851556.	
Lombardo M, Giannini D, Lombardo G, Serrao S. Randomized controlled trial comparing transepithelial corneal cross-linking using iontophoresis with the Dresden protocol in progressive keratoconus. *Ophthalmology.* 2017;124(6):804-812. doi: 10.1016/j.ophtha.2017.01.040.	Lombardo M, Serrao S, Lombardo G, Schiano-Lomoriello D. Two-year outcomes of a randomized controlled trial of transepithelial corneal crosslinking with iontophoresis for keratoconus. *J Cataract Refract Surg.* 2019;45(7):992-1000. doi: 10.1016/j.jcrs.2019.01.026. Lombardo M, Serrao S, Raffa P, Rosati M, Lombardo G. Novel technique of transepithelial corneal cross-linking using iontophoresis in progressive keratoconus. *J Ophthalmol.* 2016;2016:7472542. doi: 10.1155/2016/7472542.
Meyer JJ, Jordan CA, Patel DV, et al. Five-year results of a prospective, randomised, contralateral eye trial of corneal crosslinking for keratoconus. *Clin Exp Ophthalmol.* 2021;49(6):542-549. doi: 10.1111/ceo.13959.	None identified
Napolitano P, Tranfa F, D'Andrea L, et al. Topographic outcomes in keratoconus surgery: epi-on versus epi-off iontophoresis corneal collagen cross-linking. *J Clin Med.* 2022;11(7):24. doi: 10.3390/jcm11071785.	None identified
Nordström M, Schiller M, Fredriksson A, Behndig A. refractive improvements and safety with topography-guided corneal crosslinking for keratoconus: 1-year results. *Br J Ophthalmol.* 2017;101(7):920-925. doi: 10.1136/bjophthalmol-2016-309210.	None identified

Primary Publication from Included Trial	Publications Reporting Additional Results
O'Brart DP, Chan E, Samaras K, Patel P, Shah SP. A randomised, prospective study to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linkage to halt the progression of keratoconus. *Br J Ophthalmol.* 2011;95(11):1519-1524. doi: 10.1136/bjo.2010.196493.	None identified
Rossi S, Orrico A, Santamaria C, et al. Standard versus trans-epithelial collagen cross-linking in keratoconus patients suitable for standard collagen cross-linking. *Clin Ophthalmol.* 2015;9:503-509. doi: 10.2147/OPTH.S73991.	None identified
Rossi S, Santamaria C, Boccia R, et al. Standard, transepithelial and iontophoresis corneal cross-linking: clinical analysis of three surgical techniques. *Int Ophthalmol.* 2018;38(6):2585-2592. doi: 10.1007/s10792–017–0772-3.	None identified
Rush SW, Rush RB. Epithelium-off versus transepithelial corneal collagen crosslinking for progressive corneal ectasia: a randomised and controlled trial. *Br J Ophthalmol.* 2017;101(4):503-508. doi: 10.1136/bjophthalmol-2016-308914.	None identified
Soeters N, Wisse RP, Godefrooij DA, Imhof SM, Tahzib NG. Transepithelial versus epithelium-off corneal cross-linking for the treatment of progressive keratoconus: a randomized controlled trial. *Am J Ophthalmol.* 2015;159(5):821-828 e823. doi: 10.1016/j.ajo.2015.02.005.	Godefrooij DA, Kandoussi ME, Soeters N, Wisse RP. Higher order optical aberrations and visual acuity in a randomized controlled trial comparing transepithelial versus epithelium-off corneal crosslinking for progressive keratoconus. *Clin Ophthalmol.* 2017;11:1931-1936. doi: 10.2147/OPTH.S139358.
Stojanovic A, Zhou W, Utheim TP. Corneal collagen cross-linking with and without epithelial removal: a contralateral study with 0.5% hypotonic riboflavin solution. *Biomed Res Int.* 2014;2014:619398. doi: 10.1155/2014/619398.	None identified
Uçakhan OO, Yeşiltaş YS. Comparative 2-year outcomes of conventional and accelerated corneal collagen crosslinking in progressive keratoconus. *Int J Ophthalmol.* 2020;13(8):1223-1230. doi: 10.18240/ijo.2020.08.07.	None identified
Wittig-Silva C, Whiting M, Lamoureux E, Lindsay RG, Sullivan LJ, Snibson GR. A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. *J Refract Surg.* 2008;24(7):S720-725. doi: 10.3928/1081597X-20080901-15.	Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology.* 2014;121(4):812-821. doi: 10.1016/j.ophtha.2013.10.028.

Appendix E. Excluded Studies With Primary Reason for Exclusion

Table E lists the publications that were excluded during full text review and the primary reason for exclusion. There may be multiple reasons for exclusion for any given publication, and the table lists only the most influential reason for exclusion.

The series of publications[12,142,146,204-210] from the US-based trials that produced results submitted in the application for US Food and Drug Administration (FDA) approval of riboflavin with an ultraviolet light source device for the collagen cross-linking procedure were excluded. These trials included a crossover of the participants initially assigned to the sham condition into the treatment condition 3 months after baseline.[146] The inclusion criteria for this report required trials to maintain a comparison group for a minimum of 12 months after the treatment group received the intended intervention. During the approval process for the riboflavin ophthalmic solutions (Photrexa and Photrexa Viscous) and ultraviolet A light source (the KXL System), FDA reviewers repeatedly expressed concerns with these trials, including: low patient enrollment (compared to planned enrollment); change in primary endpoint from 3 months to 12 months; treatment of participants assigned to sham condition with collagen cross-linking after 3 months; statistical analysis plan not finalized until after study enrollment and follow-up were completed; and device used in the clinical trials (IROC UV-X) being different from to-be-marketed device (the KXL System).[140,141,179,211,212]

