



# Louisiana

## Keratoprosthesis

**Policy #** 00450

**Original Effective Date:** 05/20/2015

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*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **When Services Are Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the Boston (Dohlman-Doane) Keratoprosthesis (Boston KPro) for the surgical treatment of severe corneal opacification in situations where cadaveric corneal transplants have failed or have a very low likelihood of success under the following conditions to be **eligible for coverage**:

- The cornea is severely opaque and vascularized; AND
- Best-corrected vision is  $\leq 20/400$  in the affected eye and  $\leq 20/40$  in the opposite eye; AND
- No end-stage glaucoma or retinal detachment is present; AND
- The patient has one of the following indications:
  - History of one or more corneal transplant graft failures
  - Stevens-Johnson syndrome
  - Ocular cicatricial pemphigoid
  - Autoimmune conditions with rare ocular involvement
  - Ocular chemical burns
  - An ocular condition unlikely to respond favorably to primary corneal transplant surgery (eg, limbal stem cell compromise or postherpetic anesthesia)

Note: Patients should be expected to be able to be compliant with postoperative care.

### **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers a permanent keratoprosthesis for all other conditions to be **investigational**.\*

Based on review of available data, the Company considers all other types of permanent keratoprostheses to be **investigational**.\*

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### **Background/Overview**

#### **CORNEA**

The cornea, a clear, dome-shaped membrane that covers the front of the eye, is a key refractive element of sight. Layers of the cornea consist of the epithelium (outermost layer); Bowman layer; the stroma, which comprises approximately 90% of the cornea; Descemet membrane; and the endothelium.

#### **Treatment**

The established surgical treatment for corneal disease is penetrating keratoplasty (PK), which involves making a large central opening through the cornea and then filling the opening with full-thickness donor cornea. In certain conditions, such as Stevens-Johnson syndrome, cicatricial pemphigoid, chemical injury, or prior failed corneal transplant, survival of transplanted cornea is poor. The keratoprosthesis was developed to restore vision in patients for whom a corneal transplant is not an option.

Keratoprosthetic devices consist of a central optic held in a cylindrical frame. The keratoprosthesis replaces the section of cornea that has been removed, and, along with being held in place by the surrounding tissue, may be covered by a membrane to further anchor the prosthesis. A variety of biologic materials are being investigated to improve the integration of prosthetic corneal implants into the stroma and other corneal layers.

The Dohlman-Doane keratoprosthesis, most commonly referred to as the Boston Keratoprosthesis (KPro), is manufactured under the auspices of the Harvard Medical School–affiliated Massachusetts Eye and Ear Infirmary. The Boston type 1 KPro uses a donor cornea between a central stem and a back plate. The Boston type 2 prosthesis is a modification of the type 1 prosthesis and is designed with an anterior extension to allow implantation through surgically closed eyelids. The AlphaCor<sup>®</sup>‡, previously known as the Chirila keratoprosthesis (Chirila KPro), consists of a polymethylmethacrylate (PMMA) device with a central optic region fused to a surrounding sponge skirt; the device is inserted in a 2-stage surgical procedure.

Autologous keratoprostheses use a central PMMA optic supported by a skirt of either tibia bone or the root of a tooth with its surrounding alveolar bone. The most common is the OOKP, which uses osteodental lamina derived from an extracted tooth root and attached alveolar bone that has been removed from the patient's jaw. Insertion of the OOKP device requires a complex staged procedure, in which the cornea is first covered with buccal mucosa. The prosthesis itself consists of a PMMA optical cylinder, which replaces the cornea, and is held in place by a biological support made from a canine tooth extracted from the recipient. A hole is drilled through the dental root and alveolar bone, and the PMMA prosthesis is placed within. This entire unit is placed into a subcutaneous ocular pocket and is then retrieved 6 to 12 months later for final insertion.

Hydroxyapatite, with a similar mineral composition to both bone and teeth (phosphate and calcium), may also be used as a bone substitute and as a bioactive prosthesis with the orbit. Collagen coating and scaffolds have also been investigated to improve growth and biocompatibility with the cornea epithelial

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cells, which form the protective layer of the eye. Many of these materials and devices are currently being tested in vitro or in animal models.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

In January 1992, the Boston KPro (Dohlman-Doane keratoprosthesis; Massachusetts Eye and Ear Infirmary) was approved by the U.S. FDA through the premarket approval process for use in patients with severe corneal opacity. The device is used when standard corneal transplant has failed or would be unlikely to succeed. There are 2 types of Boston KPro. Type 1 is used in eyes when eyelids, blink mechanism, and tear film are intact. Type 2 is used with severe dry eye and in eyes with mucosal keratinization and obliteration of normal conjunctival fornices.

