Medical Policy

**MP 7.01.149**
Amniotic Membrane and Amniotic Fluid

**BCBSA Ref. Policy:** 7.01.149  
**Last Review:** 04/18/2019  
**Effective Date:** 07/15/2019  
**Section:** Surgery

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**POLICY**

Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products (AmnioBand® Membrane, Biovance®, Episcove®, EpiFix®, Grafix™) may be considered medically necessary.

Human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) may be considered medically necessary for the treatment of the following ophthalmic indications:

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy (see Policy Guidelines);
- Corneal ulcers and melts that do not respond to initial conservative therapy (see Policy Guidelines);
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment;
- Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty);
- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient;
- Moderate or severe Stevens-Johnson syndrome;
- Persistent epithelial defects that do not respond to conservative therapy (See Policy Guidelines);
- Severe dry eye (DEWS 3 or 4) with ocular surface damage and inflammation that remains
symptomatic after Steps 1, 2, and 3 of the dry eye disease management algorithm (see Policy Guidelines); or

- Moderate or severe acute ocular chemical burn.

Human amniotic membrane grafts with suture or glue may be considered medically necessary for the treatment of the following ophthalmic indications:

- Corneal perforation when corneal tissue is not immediately available; or
- Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

Human amniotic membrane grafts with or without suture are considered investigational for all ophthalmic indications not outlined above.

Injection of micronized or particulated human amniotic membrane is considered investigational for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis.

Injection of human amniotic fluid is considered investigational for all indications.

All other human amniotic membrane products and indications not listed above are considered investigational, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency.

POLICY GUIDELINES

Nonhealing of diabetic wounds is defined as less than a 20% decrease in wound area with standard wound care for at least 2 weeks, based on the entry criteria for clinical trials (eg, Zelen et al, 2015).

Conservative therapy for neurotrophic keratitis may include 5 days of pressure patching, therapeutic contact lens, topical lubricants, and topical antibiotics.

Conservative therapy for corneal ulcers and melts may include 2 days of patching, therapeutic contact lens, and topical antimicrobial agents.

A persistent epithelial defect is one that failed to close completely after 5 days of conservative treatment or has failed to demonstrate a decrease in size after 2 days of conservative treatment. Conservative treatment of a persistent epithelial defect may include 5 days of the following: topical lubricants, topical antibiotics, therapeutic contact lens, or patching.

Tear Film and Ocular Surface Society staged management for dry eye disease (Jones et al, 2017)

Step 1:
- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if meibomian gland dysfunction is present, then consider lipid containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:
If above options are inadequate consider:
- Non-preserved ocular lubricants to minimize preservative-induced toxicity
• Tea tree oil treatment for Demodex (if present)
• Tear conservation
• Punctal occlusion
• Moisture chamber spectacles/goggles
• Overnight treatments (such as ointment or moisture chamber devices)
• In-office, physical heating and expression of the meibomian glands
• In-office intense pulsed light therapy for meibomian gland dysfunction
• Prescription drugs to manage dry eye disease
• Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
• Topical corticosteroid (limited-duration)
• Topical secretagogues
• Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
• Topical LFA-1 antagonist drugs (such as lifitegrast)
• Oral macrolide or tetracycline antibiotics

Step 3:
If above options are inadequate consider:
• Oral secretagogues
• Autologous/allogeneic serum eye drops
• Therapeutic contact lens options
• Soft bandage lenses
• Rigid scleral lenses

Step 4:
If above options are inadequate consider:
• Topical corticosteroid for longer duration
• Amniotic membrane grafts
• Surgical punctal occlusion
• Other surgical approaches (eg tarsorrhaphy, salivary gland transplantation)

Dry eye severity level DEWS 3 to 4
Discomfort, severity, and frequency - Severe frequent or constant
Visual symptoms - chronic and/or constant, limiting to disabling
Conjunctival Injection - +/- or +/+
Conjunctive Staining - moderate to marked
Corneal Staining - marked central or severe punctate erosions
Corneal/tear signs - Filamentary keratitis, mucus clumping, increase in tear debris
Lid/meibomian glands - Frequent
Tear film breakup time - < 5
Schirmer score (mm/5 min) - < 5

Coding
There are specific HCPCS codes for some of these products (see Codes table below). If no specific HCPCS code exists for the product, an unlisted code such as Q4100 would be used.

There are no specific codes for AmnioFix or OrthoFlo. It might be reported using the code for another MiMedx product such as:
Q4145: Epifix, injectable, 1 mg, or the not otherwise specified code Q4100.

There is no specific code for this type of injection. It might be reported with one of the musculoskeletal system injection codes (eg, 20550), the unlisted general musculoskeletal system code (20999), or if subcutaneous or intramuscular, the therapeutic injection code (96372).