Table E. Excluded Studies With Primary Reason for Exclusion

Reference Information	Primary Reason for Exclusion
Achiron A, El-Hadad O, Leadbetter D, et al. Progression of pediatric keratoconus after corneal cross-linking: a systematic review and pooled analysis. *Cornea.* 2022;41(7):874-878. doi: 10.1097/ICO.0000000000002808.	Study Design
Al Fayez MF, Alfayez S, Alfayez Y. Transepithelial versus epithelium-off corneal collagen cross-linking for progressive keratoconus: a prospective randomized controlled trial. *Cornea.* 2015;34 Suppl 10:S53-56. doi: 10.1097/ICO.0000000000000547.	Publication Type
Amigo A, Bonaque S. Safety of extended use of hypoosmolar riboflavin in crosslinking. *J Cataract Refract Surg.* 2014;40(1):171-172. doi: 10.1016/j.jcrs.2013.11.010.	Publication Type
Anonymous. Corrigendum. *Ophthalmology.* 2017;124(12):1878. doi: 10.1016/j.ophtha.2017.09.014.	Publication Type
Arance-Gil A, Villa-Collar C, Perez-Sanchez B, Carracedo G, Gutierrez-Ortega R. Epithelium-off vs. transepithelial corneal collagen crosslinking in progressive keratoconus: 3 years of follow-up. *J Optom.* 2021;14(2):189-198. doi: 10.1016/j.optom.2020.07.005.	Study Design
Aydin E, Aslan MG. The efficiency and safety of oxygen-supplemented accelerated transepithelial corneal cross-linking. *Int Ophthalmol.* 2021;41(9):2993-3005. doi: 10.1007/s10792−021−01859-1.	Aim
Benito-Pascual B, Kandel H, Abbondanza M, Mills R, Sullivan L, Watson SL. Efficacy and safety of standard corneal cross-linking procedures performed with short versus standard riboflavin induction: a Save Sight Keratoconus Registry study. *Cornea.* 2023;42(3):326-331. doi: 10.1097/ICO.0000000000003058.	Outcomes
Bilgihan K, Yuksel E. A new simple corneal limbal protection technique during corneal collagen cross-linking. *Eye Contact Lens.* 2015;41(2):130-131. doi: 10.1097/ICL.0000000000000144.	Study Design

Reference Information	Primary Reason for Exclusion
Borchert GA, Kandel H, Watson SL. Epithelium-on versus epithelium-off corneal collagen crosslinking for keratoconus: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol.* 2023;08:08. doi: 10.1007/s00417−023−06287-8.	Study Design
Borchert GA, Watson SL, Kandel H. Oxygen in corneal collagen crosslinking to treat keratoconus: a systematic review and meta-analysis. *Asia Pac J Ophthalmol (Phila).* 2022;11(5):453-459. doi: 10.1097/APO.0000000000000555.	Study Design
Borgardts K, Menzel-Severing J, Fischinger I, Geerling G, Seiler TG. Innovations in corneal crosslinking. *Curr Eye Res.* 2023;48(2):144-151. doi: 10.1080/02713683.2022.2146725.	Study Design
Buzzonetti L, Petrocelli G. Transepithelial corneal cross-linking in pediatric patients: early results. *J Refract Surg.* 2012;28(11):763-767. doi: 10.3928/1081597X-20121011−03.	Publication Type
Cantemir A, Alexa AI, Galan BG, et al. Iontophoretic collagen cross-linking versus epithelium-off collagen cross-linking for early stage of progressive keratoconus - 3 years follow-up study. *Acta Ophthalmol.* 2017;95(7):e649-e655. doi: 10.1111/aos.13538.	Study Design
Cassagne M, Delafoy I, Mesplie N, Fournie P, Cochener B, Malecaze F. Transepithelial corneal collagen crosslinking using iontophoresis: preliminary clinical results. *Invest Ophthalmol Vis Sci.* 2014;55(13):4216.	Publication Type
Chunyu T, Xiujun P, Zhengjun F, Xia Z, Feihu Z. Corneal collagen cross-linking in keratoconus: a systematic review and meta-analysis. *Sci Rep*. 2014;4:5652. doi: 10.1038/srep05652.	Study Design
Craig JA, Mahon J, Yellowlees A, et al. Epithelium-off photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus and keratectasia: a systematic review and meta-analysis. *Ocul Surf*. 2014;12(3):202-214. doi: 10.1016/j.jtos.2014.05.002.	Study Design
Cummings AB, McQuaid R, Naughton S, Brennan E, Mrochen M. Optimizing corneal cross-linking in the treatment of keratoconus: a comparison of outcomes after standard- and high-intensity protocols. *Cornea.* 2016;35(6):814-822. doi: 10.1097/ICO.0000000000000823.	Study Design
D'Oria F, Palazon A, Alio JL. Corneal collagen cross-linking epithelium-on vs. epithelium-off: a systematic review and meta-analysis. *Eye Vis (Lond).* 2021;8(1):34. doi: 10.1186/s40662−021−00256−0.	Study Design
De Bernardo M, Cornetta P, Rosa N. Safety and efficacy of sequential intracorneal ring segment implantation and cross-linking in pediatric keratoconus. *Am J Ophthalmol.* 2017;181:182-183. doi: 10.1016/j.ajo.2017.06.039.	Publication Type
Di Y, Wang J, Li Y, Jiang Y. Comparison of standard and transepithelial corneal cross-linking for the treatment of keratoconus: a meta-analysis. *J Ophthalmol.* 2021;2021:6679770. doi: 10.1155/2021/6679770.	Study Design
Ding L, Sun L, Zhou X. Network meta-analysis comparing efficacy and safety of different protocols of corneal cross-linking for the treatment of progressive keratoconus. *Graefes Arch Clin Exp Ophthalmol.* 2023;261(10):2743-2753. doi: 10.1007/s00417−023−06026-z.	Study Design
Epstein RJ, Belin MW, Gravemann D, Littner R, Rubinfeld RS. Epismart crosslinking for keratoconus: a phase 2 study. *Cornea*. 2023;42(7):858-866. doi: 10.1097/ICO.0000000000003136.	Population
Eraslan M, Toker E, Cerman E, Ozarslan D. Efficacy of epithelium-off and epithelium-on corneal collagen cross-linking in pediatric keratoconus. *Eye Contact Lens.* 2017;43(3):155-161. doi: 10.1097/ICL.0000000000000255.	Study Design