In August 2002, the AlphaCor (Chirila keratoprosthesis) was cleared for marketing by FDA through the 510(k) process. FDA determined that this device was substantially equivalent to the Dolman-Doane keratoprosthesis. The AlphaCor device is indicated as a keratoprosthesis in adults with corneal opacity when standard penetrating keratoplasty with donor tissue is not suitable, when patients have declined standard penetrating keratoplasty, or when adjunctive procedures to prevent graft rejection are contraindicated.

### Centers for Medicare and Medicaid Services (CMS)

There is no Medicare national coverage policy. In 2006, Medicare has established an Ambulatory Payment Classification 0293 for level V anterior segment eye procedures that includes CPT code 65770 (keratoprosthesis) and a HCPCS code for the prosthesis (C1818 - integrated keratoprosthesis OR L8609 - artificial cornea).

## **Rationale/Source**

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common

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adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The keratoprosthesis is intended for the relatively small number of patients with severe corneal damage who have lost vision and for whom a corneal transplant is not expected to result in satisfactory outcomes. These criteria generally refer to the population of patients who have failed 1 or more corneal transplants and who therefore have very few options to prevent blindness. Because this surgery is considered a salvage procedure with no acceptable alternative treatments, comparative studies are limited and/or lacking. The available literature primarily consists of retrospective case series. This evidence review examines the types of devices currently being tested in humans, focusing on reports that permit assessment of integration within the eye, durability, visual outcomes, and adverse events following implantation.

### **BOSTON (DOHLMAN-DOANE) KERATOPROSTHESIS (KPRO)**

#### **Systematic Reviews**

A 2015 systematic review from the American Academy of Ophthalmology identified 22 studies on the efficacy and safety of the Boston KPro. Studies were published in English and retrospective series had to include at least 25 eyes. The 22 studies included a total of 2176 eyes; sample sizes in individual studies ranged from 30 to 300 eyes. The proportion of patients with visual acuity of 20/200 after surgery ranged from 54% to 84% in the 10 studies reporting this outcome. Five articles reported that 11% to 39% of treated eyes attained visual acuities of 20/40 or better. Reviewers noted that published data were skewed toward visual improvement. Fourteen articles reported retention rates (eyes retaining the KPro device without loss, extrusion or dehiscence of the device), and these rates ranged from 65% to 100% (mean, 88%). The most common reasons for KPro loss were corneal melts with device exposure or extrusion, endophthalmitis, infectious keratitis, or corneal ulceration. The most common complication was retroprosthetic membrane formation, which ranged from 1% to 65% (mean, 30%) in the 13 studies reporting complications.

A systematic review by Ahmad et al (2016) examined 26 studies on repeat PK vs Boston KPro implantation after failed PK.<sup>2</sup> Studies selected focused on patients with corneal opacity who had failed one or more PKs. Studies were excluded if they only selected patients with ocular surface disease. The primary outcome of interest was the proportion of patients with visual acuity of 20/200 or better at 2 or more years postsurgery. In a meta-analysis of 9 studies, the likelihood of 20/200 vision or better at least 2 years after repeat PK surgery was 42% (95% confidence interval [CI], 30% to 56%). A total of 104 eyes from 98 patients underwent KPro after failed PK surgery; 31 patients had only 1 previous PK. In a meta-analysis of data on KPro implantation after failed PK surgery, the probability of maintaining visual acuity of 20/200 or better at 2 years was 80% (95% CI, 68% to 88%). Among patients with a history of one failed PK, the probability of maintaining a visual acuity of 20/200 or better at 2 years was 74% (95% CI, 45% to 89%). (Reviewers did not specify the number of patients receiving KPro who were included in the analysis of 20/200 vision at 2 years.) In terms of complications after KPro following failed PK, at 2 years 29% of patients had elevated intraocular pressure and 8% needed surgery for glaucoma. In an analysis limited to patients undergoing KPro after 1 failed PK, complication rates ranging from 29% to 10% (which did not differ significantly from

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patients with KPro after >1 failed PKs). Reviewers did not report the number of patients included in the complication analyses.