There are codes for the placement of amniotic membrane on the ocular surface:
65778: Placement of amniotic membrane on the ocular surface; without sutures
65779: single layer, sutured.

There are several new HCPCS codes effective 1/1/2019 for these types of products. See below and the coding table.
Q4183 Surgigraft, per square centimeter
Q4184 Cellesta, per square centimeter
Q4185 Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4186 Epifix, per square centimeter; Replacing Q4131 Epifix or Epicord, per square centimeter
Q4187 Epicord, per square centimeter; Replacing Q4131 Epifix or Epicord, per square centimeter
Q4188 Amnioarmor, per square centimeter
Q4189 Artacent ac, 1 mg
Q4190 Artacent ac, per square centimeter
Q4191 Restorigin, per square centimeter
Q4192 Restorigin, 1 cc
Q4194 Novachor, per square centimeter
Q4198 Novachor, per square centimeter
Q4201 Matrion, per square centimeter
Q4204 Xwrap, per square centimeter

**BENEFIT APPLICATION**

**BLUECARD/NATIONAL ACCOUNT ISSUES**

None.

**BACKGROUND**

**Human Amniotic Membrane**

HAM consists of two conjoined layers, the amnion, and chorion, and forms the innermost lining of the amniotic sac or placenta. When prepared for use as an allograft, the membrane is harvested immediately after birth, cleaned, sterilized, and either cryopreserved or dehydrated. Many products available using amnion, chorion, amniotic fluid, and umbilical cord are being studied for the treatment of a variety of conditions, including chronic full-thickness diabetic lower-extremity ulcers, venous ulcers, knee osteoarthritis, plantar fasciitis, and ophthalmic conditions. The products are formulated either as patches, which can be applied as wound covers, or as suspensions or particulates, or connective tissue extractions, which can be injected or applied topically (see Table 1).

The fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist. There is evidence the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause a substantial immune response. It is believed these properties are retained in cryopreserved HAM and dehydrated HAM products, resulting in a readily available tissue with regenerative potential. In support, one
Amniotic Membrane and Amniotic Fluid

A dehydrated HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.2

Use of a HAM graft, which is fixated by sutures, is an established treatment for disorders of the corneal surface, including neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Amniotic membrane products that are inserted like a contact lens have more recently been investigated for the treatment of corneal and ocular surface disorders. Amniotic membrane patches are also being evaluated for the treatment of various other conditions, including skin wounds, burns, leg ulcers, and prevention of tissue adhesion in surgical procedures.1,4 Additional indications studied in preclinical models include tendonitis, tendon repair, and nerve repair. The availability of HAM opens the possibility of regenerative medicine for an array of conditions.

Amniotic Fluid

Amniotic fluid surrounds the fetus during pregnancy and provides protection and nourishment. In the second half of gestation, most of the fluid is a result of micturition and secretion from the respiratory tract and gastrointestinal tract of the fetus, along with urea.1 The fluid contains proteins, carbohydrates, peptides, fats, amino acids, enzymes, hormones, pigments, and fetal cells. Use of human and bovine amniotic fluid for orthopedic conditions was first reported in 1927.1,2 Amniotic fluid has been compared with synovial fluid, containing hyaluronan, lubricant, cholesterol, and cytokines. Injection of amniotic fluid or amniotic fluid–derived cells is currently being evaluated for the treatment of osteoarthritis and plantar fasciitis.

Amniotic membrane and amniotic fluid are also being investigated as sources of pluripotent stem cells.3 Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type. The use of stem cells in orthopedic applications is addressed in evidence review 8.01.52.

Table 1. Amniotic Membrane and Amniotic Fluid Preparations: Preparation and Components