Reference Information	Primary Reason for Exclusion
Fard AM, Patel SP, Nader ND. The efficacy of 2 different phakic intraocular lens implant in keratoconus as an isolated procedure or combined with collagen crosslinking and intra-stromal corneal ring segments: a systematic review and meta-analysis. *Int Ophthalmol.* 2023;43(11):4383-4393. doi: 10.1007/s10792–023–02813-z.	Study Design
Fard AM, Reynolds AL, Lillvis JH, Nader ND. Corneal collagen cross-linking in pediatric keratoconus with three protocols: a systematic review and meta-analysis. *J AAPOS.* 2020;24(6):331-336. doi: 10.1016/j.jaapos.2020.08.013.	Study Design
Godefrooij DA, Mangen MJ, Chan E, et al. Cost-effectiveness analysis of corneal collagen crosslinking for progressive keratoconus. *Ophthalmology.* 2017;124(10):1485-1495. doi: 10.1016/j.ophtha.2017.04.011.	Setting
Godefrooij DA, van Geuns P, de Wit GA, Wisse RP. What are the costs of corneal cross-linking for the treatment of progressive keratoconus? *J Refract Surg.* 2016;32(5):355. doi: 10.3928/1081597X-20160318–01.	Publication Type
Goldich Y, Marcovich AL, Barkana Y, et al. Clinical and corneal biomechanical changes after collagen cross-linking with riboflavin and UV irradiation in patients with progressive keratoconus: results after 2 years of follow-up. *Cornea.* 2012;31(6):609-614. doi: 10.1097/ICO.0b013e318226bf4a.	Study Design
Greenstein SA, Fry KL, Hersh MJ, Hersh PS. Higher-order aberrations after corneal collagen crosslinking for keratoconus and corneal ectasia. *J Cataract Refract Surg.* 2012;38(2):292-302. doi: 10.1016/j.jcrs.2011.08.041.	Outcomes
Greenstein SA, Fry KL, Hersh PS. In vivo biomechanical changes after corneal collagen cross-linking for keratoconus and corneal ectasia: 1-year analysis of a randomized, controlled, clinical trial. *Cornea.* 2012;31(1):21-25. doi: 10.1097/ICO.0b013e31821eea66.	Outcomes
Greenstein SA, Hersh PS. Corneal crosslinking for progressive keratoconus and corneal ectasia: summary of US multicenter and subgroup clinical trials. *Transl Vis Sci Technol.* 2021;10(5):13. doi: 10.1167/tvst.10.5.13.	Study Design
Greenstein SA, Shah VP, Fry KL, Hersh PS. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg.* 2011;37(4):691-700. doi: 10.1016/j.jcrs.2010.10.052.	Outcomes
Greenstein S, Hersh P. Concurrent vs sequential corneal collagen crosslinking and Intacs® for keratoconus and corneal ectasia. *Invest Ophthalmol Vis Sci.* 2013;54(15).	Publication Type
Guell JL, Verdaguer P, Elies D, Gris O, Manero F. Persistent stromal scar after PRK and CXL: different preoperative findings, similar complication. *J Refract Surg.* 2015;31(3):211-212.	Study Design
Gustafsson I, Ivarsen A, Hjortdal J. Early findings in a prospective randomised study on three cross-linking treatment protocols: interruption of the iontophoresis treatment protocol. *BMJ Open Ophthalmol.* 2023;8(1):09. doi: 10.1136/bmjophth-2023–001406.	Aim
Hamida Abdelkader SM, Fernandez J, Rodriguez-Vallejo M, Sanchez-Garcia A, Pinero DP. Comparison of different methods of corneal collagen crosslinking: a systematic review. *Semin Ophthalmol.* 2021;36(3):67-74. doi: 10.1080/08820538.2021.1890784.	Study Design
Hamida Abdelkader SM, Fernandez J, Rodriguez-Vallejo M, Sanchez-Garcia A, Pinero DP. Comparison of different methods of corneal collagen crosslinking: a systematic review. *Semin Ophthalmol.* 2021;36(3):67-74. doi: 10.1080/08820538.2021.1890784.	Study Design
Hashemi H, Amanzadeh K, Seyedian M, et al. Accelerated and standard corneal cross-linking protocols in patients with Down syndrome: a non-inferiority contralateral	Setting