### Case Series

Representative larger series include a 2013 report from the Boston Type 1 Keratoprosthesis Study Group assessed retention of the KPro device in 300 eyes of 300 patients. At a mean follow-up of 17.1 months (range, 1 week to 6 years), 93% of the keratoprostheses were retained. The probability of retention was 94% at 1 year and 89% at 2 years. Mean device durability was 3.8 years. Risk factors for keratoprosthesis loss were autoimmune disease, ocular surface exposure, and number of prior failed PK procedures. Additional data on this cohort were published in 2016. Preoperative visual acuity, available for 47% of eyes, was 20/1205. During a mean follow-up of 17 months (range, 1 week to 6 years), visual acuity improved significantly for 85% of eyes to a final mean of 20/150. Median time to achieve visual acuity of 20/200 was 1 month, and this level of acuity lasted for a mean of 48 months among patients with sufficient follow-up.

In 2014, Srikumaran et al reported mean follow-up of 46.7 months (range, 6 weeks to 8.7 years) for 139 eyes of 133 patients who had received a Boston KPro at 1 of 5 tertiary referral centers in the United States. Twenty-seven percent of eyes underwent a primary KPro procedure while 73% had a prior donor graft failure. Postoperatively, visual acuity improved to at least 20/200 in 70% of eyes. The probability of maintaining visual acuity of at least 20/200 was 50%, and device retention was estimated at 67% at 7 years. The 7-year cumulative incidence of complications was 49.7% for retroprosthetic membrane formation, 21.6% for glaucoma surgery, 18.6% for retinal detachment, and 15.5% for endophthalmitis.

A prospective series of 265 eyes (265 patients) from 18 medical centers, published by the Boston Type 1 Keratoprosthesis Study Group (2012), focused on the time to development of retroprosthetic membranes. Most eyes (85.4%) had undergone an average of 2.2 (range, 1-8) PKs before keratoprosthesis implantation. The remaining eyes (14.6%) were considered at high-risk for PK failure and had received a primary keratoprosthesis. At a mean follow-up of 17.8 months, retroprosthetic membranes had formed in 31.7% of eyes. The mean time to development of retroprosthetic membranes was 216.7 days (range, 7 days to 4 years). Risk factors were the indication for the keratoprosthesis. Specifically, infectious keratitis had a hazard ratio of 3.2 (95% CI, 1.7 to 6.2) and aniridia had a hazard ratio of 3.1 (95% CI, 1.1 to 8.9).

In 2010, Dunlap et al retrospectively analyzed 122 patients (126 eyes) at 2 centers who received a Boston type 1 keratoprosthesis between 2004 and 2007. For most patients, the affected eye had a visual acuity of less than 20/400, and the contralateral eye did not have better vision. Of the 126 eyes, 112 had a history of multiple failed corneal grafts, and 14 had received the keratoprosthesis as a primary procedure due to the presence of limbal stem cell deficiency or significant ocular surface diseases. Following implantation, 96 (76%) eyes had improved vision, 22 (17.4%) eyes did not improve, and 8 (6.3%) eyes lost vision. At 3-month follow-up, 54% of eyes had 20/200 vision or better, with 18% achieving 20/40 or better. In approximately 45% of the eyes, visual acuity remained less than 20/400. The percentage of patients with improved visual outcomes was lower than in other published studies, due in part to the presence of comorbid conditions (eg, glaucoma, retinal detachment).

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### Adverse Events

In 2015, Odorcic et al published a literature review on fungal infections after Boston type 1 KPro. They identified 15 relevant publications, primarily retrospective case series. Annual rates of fungal infections reported in these studies ranged from 0.9 to 2 per 100 patients. The largest case series assessed 291 eyes, and the cumulative incidence of fungal endophthalmitis was 2.4% over 10 years.

In 2016, Chan et al retrospectively reviewed 110 patients (128 eyes) who received a Boston type 1 KPro, focusing on corneal melts, leaks, and extrusions. Mean follow-up was 29 months (range, 3-77 months). Melt-related complications requiring surgical repair occurred in 16% (20/128) of eyes; 7 of these eyes had multiple episodes. The average time to a melt complication was 13 months after KPro implantation. Risk factors significantly associated with melt-related complications were previous infectious keratitis, and conjunctival deficiency caused by Stevens-Johnson syndrome, mucous membrane pemphigoid, or previous chemical injury.