<table>
<thead>
<tr>
<th>Product (Supplier)</th>
<th>Preparation</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cryopreserved,</td>
<td>Amnion</td>
</tr>
<tr>
<td></td>
<td>Dehydrated, or</td>
<td>Chorion</td>
</tr>
<tr>
<td></td>
<td>Extracted</td>
<td>Amniotic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Umbilical</td>
</tr>
<tr>
<td>Patch</td>
<td></td>
<td>Cord</td>
</tr>
<tr>
<td>Affinity™ (NuTech Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>AlloWrap™ (AlloSource)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>AmbioDisk® (IOP Ophthalmics)</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>AmbioDry5® (IOP Ophthalmics)</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>AmnioBand® Membrane (MTF Wound Care)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioClear™ (Liventa Bioscience)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>AmnioExcel® (Derma Sciences)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioFix® (MiMedx)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioGraft® (Bio-Tissue)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Artacent® Wound (Tides Medical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>BioDDryFlex® (BioD)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>BioFence™ (BioD)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>BioSkin (HRT)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Biovance® (Alliqua Biomedical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Product (Supplier)</td>
<td>Preparation</td>
<td>Components</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>Clarix® (Amniox Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Cygnus (Vivex Biomedical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Cygnus Max (Vivex Biomedical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>EpiCord™ (MiMedx)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Epifix® (MiMedx)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Dermavest™ (Aedicell)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Grafix® (Osiris)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Guardian/AmnioBand® (MTF Wound Care)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Neox® 100 (Amniox Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Neox® Cord (Amniox Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Neox® Wound Allograft (Amniox Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>NuShield™ (NuTech Medical)</td>
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<td>X</td>
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<tr>
<td>PalinGen® Membrane (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Plurivest™ (Aedicell)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Prokera® (Bio-Tissue)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Revitalon™ (Medline Industries)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>WoundEx® (Skye Biologics)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Suspension, particulate, or extraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AmnioBand® Particulate (MTF Wound Care)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioMatrix® (Derma Sciences)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioVisc™ (Lattice Biologics)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>Bioskin® Flow (HRT)</td>
<td>E</td>
<td>X</td>
</tr>
<tr>
<td>Clarix® Flo (Amniox Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Interfyl™ (Alliqua Biomedical)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>Neox® Flo (Amniox Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>OrthoFlo™ (MiMedx)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>PalinGen® Flow (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>PalinGen® SportFlow (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>ProMatrX™ ACF (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>ReNu™ (NuTech Medical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>WoundEx® Flow (Skye Biologics)</td>
<td>E</td>
<td>X</td>
</tr>
</tbody>
</table>

C: cryopreserved; D: dehydrated; E: extracted connective tissue; HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation; NS: not specified.

**Regulatory Status**

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. HAM products and amniotic fluid products are included in these regulations.
In 2003, Prokera™ was cleared for marketing by the Food and Drug Administration through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). The Food and Drug Administration determined that this device was substantially equivalent to the Symblepharon Ring. The Prokera™ device is intended “for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred.” The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

AmnioClip (FORTECH GmbH) is a ring designed to hold the amniotic membrane in the eye without sutures or glue fixation. A mounting device is used to secure the amniotic membrane within the AmnioClip. The AmnioClip currently has CE approval in Europe.

**RATIONALE**

This evidence review was created in April 2015 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 27, 2018. The following conclusions are based on a review of the evidence, including, but not limited to, published evidence and clinical expert opinion, via BCBSA’s Clinical Input Process.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 technology, two domains are examined: the relevance, and 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 (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common 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.

**Diabetic Lower-Extremity Ulcers**

**Dehydrated Amniotic Membrane or Placental Membrane**

**Clinical Context and Therapy Purpose**

The purpose of dehydrated amniotic membrane or placental membrane in patients who have diabetic lower-extremity ulcers is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does amniotic membrane or placental membrane improve the net health outcome in patients with diabetic lower-extremity ulcers?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest are patients with diabetic lower-extremity ulcers that have failed to heal with the standard of care (SOC) therapy.
Interventions

The therapy being considered is an amniotic membrane or placental membrane applied every one to two weeks. It is applied in addition to the SOC.

Comparators

The following therapies are currently being used to make decisions about the healing of diabetic lower-extremity ulcers: SOC, which involves moist dressing, dry dressing, compression therapy, and offloading.

Outcomes

The primary endpoints of interest for trials of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds:

Incidence of complete wound closure.

Time to complete wound closure (reflecting accelerated wound closure).

Incidence of complete wound closure following surgical wound closure.

Pain control.

Timing

Complete ulcer healing with advanced wound therapies may be measured at 6 to 12 weeks.

Setting

The setting is outpatient care by a wound care specialist.

Review of Evidence

At least six RCTs have evaluated rates of healing with amniotic membrane grafts or placental membrane graft compared to SOC or an advanced wound therapy in patients with chronic diabetic foot ulcers (see Table 2). The number of patients in these studies ranged from 25 to 155. Human amniotic membrane (HAM) or placental membrane grafts improved healing compared to SOC by 22% (EpiCord vs Alginate dressing) to 60% (EpiFix) in the intention-to-treat (ITT) analysis (see Table 3). In a 2018 trial, the cryopreserved placental membrane Grafix was found to be non-inferior to an advanced fibroblast-derived wound therapy (Dermagraft)