Reference Information	Primary Reason for Exclusion
randomized trial. *Ophthalmol Ther.* 2020;9(4):1011-1021. doi: 10.1007/s40123–020–00303-4.	
Hashemi H, Miraftab M, Seyedian MA, et al. Long-term results of an accelerated corneal cross-linking protocol (18 mw/cm2) for the treatment of progressive keratoconus. *Am J Ophthalmol.* 2015;160(6):1164-1170 e1161. doi: 10.1016/j.ajo.2015.08.027.	Setting
Hashemi H, Mohebbi M, Asgari S. Standard and accelerated corneal cross-linking long-term results: a randomized clinical trial. *Eur J Ophthalmol.* 2020;30(4):650-657. doi: 10.1177/1120672119839927.	Setting
Hashemi H, Roberts CJ, Ambrosio R, Jr., et al. Comparative contralateral randomized clinical trial of standard (3 mw/cm(2)) versus accelerated (9 mw/cm(2)) cxl in patients with Down syndrome: 3-year results. *J Refract Surg.* 2022;38(6):381-388. doi: 10.3928/1081597X-20220329–01.	Setting
Hashemian H, Jabbarvand M, Khodaparast M, Ameli K. Evaluation of corneal changes after conventional versus accelerated corneal cross-linking: a randomized controlled trial. *J Refract Surg.* 2014;30(12):837-842. doi: 10.3928/1081597X-20141117–02.	Setting
Henriquez MA, Izquierdo L, Jr., Bernilla C, Zakrzewski PA, Mannis M. Riboflavin/Ultraviolet A corneal collagen cross-linking for the treatment of keratoconus: visual outcomes and Scheimpflug analysis. *Cornea.* 2011;30(3):281-286. doi: 10.1097/ICO.0b013e3181eeaea1.	Setting
Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg.* 2011;37(1):149-160. doi: 10.1016/j.jcrs.2010.07.030.	Study Design
Institute for Quality and Efficiency in Health Care. UV cross-linking with riboflavin in keratoconus version 1.1. 2016; https://www.iqwig.de/download/n15–05_keratokonus_extract-of-final-report_v1-1.pdf. Accessed November 27, 2023.	Study Design
Iqbal M, Elmassry A, Saad H, et al. Standard cross-linking protocol versus accelerated and transepithelial cross-linking protocols for treatment of paediatric keratoconus: a 2-year comparative study. *Acta Ophthalmol.* 2020;98(3):e352-e362. doi: 10.1111/aos.14275.	Setting
Iqbal M, Elmassry A, Tawfik A, et al. Standard cross-linking versus photorefractive keratectomy combined with accelerated cross-linking for keratoconus management: a comparative study. *Acta Ophthalmol.* 2019;97(4):e623-e631. doi: 10.1111/aos.13986.	Setting
Iqbal M, Gad A, Kotb A, Abdelhalim M. Analysis of the outcomes of three different cross-linking protocols for treatment of paediatric keratoconus: a multicentre randomized controlled trial. *Acta Ophthalmol.* 2023;04:04. doi: 10.1111/aos.15686.	Setting
Jiang LZ, Jiang W, Qiu SY. Conventional vs. pulsed-light accelerated corneal collagen cross-linking for the treatment of progressive keratoconus: 12-month results from a prospective study. *Exp Ther Med.* 2017;14(5):4238-4244. doi: 10.3892/etm.2017.5031.	Setting
Jiang Y, Yang S, Li Y, Cui G, Lu TC. Accelerated versus conventional corneal collagen cross-linking in the treatment of keratoconus: a meta-analysis and review of the literature. *Interdiscip Sci.* 2019;11(2):282-286. doi: 10.1007/s12539–019–00336-9.	Study Design
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Reference Information	Primary Reason for Exclusion
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Kanellopoulos AJ. Ten-year outcomes of progressive keratoconus management with the Athens protocol (topography-guided partial-refraction PRK combined with CXL). *J Refract Surg*. 2019;35(8):478-483. doi: 10.3928/1081597X-20190627–01.	Study Design
Karam M, Alsaif A, Aldubaikhi A, et al. Accelerated corneal collagen cross-linking protocols for progressive keratoconus: systematic review and meta-analysis. *Cornea*. 2023;42(2):252-260. doi: 10.1097/ICO.0000000000003124.	Study Design
Kim BZ, Jordan CA, McGhee CN, Patel DV. Natural history of corneal haze after corneal collagen crosslinking in keratoconus using Scheimpflug analysis. *J Cataract Refract Surg*. 2016;42(7):1053-1059. doi: 10.1016/j.jcrs.2016.04.019.	Outcomes
Kobashi H, Hieda O, Itoi M, et al. Corneal cross-linking for paediatric keratoconus: a systematic review and meta-analysis. *J Clin Med*. 2021;10(12):15. doi: 10.3390/jcm10122626.	Study Design
Kobashi H, Rong SS. Corneal collagen cross-linking for keratoconus: systematic review. *Biomed Res Int*. 2017;2017:8145651. doi: 10.1155/2017/8145651.	Study Design
Kobashi H, Tsubota K. Accelerated versus standard corneal cross-linking for progressive keratoconus: a meta-analysis of randomized controlled trials. *Cornea*. 2020;39(2):172-180. doi: 10.1097/ICO.0000000000002092.	Study Design
Koppen C, Leysen I, Tassignon MJ. Riboflavin/UVA cross-linking for keratoconus in Down syndrome. *J Refract Surg*. 2010;26(9):623-624. doi: 10.3928/1081597X-20100824–01.	Publication Type
Labiris G, Giarmoukakis A, Sideroudi H, Kozobolis V. Impact of keratoconus, cross-linking and cross-linking combined with topography-guided photorefractive keratectomy on self-reported quality of life: a 3-year update. *Cornea*. 2013;32(9):e186-188. doi: 10.1097/ICO.0b013e318296e13c.	Study Design
Labiris G, Sideroudi H, Angelonias D, Georgantzoglou K, Kozobolis VP. Impact of corneal cross-linking combined with photorefractive keratectomy on blurring strength. *Clin Ophthalmol*. 2016;10:571-576. doi: 10.2147/OPTH.S100770.	Study Design
Lang PZ, Hafezi NL, Khandelwal SS, Torres-Netto EA, Hafezi F, Randleman JB. Comparative functional outcomes after corneal crosslinking using standard, accelerated, and accelerated with higher total fluence protocols. *Cornea*. 2019;38(4):433-441. doi: 10.1097/ICO.0000000000001878.	Study Design
Lange C, Bohringer D, Reinhard T. Corneal endothelial loss after crosslinking with riboflavin and ultraviolet-A. *Graefes Arch Clin Exp Ophthalmol*. 2012;250(11):1689-1691. doi: 10.1007/s00417–012-2101-x.	Study Design
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Li W, Wang B. Efficacy and safety of transepithelial corneal collagen crosslinking surgery versus standard corneal collagen crosslinking surgery for keratoconus: a meta-analysis of randomized controlled trials. *BMC Ophthalmol*. 2017;17(1):262. doi: 10.1186/s12886–017–0657-2.	Study Design
Li Y, Lu Y, Du K, et al. Comparison of efficacy and safety between standard, accelerated epithelium-off and transepithelial corneal collagen crosslinking in	Study Design