Posterior segment complications were reported by Goldman et al (2013). Of 83 eyes (93 procedures) with follow-up of at least 6 months (range, 6-84 months), 38 (40.9%) eyes had at least 1 postoperative posterior segment complication, which included retinal detachment (16.9%), choroidal detachment (16.9%), and sterile vitritis (14.5%). Visual acuity was worse in eyes that experienced posterior segment complications than in eyes that did not.

### Section Summary: Boston Keratoprosthesis

Numerous case series and systematic reviews of these series have assessed thousands of eyes implanted with the Boston KPro device. A 2015 systematic review of KPro efficacy included 22 series with a total of 2176 eyes. Studies with longer follow-up (ie, at least 2 years) have shown improved visual outcomes in a substantial percentage of patients with Boston KPro. This procedure is high-risk and is associated with numerous complications (eg, the growth of retroprosthetic membranes) and a probable need for additional surgery, thus careful patient selection is important.

### ALPHACOR DEVICE

Studies have suggested that, with the AlphaCor device, thinning or “melting” of the anterior corneal surface can lead to loss of biointegration. This complication appears most prevalent in patients with ocular herpes, hence, the AlphaCor device is contraindicated in these patients.

Several case series have evaluated the AlphaCor. One of the larger was published by Hicks et al (2003). It included 40 devices implanted in 38 patients. At an average 30-month follow-up, 42% of eyes had visual acuity better than 20/200. Hoffart et al (2015) evaluated the AlphaCor device implanted in 12 patients. At a mean follow-up of 25 months, 8 (67%) of devices were retained, and patients had a mean gain in best-corrected visual acuity of 2.5 lines. The most common complication was corneal necrosis, observed in 7 (59%) patients, two of whom had a history of ocular herpes.

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### Section Summary: AlphaCor Device

Only a few published case series have evaluated the AlphaCor device, and hence there are insufficient data on improvements in vision outcomes this device. Moreover, the device has been associated with complications, including thinning or melting of the anterior corneal surface and corneal necrosis.

### OSTEO-ODONTO-KERATOPROSTHESIS

A systematic review by Tan et al (2012) included 8 case series describing surgical outcomes and complication rates of the osteo-odonto-keratoprosthesis (OOKP). Sample sizes ranged from 4 to 181 eyes. None of the studies was conducted in the United States. At 5 years, the pooled anatomic survival rate was 88% (range, 67%-100%) and, at 20 years, based on pooled data from 3 series, the anatomic survival rate was 81% (range, 65%-98%). About half of the patients obtained visual acuity better than 6/18. Visual acuity in the other patients was not described.

One of the largest case series (included in the Tan systematic review) is that by Falcinelli et al (2005), who reported on OOKP in 181 patients. At a median follow-up of 12 years, survival analysis estimated that the probability of retaining an anatomically intact OOKP 18 years after surgery with reasonable visual acuity was 85%.

In 2008, investigators from Spain retrospectively reviewed 227 patients who underwent OOKP (n=145) or osteokeratoprosthesis (OKP; n=82) using tibial bone in patients who lacked canine teeth to assemble the prosthesis. A second publication in 2011 from the same study examined the impact of clinical factors on long-term functional and anatomic outcomes. The primary diagnosis was chemical or thermal burn (48%), Steven-Johnson syndrome and Lyell syndrome (13%), cicatricial pemphigoid (11%), trachoma (11%), and other or not assignable (17%). Mean preoperative decimal best-corrected visual acuity was 0.00062 (range, light perception to 0.10). (On the decimal visual acuity scale, 0 = no light perception, 0.00001 = light perception, 0.0001 = light projection, and 0.001 = counting fingers.) Functional survival was defined as best-corrected visual acuity of 0.05 or more, and anatomic survival as retention of the keratoprosthesis lamina. Mean follow-up was 8.4 years for OOKP and 3.5 years for OKP. Anatomic success at 10 years was estimated to be 66% for OOKP and 47% for OKP. Functional success at 10 years was estimated to be 38% for OOKP and 17% for OKP. The best functional survival was in the Stevens-Johnson group, followed by chemical burn and trachoma. The least favorable prognosis was thermal burn. Complications included extrusion of the keratoprosthesis (28%), retinal detachment (16%), uncontrolled glaucoma (11%), infection (9%), retroprosthetic membrane (5%), and vitreous hemorrhage (3%). In cases without complications, functional survival was 57% at 5 years and 42% at 10 years.

