Corneal Collagen Cross-linking

Corneal collagen cross-linking (CXL) is a photochemical procedure for the treatment of progressive keratoconus and corneal ectasia. Keratoconus is a naturally occurring dystrophy of the cornea characterized by progressive deformation (steepening) of the cornea while corneal ectasia is keratoconus that occurs after refractive surgery. Both lead to functional vision loss and need to corneal transplantation.

Keratoconus and Ectasia
Keratoconus is a bilateral dystrophy characterized by progressive ectasia (paracentral steepening and stromal thinning) that impairs visual acuity. While frequently diagnosed at a young age, the progression of keratoconus is variable. Results from a longitudinal study with 7 years of follow-up showed that, over the study period, there was a decrease of 2 high- and 4 low-contrast letters in best-corrected visual acuity (BCVA). About 1 in 5 patients showed a decrease of 10 or more letters in high-contrast visual acuity and one-third of patients showed a decrease of 10 or more letters in low-contrast visual acuity. Over 8 years of follow-up, there was a mean increase of 1.44 diopters (D) in First Definite Apical Clearance Lens (a rigid contact lens to measure corneal curvature) and 1.6 D in flatter keratometric reading.

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

Treatment
The initial treatment for keratoconus often consists of hard contact lenses. A variety of keratorefractive procedures have also been attempted, broadly divided into subtractive and additive techniques. Subtractive techniques include photorefractive keratectomy or laser in situ keratomileusis (LASIK), although generally, results of these techniques have been poor. Implantation of intrastromal corneal ring segments (see evidence review 9.03.14) is an additive technique in which the implants are intended to reinforce the cornea, prevent further deterioration, and potentially obviate the need for penetrating keratoplasty. Penetrating keratoplasty (ie, corneal grafting) is the last line of treatment. About 20% of patients with keratoconus will require corneal transplantation. All of these treatments attempt to improve the refractive errors, but are not disease-modifying.

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

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

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

1. Epithelium-off CXL (also known as “epi-off”): In this method, about 8 mm of the central corneal epithelium is removed under topical anesthesia to allow better diffusion of the photosensitizer riboflavin into the stroma. Following de-epithelialization, a solution with riboflavin is applied to the cornea (every 1-3 minutes for 30 minutes) until the stroma is completely penetrated. The cornea is then irradiated for 30 minutes with ultraviolet A 370 nm, a maximal wavelength for absorption by riboflavin, while the riboflavin continues to be applied. The interaction of riboflavin and UVA causes the formation of reactive oxygen species, leading to additional covalent bonds (cross-linking) between collagen molecules, resulting in stiffening of the cornea. Theoretically, by using a homogeneous light source and absorption by riboflavin, the structures beyond a 400-micron thick stroma (endothelium, anterior chamber, iris, lens, retina) are not exposed to an ultraviolet dose that is above the cytotoxic threshold.

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

Currently, the only CXL treatment approved by the Food and Drug Administration (FDA) is the epithelium-off method. There are no FDA-approved CXL treatments using the epithelium-on method. CXL is being evaluated primarily for corneal stabilization in patients with progressive corneal thinning, such as keratoconus and corneal ectasia following refractive surgery. CXL may also have anti-edematous and antimicrobial properties.

REGULATORY STATUS
In 2016, riboflavin 5-phosphate in 20% dextran ophthalmic solution (Photorexa Viscous®; Avedro) and riboflavin 5-phosphate ophthalmic solution (Photorexa®; Avedro) were approved by the U.S. Food and Drug Administration for use with KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia after refractive surgery.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy
Corneal collagen cross-linking is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application
This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Corneal Collagen Cross-linking is covered
Not Applicable

When Corneal Collagen Cross-linking is not covered
Corneal collagen cross-linking is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.
Corneal Collagen Cross-linking

Policy Guidelines

The evidence for corneal CXL in individuals who have keratoconus includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are change in disease status, functional outcomes, and treatment-related morbidity. There is evidence from RCTs, including several pivotal trials, that CXL leads to short-term improvements in corneal steepening and visual acuity compared with untreated eyes, and results from 1 trial have reported that these benefits are maintained at 2 to 3 years. From these RCTs, one can conclude that CXL reduces, and in some cases, reverses the corneal steepening that leads to a reduction in visual acuity in the short term. Greater uncertainty exists regarding the long-term outcomes of corneal CXL for the treatment of keratoconus. Some retrospective studies have reported positive outcomes to 10 years, although these reports have small sample sizes at long-term follow-up and limited information on the entire population of patients treated with corneal CXL during the same time period. There is a need for prospective studies with larger numbers of patients who are followed over many years to determine whether corneal CXL improves longer term outcomes. Several trials are ongoing, and their results are expected soon. Longer term outcomes from large cohorts will also be useful to evaluate potential long-term complications of this new treatment approach. Although one device is currently under U.S. Food and Drug Administration (FDA) review, no corneal CXL devices have received FDA approval at this time. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0402T

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Corneal Collagen Cross-linking


Medical Director review 3/2017
Specialty Matched Consultant Advisory Panel- 6/2018

Policy Implementation/Update Information

7/10/12 New policy issued. Corneal collagen cross-linking is considered **investigational**. BCBSNC does not provide coverage for investigational services or procedures. Medical director review 6/2012. Specialty matched consultant advisory panel review meeting 6/20/12. Notification given 7/10/12. Effective date 10/16/2012. (lpr)

4/16/13 Reference added. No change to policy statement. (lpr)

7/16/13 Specialty matched consultant advisory panel review 6/19/2013. No change to policy statement. (lpr)

5/27/14 Reference updated. Updated regulatory status. No change to policy statement. (lpr)

7/15/14 Specialty matched consultant advisory panel review meeting 6/24/2014. No change to policy statement. (lpr)


12/30/15 Added CPT code 0402T to Billing/Coding section for effective date 1/1/2016. (lpr)

4/29/16 Updated Policy Guidelines and Regulatory Status. Reference added. No change to policy statement. (lpr)

7/26/16 Specialty Matched Consultant Advisory Panel review 6/29/2016. No change to policy statement. (lpr)

4/28/17 Updated Description section. Reference added. Medical Director review 3/2017. No change to policy statement. (lpr)

7/28/17 Specialty Matched Consultant Panel review 6/28/2017. No change to policy statement. (lpr)
Corneal Collagen Cross-linking

8/10/18  Specialty Matched Consultant Panel review 6/2018. No change to policy statement.
Reference added. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.