Reference Information	Primary Reason for Exclusion
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Lin JT. The dynamic safety for cross-linking in thin corneas with extra protection under a contact lens. *J Refract Surg.* 2015;31(7):495. doi: 10.3928/1081597X-20150623-10.	Publication Type
Liu B, Shang X, Tan X, et al. Clinical and morphological in vivo confocal microscopy findings following a modified biphasic higher fluence transepithelial corneal crosslinking. *Curr Eye Res.* 2023:1-12. doi: 10.1080/02713683.2023.2276680.	Setting
Liu Y, Liu Y, Zhang YN, et al. Systematic review and meta-analysis comparing modified cross-linking and standard cross-linking for progressive keratoconus. *Int J Ophthalmol.* 2017;10(9):1419-1429. doi: 10.18240/ijo.2017.09.15.	Study Design
M JL, Greenstein SA, Gelles JD, Hersh PS. Corneal haze after transepithelial collagen cross-linking for keratoconus: a Scheimpflug densitometry analysis. *Cornea.* 2020;39(9):1117-1121. doi: 10.1097/ICO.0000000000002334.	Outcomes
Madeira C, Vasques A, Beato J, et al. Transepithelial accelerated versus conventional corneal collagen crosslinking in patients with keratoconus: a comparative study. *Clin Ophthalmol.* 2019;13:445-452. doi: 10.2147/OPTH.S189183.	Study Design
Magli A, Forte R, Tortori A, Capasso L, Marsico G, Piozzi E. Epithelium-off corneal collagen cross-linking versus transepithelial cross-linking for pediatric keratoconus. *Cornea.* 2013;32(5):597-601. doi: 10.1097/ICO.0b013e31826cf32d.	Study Design
Malta J, Kaz Soong H, Moscovici BK, Campos M. Two-year follow-up of corneal cross-linking and refractive surface ablation in patients with asymmetric corneal topography. *Br J Ophthalmol.* 2019;103(1):137-142. doi: 10.1136/bjophthalmol-2017-310840.	Setting
McAnena L, Doyle F, O'Keefe M. Cross-linking in children with keratoconus: a systematic review and meta-analysis. *Acta Ophthalmol.* 2017;95(3):229-239. doi: 10.1111/aos.13224.	Study Design
Meiri Z, Keren S, Rosenblatt A, Sarig T, Shenhav L, Varssano D. Efficacy of corneal collagen cross-linking for the treatment of keratoconus: a systematic review and meta-analysis. *Cornea.* 2016;35(3):417-428. doi: 10.1097/ICO.0000000000000723.	Study Design
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Nath S, Shen C, Koziarz A, et al. Transepithelial versus epithelium-off corneal collagen cross-linking for corneal ectasia: a systematic review and meta-analysis. *Ophthalmology.* 2021;128(8):1150-1160. doi: 10.1016/j.ophtha.2020.12.023.	Study Design
Ng SM, Hawkins BS, Kuo IC. Transepithelial versus epithelium-off corneal crosslinking for progressive keratoconus: findings from a Cochrane systematic review. *Am J Ophthalmol.* 2021;229:274-287. doi: 10.1016/j.ajo.2021.05.009.	Study Design
Ng SM, Ren M, Lindsley KB, Hawkins BS, Kuo IC. Transepithelial versus epithelium-off corneal crosslinking for progressive keratoconus. *Cochrane Database Syst Rev.* 2021;3(3):CD013512. doi: 10.1002/14651858.CD013512.pub2.	Study Design
Niazi S, Alio Del Barrio J, Sanginabadi A, et al. Topography versus non-topography-guided photorefractive keratectomy with corneal cross-linking variations in keratoconus. *Int J Ophthalmol.* 2022;15(5):721-727. doi: 10.18240/ijo.2022.05.05.	Setting

Reference Information	Primary Reason for Exclusion
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Nicula CA, Rednik AM, Bulboaca AE, Nicula D. Comparative results between "epi-off" conventional and accelerated corneal collagen crosslinking for progressive keratoconus in pediatric patients. *Ther Clin Risk Manag.* 2019;15:1483-1490. doi: 10.2147/TCRM.S224533.	Study Design
Ortiz-Toquero S, Rodriguez G, Martin R. Clinical guidelines for the management of keratoconus patients with gas permeable contact lenses based on expert consensus and available evidence. *Curr Opin Ophthalmol.* 2021;32(Suppl 2):S1-S11. doi: 10.1097/ICU.0000000000000728.	Intervention
Razmjoo H, Rahimi B, Kharraji M, Koosha N, Peyman A. Corneal haze and visual outcome after collagen crosslinking for keratoconus: a comparison between total epithelium off and partial epithelial removal methods. *Adv Biomed Res.* 2014;3:221. doi: 10.4103/2277-9175.145677.	Follow-up
Rechichi M, Mazzotta C, Oliverio GW, et al. Selective transepithelial ablation with simultaneous accelerated corneal crosslinking for corneal regularization of keratoconus: STARE-X protocol. *J Cataract Refract Surg.* 2021;47(11):1403-1410. doi: 10.1097/j.jcrs.0000000000000640.	Study Design
Renesto Ada C, Melo LA, Jr., Sartori Mde F, Campos M. Sequential topical riboflavin with or without ultraviolet a radiation with delayed intracorneal ring segment insertion for keratoconus. *Am J Ophthalmol.* 2012;153(5):982-993 e983. doi: 10.1016/j.ajo.2011.10.014.	Setting
Rosenblat EA, Greenstein SA, Hersh PS. Corneal thickness changes and results of collagen crosslinking using riboflavin/dextran or hypotonic riboflavin. *Invest Ophthalmol Vis Sci.* 2014;55(13):4223.	Publication Type
Rosenblat E, Hersh PS. Intraoperative corneal thickness change and clinical outcomes after corneal collagen crosslinking: standard crosslinking versus hypotonic riboflavin. *J Cataract Refract Surg.* 2016;42(4):596-605. doi: 10.1016/j.jcrs.2016.01.040.	Aim
Sachdev GS, Ramamurthy S, B S, Dandapani R. Comparative analysis of safety and efficacy of topography-guided customized cross-linking and standard cross-linking in the treatment of progressive keratoconus. *Cornea.* 2021;40(2):188-193. doi: 10.1097/ICO.0000000000002492.	Study Design
Sadoughi MM, Einollahi B, Baradaran-Rafii A, Roshandel D, Hasani H, Nazeri M. Accelerated versus conventional corneal collagen cross-linking in patients with keratoconus: an intrapatient comparative study. *Int Ophthalmol.* 2018;38(1):67-74. doi: 10.1007/s10792–016–0423–0.	Study Design
Salmon HA, Chalk D, Stein K, Frost NA. Cost effectiveness of collagen crosslinking for progressive keratoconus in the UK NHS. *Eye (Lond).* 2015;29(11):1504-1511. doi: 10.1038/eye.2015.151.	Setting
Saluja G, Maharana PK. Cool cross-linking: riboflavin at 4 degrees C for pain management after cross-linking for keratoconus patients, a randomized clinical trial. *Cornea.* 2021;40(10):e19. doi: 10.1097/ICO.0000000000002703.	Publication Type
Sandali O, Ghouali W, Basli E, et al. Increased reaction after cross-linking in keratoconus melanoderm patients. *Ocul Immunol Inflamm.* 2014;22(4):333-335. doi: 10.3109/09273948.2013.845229.	Study Design
Sarac O, Caglayan M, Uysal BS, Uzel AGT, Tanriverdi B, Cagil N. Accelerated versus standard corneal collagen cross-linking in pediatric keratoconus patients: 24 months follow-up results. *Cont Lens Anterior Eye.* 2018;41(5):442-447. doi: 10.1016/j.clae.2018.06.001.	Study Design