Hughes et al (2008) reported on vitreoretinal complications of the OOKP in a retrospective review of 35 patients performed at 1 hospital in England between 1996 and 2005. Diagnoses were Stevens-Johnson syndrome in 15 patients, chemical injury in 5, mucous membrane pemphigoid in 3, and topical medication toxicity in 3. Follow-up at a mean 57 months (range, 13-105 months) revealed 9 vitreoretinal complications in 8 (23%) patients, which included vitreous hemorrhage, retinal detachment, and intraoperative choroidal hemorrhage. A 2008 report on 36 patients treated at the same hospital between 1996 and 2006 (likely to

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have reported patients assessed by Hughes) estimated that the probability of retaining visual acuity was 53% at 5 years and 44% at 9 years. In addition to the vitreoretinal complications causing loss of vision, resorption of the bony lamina led to visual or anatomic compromise in 7 (19%) cases.

### **Section Summary: Osteo-Odonto-Keratoprosthesis**

A 2012 systematic review identified 8 case series evaluating OOKP, all of which were conducted outside of the United States, and no subsequent studies were identified. Pooled analyses of case series data found high anatomic survival rates at 5 and 20 years. However, vision outcomes were not well-described. The systematic review reported that half of the patients obtained visual acuity better than 6/18. OOKP is a complex surgical procedure and has been associated with a number of complications, including extrusion of the keratoprosthesis, retinal detachment, and vitreoretinal complications.

### **SUMMARY OF EVIDENCE**

For individuals who have corneal blindness and have failed or are not candidates for corneal transplantation who receive a Boston KPro, the evidence includes case series and systematic reviews. Relevant outcomes are change in disease status, morbid events, quality of life, and treatment-related morbidity. Numerous case series have been published. Together, studies have assessed thousands of eyes. A 2015 systematic review of Boston KPro efficacy included 22 series with a total of 2176 eyes. Systematic reviews and case series with longer follow-up (ie, at least 2 years) have shown improvement in visual outcomes in a substantial percentage of patients with Boston KPro. This procedure is high-risk and associated with numerous complications (eg, the growth of retro prosthetic membranes) and a probable need for additional surgery, thus careful patient selection is important. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have corneal blindness and have failed or are not candidates for corneal transplantation who receive a keratoprosthesis using the AlphaCor device, the evidence includes case series. Relevant outcomes are change in disease status, morbid events, quality of life, and treatment-related morbidity. Only a few published case series have evaluated the AlphaCor device. There are insufficient data on improvement in vision outcomes using the AlphaCor device. Moreover, the device has been associated with complications, including thinning or melting of the anterior corneal surface and corneal necrosis. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have corneal blindness and have failed, or are not candidates for corneal transplantation who receive an osteo-odonto-keratoprosthesis, the evidence includes case series and a systematic review. Relevant outcomes are change in disease status, morbid events, quality of life, and treatment-related morbidity. A 2012 systematic review of case series, all conducted outside of the United States, found high anatomic survival rates at 5 and 20 years, but vision outcomes were not well-described. Osteo-odonto-keratoprosthesis is a complex surgical procedure and has been associated with a number of complications, including extrusion of the keratoprosthesis, retinal detachment, and vitreoretinal complications. The evidence is insufficient to determine the effects of the technology on health outcomes.

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05/07/2015 Medical Policy Committee review

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# Louisiana

## Keratoprosthesis

Policy # 00450

Original Effective Date: 05/20/2015

Current Effective Date: 05/16/2018

05/20/2015 Medical Policy Implementation Committee approval. New policy.  
 05/05/2016 Medical Policy Committee review  
 05/18/2016 Medical Policy Implementation Committee approval. A bullet stating “an ocular condition unlikely to respond favorably to primary corneal transplant surgery” was added to the medically necessary policy statement. In medically necessary policy statement, “multiple graft failures changed” to “history of 1 or more” graft failures.  
 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes  
 05/04/2017 Medical Policy Committee review  
 05/17/2017 Medical Policy Implementation Committee approval. No change to coverage.  
 05/03/2018 Medical Policy Committee review  
 05/16/2018 Medical Policy Implementation Committee approval. No change to coverage.  
 Next Scheduled Review Date: 05/2019

### Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	65770
HCPCS	C1818, L8609
ICD-10 Diagnosis	H17.10-H17.13 H54.0 H54.40-H54.42 L51.1 T26.60XA-T26.62XA T85.318A T85.328A T85.398A T85.72XA T85.79XA T86.840-T86.842

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  - 3. Reference to federal regulations.

**\*\*Medically Necessary (or "Medical Necessity")** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

† Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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