Reference Information	Primary Reason for Exclusion
Sarma P, Kaur H, Hafezi F, et al. Short- and long-term safety and efficacy of corneal collagen cross-linking in progressive keratoconus: a systematic review and meta-analysis of randomized controlled trials. *Taiwan J Ophthalmol.* 2023;13(2):191-202. doi: 10.4103/2211-5056.361974.	Study Design
Serrao S, Lombardo G, Giannini D, Lombardo M. Corneal topography and aberrometry changes one-year after transepithelial corneal cross-linking using iontophoresis versus standard corneal cross-linking. *Invest Ophthalmol Vis Sci.* 2017;58(8).	Publication Type
Serrao S, Lombardo G, Lombardo M. Adverse events after riboflavin/UV-A corneal cross-linking: a literature review. *Int Ophthalmol.* 2022;42(1):337-348. doi: 10.1007/s10792−021−02019-1.	Study Design
Seyedian MA, Aliakbari S, Miraftab M, Hashemi H, Asgari S, Khabazkhoob M. Corneal collagen cross-linking in the treatment of progressive keratoconus: a randomized controlled contralateral eye study. *Middle East Afr J Ophthalmol.* 2015;22(3):340-345. doi: 10.4103/0974-9233.159755.	Setting
Shajari M, Kolb CM, Agha B, et al. Comparison of standard and accelerated corneal cross-linking for the treatment of keratoconus: a meta-analysis. *Acta Ophthalmol.* 2019;97(1):e22-e35. doi: 10.1111/aos.13814.	Study Design
Sherif AM. Accelerated versus conventional corneal collagen cross-linking in the treatment of mild keratoconus: a comparative study. *Clin Ophthalmol.* 2014;8:1435-1440. doi: 10.2147/OPTH.S59840.	Setting
Shetty R, Pahuja NK, Nuijts RM, et al. Current protocols of corneal collagen cross-linking: visual, refractive, and tomographic outcomes. *Am J Ophthalmol.* 2015;160(2):243-249. doi: 10.1016/j.ajo.2015.05.019.	Setting
Singh T, Taneja M, Murthy S, Vaddavalli PK. Evaluation of safety and efficacy of different protocols of collagen cross linking for keratoconus. *Rom J Ophthalmol.* 2020;64(2):158-167.	Setting
Steinwender G, Pertl L, El-Shabrawi Y, Ardjomand N. Complications from corneal cross-linking for keratoconus in pediatric patients. *J Refract Surg.* 2016;32(1):68-69. doi: 10.3928/1081597X-20151210−03.	Study Design
Stulting RD. Corneal collagen cross-linking. *Am J Ophthalmol.* 2012;154(3):423-424 e421. doi: 10.1016/j.ajo.2012.05.005.	Publication Type
Sykakis E, Karim R, Evans JR, et al. Corneal collagen cross-linking for treating keratoconus. *Cochrane Database Syst Rev.* 2015;2015(3):CD010621. doi: 10.1002/14651858.CD010621.pub2.	Study Design
Tomita M, Mita M, Huseynova T. Accelerated versus conventional corneal collagen crosslinking. *J Cataract Refract Surg.* 2014;40(6):1013-1020. doi: 10.1016/j.jcrs.2013.12.012.	Study Design
Turhan SA, Yargi B, Toker E. Efficacy of conventional versus accelerated corneal cross-linking in pediatric keratoconus: two-year outcomes. *J Refract Surg.* 2020;36(4):265-269. doi: 10.3928/1081597X-20200302−01.	Study Design
Tzamalis A, Diafas A, Vinciguerra R, Ziakas N, Kymionis G. Repeated corneal cross-linking (CXL) in keratoconus progression after primary treatment: updated perspectives. *Semin Ophthalmol.* 2021;36(7):523-530. doi: 10.1080/08820538.2021.1893762.	Study Design
Vandepeer M, Forel D, Jacobsen JH, et al. Corneal collagen crosslinking for the treatment of progressive keratoconus. *Swiss Federal Office of Public Health*. 2021; https://www.bag.admin.ch/dam/bag/en/dokumente/kuv-leistungen/leistungen-und-tarife/hta/berichte/h0054uvcl-hta-shortreport.pdf.download.pdf/h0054uvcl-hta-shortreport.pdf. Accessed November 27, 2023.	Study Design

Reference Information	Primary Reason for Exclusion
Vandevenne MMS, Berendschot T, Winkens B, et al. Efficacy of customized corneal crosslinking versus standard corneal crosslinking in patients with progressive keratoconus (C-CROSS study): study protocol for a randomized controlled trial. *BMC Ophthalmol.* 2023;23(1):224. doi: 10.1186/s12886–023–02976-4.	Publication Type
Vellara H, Gokul A, Meyer J, McGhee C, Patel D. The effect of accelerated corneal collagen cross-linking on corneal biomechanical properties. *Clin Experiment Ophthalmol.* 2017;45:76. doi: 10.1111/ceo.13051/full.	Publication Type
Vinciguerra P, Camesasca FI, Romano MR. Corneal crosslinking and lens opacity. *Ophthalmology*. 2011;118(12):2519 e2511-2512. doi: 10.1016/j.ophtha.2011.07.055.	Publication Type
Wan KH, Ip CKY, Kua WN, et al. Transepithelial corneal collagen cross-linking using iontophoresis versus the Dresden protocol in progressive keratoconus: a meta-analysis. *Clin Exp Ophthalmol.* 2021;49(3):228-241. doi: 10.1111/ceo.13918.	Study Design
Wen D, Li Q, Song B, et al. Comparison of standard versus accelerated corneal collagen cross-linking for keratoconus: a meta-analysis. *Invest Ophthalmol Vis Sci.* 2018;59(10):3920-3931. doi: 10.1167/iovs.18-24656.	Study Design
Wen D, Song B, Li Q, et al. Comparison of epithelium-off versus transepithelial corneal collagen cross-linking for keratoconus: a systematic review and meta-analysis. *Cornea*. 2018;37(8):1018-1024. doi: 10.1097/ICO.0000000000001632.	Study Design
Yuksel E, Bektas C, Bilgihan K. Transepithelial versus epithelium-off corneal cross-linking for the treatment of progressive keratoconus: a randomized controlled trial. *Am J Ophthalmol.* 2015;160(2):399-400. doi: 10.1016/j.ajo.2015.05.022.	Publication Type
Zaheryani SMS, Movahedan H, Salouti R, et al. Corneal collagen cross-linking using epithelium disruptor instrument in progressive keratoconus. *J Curr Ophthalmol.* 2020;32(3):256-262. doi: 10.4103/JOCO.JOCO_59_20.	Setting
Zhang X, Zhao J, Li M, Tian M, Shen Y, Zhou X. Conventional and transepithelial corneal cross-linking for patients with keratoconus. *PLoS One*. 2018;13(4):e0195105. doi: 10.1371/journal.pone.0195105.	Study Design

Appendix F. Additional Methods

Participant Characteristics and Association with Outcomes

When discussing risk and protective factors or variables in statistical models in Center research products, in almost all cases, we are referring to associations of participant characteristics with outcomes, and not causation of outcomes. This is important because participant characteristics, such as race and ethnicity, serve as proxy or surrogate measures for underlying etiological factors not measured or evaluated in analyses. Etiological factors that might cause differences in outcomes for subgroups of participants could include systemic racism or other forms of systemic discrimination, stress, poverty, housing instability, or epigenetics. For example, by describing any differences in outcomes by race and ethnic groups, we are noting observed associations; these associations are not caused by biological determinants of being Black, White, or Hispanic.

Risk of Bias

Table F1. Risk-of-Bias Assessment: Randomized Controlled Trials

Domain	Domain Elements[a]
Randomization	• An appropriate method of randomization is used to allocate participants or clusters to groups, such as a computer random number generator • Baseline characteristics between groups or clusters are similar
Allocation concealment	• An adequate concealment method is used to prevent investigators and participants from influencing enrollment or intervention allocation
Intervention	• Intervention and comparator intervention applied equally to groups • Co-interventions appropriate and applied equally to groups • Control selected is an appropriate intervention
Outcomes	• Outcomes are measured using valid and reliable measures • Investigators use single outcome measures and do not rely on composite outcomes, or outcome of interest can be calculated from composite outcome • The trial has an appropriate length of follow-up and groups are assessed at same time points • Outcome reporting of entire group or subgroups is not selective
Masking (blinding) of investigators and participants	• Investigators and participants are unaware (masked or blinded) of intervention status
Masking (blinding) of outcome assessors	• Outcome assessors are unaware (masked or blinded) of intervention status
Intention-to-treat analysis	• Participants are analyzed based on random assignment (intention-to-treat analysis)
Statistical analysis	• Participants lost to follow-up unlikely to significantly bias results (i.e., complete follow-up of ≥ 80% of participants overall and nondifferential, ≤ 10% difference between groups) • The most appropriate summary estimate (e.g., risk ratio, hazard ratio) is used • Paired or conditional analysis used for crossover RCT • Clustering appropriately accounted for in a cluster-randomized trial (e.g., use of an intraclass correlation coefficient)

Domain	Domain Elements[a]

Other biases (as appropriate)	• List others in table footnote and describe, such as:
	  ○ Sample size adequacy
	  ○ Interim analysis or early stopping
	  ○ Recruitment bias, including run-in period used inappropriately
	  ○ Use of unsuitable crossover intervention in a crossover RCT

Interest disclosure	• Disclosures of interest are provided for authors/funders/commissioners of study • Interests are unlikely to significantly affect study validity
Funding	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Note. [a] The elements included in each domain are assessed and rated as yes, no, unclear, *or* not applicable *based on performance and documentation of individual elements in each domain. The overall risk of bias for a study is assessed as* high, moderate, *or* low *based on assessment of how well overall study methods and processes were performed to limit bias and ensure validity.*
Abbreviation. RCT: randomized controlled trial.

Table F2. Risk of Bias Assessment: Nonrandomized Studies

Domain	Domain Elements[a]
Participant selection	For cohort studies: • The 2 groups being studied are selected from source populations comparable in all respects other than factor under investigation, or statistical adjustment is used appropriately to achieve this • The study indicates how many of people asked to take part did so in each of the groups being studied • The likelihood some eligible participants might have outcome at time of enrollment is assessed and considered in analysis • Fewer than 20% of individuals or clusters in each arm of study dropped out before study was completed For case-control studies: • Cases and controls are clearly specified and defined, with inclusion and exclusion criteria applied appropriately • Cases may be selected by meeting inclusion criteria, controls may be selected by meeting inclusion criteria and then being matched to cases • Sampling selection (ratio of cases to control) is justified • Cases and controls selected from same population and same timeframe; when not all cases and controls are selected from same population, these are randomly selected • Among cases, investigators confirm that exposure occurred before development of disease being studied and/or likelihood that some eligible participants might have outcome at time of enrollment is assessed and considered in analysis
Intervention	• The assessment of exposure to intervention is reliable • Exposure level or prognostic factors are assessed at multiple times across length of study, if appropriate • For case-control studies, assessors of (intervention) exposure status are unaware (masked or blinded) to case or control status of participants, and there is a method to limit effects of recall bias on assessment of exposure to intervention
Control	• Control condition represents an appropriate comparator
Outcome	• There is a precise definition of outcomes used • Outcomes are measured using valid and reliable measures, evidence from other sources is used to demonstrate method of outcome assessment is valid and reliable • Investigators use single outcome measures and do not rely on composite outcomes, or outcome of interest can be calculated from composite outcome • The study has an appropriate length of follow-up for outcome reported and groups are assessed at same time points • Outcome reporting of entire group or subgroups is not selective • When patient-reported outcomes are used, there is a method for validating measure
Masked outcome assessment	• The assessment of outcome(s) is made blind to exposure status. Where outcome assessment blinding was not possible, there is recognition that knowledge of exposure status could have influenced assessment of outcome. • For case-control study: assessors of exposure status are unaware (masked or blinded) of case or control status of participant
Confounding	• The main potential confounders are identified and considered in design and analysis of study

Domain	Domain Elements[a]
Statistical analysis	• Comparison is made between full participants and those who dropped out or were lost to follow-up, by exposure status • If groups were not followed for an equal length of time, analysis was adjusted for differences in length of follow-up • All major confounders are adjusted for using multiple variable logistic regression or other appropriate statistical methods • Confidence intervals (or information used to calculate them) are provided • For case-control studies that use matching, conditional analysis is conducted or matching factors are adjusted for in analysis
Other biases (as appropriate)	• List others in table footnote and describe • Sample size adequacy
Interest disclosure	• Disclosures of interest are provided for authors/funders/commissioners of study • Interests are unlikely to significantly affect study validity
Funding source	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Note. [a] *The elements included in each domain are assessed and rated as* yes, no, unclear, *or* not applicable *based on performance and documentation of individual elements in each domain. The overall risk of bias for a study is assessed as* high, moderate, *or* low *based on assessment of how well overall study methods and processes were performed to limit bias and ensure validity.*

Table F3. Risk of Bias Assessment: Economic Modeling Studies

Domain	Domain Elements[a]
Target population	• Target population and care setting described • Describe and justify basis for any target population stratification, identify any previously identifiable subgroups • If no subgroup analyses were performed, justify why these were not required
Perspective	• State and justify analytic perspective (e.g., societal, payer, etc.)
Time horizon	• Describe and justify time horizon(s) used in analysis
Discount rate	• State and justify discount rate used for costs and outcomes
Comparators	• Describe and justify selected comparators • Competing alternatives appropriate and clearly described
Modelling	• Model structure (e.g., scope, assumptions made) is described and justified • Model diagram provided, if appropriate • Model validation is described (may involve validation of different aspects such as structure, data, assumptions, and coding and different validation models such as comparison with other models) • Data sources listed and assumptions for use justified • Statistical analyses are described
Effectiveness	• Estimates of efficacy/effectiveness of interventions are described and justified • The factors likely to have an impact on effectiveness (e.g., adherence, diagnostic accuracy, values, and preferences) are described and an explanation of how these were factored into analysis is included • The quality of evidence for relationship between intervention and outcomes, and any necessary links, is described
Outcomes	• All relevant outcomes are identified, measured, and valued appropriately (including harms/adverse events) for each intervention, and justification for information/assumptions is given • Any quality of life measures used in modelling are described and use justified • Any other outcomes that were considered but rejected are described with rationale for rejection • Ethical and equity-related outcomes are considered and included when appropriate
Resource use/costs	• All resources used are identified, valued appropriately, and included in analyses • Methods for costing are reporting (e.g., patient level) • Resource quantities and unit costs are both reported • Methods for costing time (e.g., lost time, productivity losses) are appropriate and a justification is provided if time costs are not considered
Uncertainty	• Sources of uncertainty in analyses are identified and justification for probability distributions used in probabilistic analyses are given • For scenario analyses, values and assumptions tested are provided and justified

Domain	Domain Elements[a]
Results	• All results are presented in a disaggregated fashion, by component, in addition to an aggregated manner • All results are presented with undiscounted totals before discounting and aggregation • Natural units are presented along with alternative units (e.g., QALYs) • The components of incremental cost-effectiveness ratio (ICER) are shown (e.g., mean costs of each intervention in numerator and mean outcomes of each intervention in denominator) • Results of scenario analyses, including variability in factors such as practice patterns and costs, are reported and described in relation to reference (base) case
Interest disclosure	• Disclosures of interest are provided for authors/funders/commissioners of study • Interests are unlikely to significantly affect study validity
Funding source	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Note. [a] *The elements included in each domain are assessed and rated as* yes, no, unclear, *or* not applicable *based on performance and documentation of individual elements in each domain. The overall risk of bias for a study is assessed as* high, moderate, *or* low *based on assessment of how well overall study methods and processes were performed to limit bias and ensure validity.*
Abbreviation. ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Methodological Quality Assessment

Table F4. Methodological Quality Assessment: Clinical Practice Guidelines

Domain	Domain Elements[a]
Rigor of development: evidence	• Systematic literature search meets quality standards for a systematic review (i.e., comprehensive search strategy with, at a minimum, 2 or more electronic databases) • The criteria used to select evidence for inclusion is clear and appropriate • The strengths and limitations of individual evidence sources is assessed and overall quality of body of evidence assessed
Rigor of development: recommendations	• Methods for developing recommendations clearly described and appropriate • There is an explicit link between recommendations and supporting evidence • The balance of benefits and harms is considered in formulating recommendations • The guideline has been reviewed by external expert peer reviewers • The updating procedure for guideline is specified in guideline or related materials (e.g., specialty society website)
Editorial independence	• There is a description of source(s) of funding and views of funder(s) are unlikely to have influenced content or validity of guideline • Disclosures of interests for guideline panel members are provided and are unlikely to have a significant impact on overall validity of guideline (e.g., a process for members to recuse themselves from participating on recommendations for which a significant conflict is provided)
Scope and purpose	• Objectives specifically described • Health question(s) specifically described • Target population(s) for guideline recommendations is specified (e.g., patients in primary care) and target users for guideline (e.g., primary care clinicians)
Stakeholder involvement	• Relevant professional groups represented • Views and preferences of target population(s) sought (e.g., clinicians and patients)
Clarity and presentation	• Recommendations are specific and unambiguous • Different management options are clearly presented • Key recommendations are easily identifiable
Applicability	• Provides advice and/or tools on how recommendation(s) can be put into practice • Description of facilitators and barriers to its application • Potential resource implications considered • Criteria for implementation monitoring, audit, and/or performance measures based on guideline are presented

Note. [a] *The elements included in each domain are assessed and rated as* yes, no, unclear, *or* not applicable *based on performance and documentation of individual elements in each domain. The overall risk of bias for a study is assessed as* high, moderate, *or* low *based on assessment of how well overall study methods and processes were performed to limit bias and ensure validity.*

GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Table F5. GRADE System for Rating the Certainty of Evidence for Outcomes

GRADE Rating	Plain Language Description	Detailed Category Description
High	New research is very unlikely to change our understanding of the relationship between this outcome and the health technology.	Center researchers are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are randomized controlled trials with few or no limitations, and the estimate of effect is likely stable.
Moderate	New research may change our understanding of the relationship between this outcome and the health technology.	Center researchers are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies are randomized controlled trials with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.
Low	New research is likely to change our understanding of the relationship between this outcome and the health technology.	Center researchers have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies are randomized controlled trials with serious limitations or nonrandomized studies without special strengths.
Very low	New research is very likely to change our understanding of the relationship between this outcome and the health technology.	Center researchers have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.
Not applicable	There is no research to report.	Center researchers did not identify any eligible articles.

Source. Adapted from 2 publications about GRADE.[213,214]
Abbreviation: GRADE: Grading of Recommendations, Assessment, Development, and Evaluations approach.