Table 2. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Active Intervention</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ananian et al (2018)⁴</td>
<td>US</td>
<td>7</td>
<td>2016-2017</td>
<td>75 patients with chronic (&gt; 4 weeks) non-healing diabetic foot ulcers between 1 cm² and 15 cm²</td>
<td>n=38, Grafix weekly for up to 8 weeks</td>
<td>n=37, Dermagraft (fibroblast-derived) weekly for up to 8 weeks</td>
</tr>
<tr>
<td>Tettelbach et al (2018)¶</td>
<td>US</td>
<td>11</td>
<td>2016-2018</td>
<td>155 patients with chronic (&gt; 4 weeks) non-healing diabetic foot ulcers</td>
<td>n=101 EpiCord plus SOC</td>
<td>n=54 SOC with alginate dressing</td>
</tr>
</tbody>
</table>
MP 7.01.149
Amniotic Membrane and Amniotic Fluid

<table>
<thead>
<tr>
<th>Study</th>
<th>Wounds Healed at 6 Weeks (ITT)</th>
<th>Wounds Healed</th>
<th>Days to Complete Healing</th>
<th>Adverse Events and Number of Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with Index Ulcer Related Adverse Events n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ananian et al (2018)</td>
<td>8 Weeks (PP) n (%)</td>
<td>62</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grafix</td>
<td>15 (48.4%)</td>
<td>1 (5.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermagraft</td>
<td>12 (38.7%)</td>
<td>4 (16.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diff (95% CI)</td>
<td>9.68% (~10.7 to 28.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower bound for non-inferiority</td>
<td>-15%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tettlebach et al (2018)</td>
<td>12 Weeks (PP) n (%)</td>
<td>134</td>
<td>155</td>
<td>155</td>
</tr>
<tr>
<td>EpiCord</td>
<td>81 (81%)</td>
<td>71 (70%)</td>
<td>42 (42%)</td>
<td></td>
</tr>
<tr>
<td>SOC</td>
<td>29 (54%)</td>
<td>26 (48%)</td>
<td>33 (61%)</td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>0.001</td>
<td>0.009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiDomenico et al (2016)</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; SOC: standard of care including debridement, nonadherent dressing, moisture dressing, a compression dressing and offloading.

Table 3. Summary of Key RCT Results
<table>
<thead>
<tr>
<th>Study</th>
<th>N or n (%)</th>
<th>Wounds Healed at 12 Weeks</th>
<th>Weekly Treatments</th>
<th>Patients With Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snyder et al (2016)</td>
<td>29 (95%)</td>
<td>65.5% (52.9% to 77.9%)</td>
<td>4.6</td>
<td>0%</td>
</tr>
<tr>
<td>Zelen et al (2015, 2016)</td>
<td>60 (100%)</td>
<td>50% (34.1% to 65.9%)</td>
<td>3.4</td>
<td>0%</td>
</tr>
<tr>
<td>Lavery et al (2014)</td>
<td>97a (97%)</td>
<td>50% (34.1% to 65.9%)</td>
<td>3.4</td>
<td>0%</td>
</tr>
</tbody>
</table>

HAM: human amniotic membrane; CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NNT: number needed to treat; NR: not reported; PP: per protocol; RCT: randomized controlled trial; RR.

a. Power analysis indicated that 94 patients per arm would be needed. However, after a prespecified interim analysis at 50% enrollment, the blinded review committee recommended the trial is stopped due to the efficacy of the treatment.

Gaps in study design and conduct are shown in Table 4. Studies without notable gaps reported power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome.
measure, and ITT analysis. Limitations from the RCT with AmnioExcel (Snyder et al [2016]) \(^\text{11}\) preclude conclusions for this product.

Table 4. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ananian et al (2018)(^\text{12})</td>
<td>2, 3. No blinding for outcomes assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tettelbach et al (2018)(^\text{11})</td>
<td>1, 2, 3. No blinding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiDomenico et al (2016)(^\text{11})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snyder et al (2016)(^\text{11})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zelen et al (2015, 2016)(^\text{8, 8})</td>
<td>1. Thirteen of 35 patients in the SOC group exited the study at 6 weeks due to less than 50% healing, which may have affected the 12 week results.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lavery et al (2014)(^\text{10})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.


d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

**Prospective Single-arm or Registry Studies**
Prospective single-arm or registry studies are described in Tables 5 and 6.

Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about a third (n=47) were diabetic foot wounds. Of those treated, 28 ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of 8 weeks and a mean of 2.4 amniotic membrane applications. Treatment of complex chronic wounds (exposed tendon or bone) with Grafix was reported by Frykberg et al (2016). With the cryopreserved placental membrane applied weekly for up to 16 weeks, 59% of wounds closed with a mean time to closure of 9 weeks.

Table 5. Summary of Prospective Single-arm Studies or Registry Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Participants</th>
<th>Treatment Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smiell et al</td>
<td>Multicenter Registry</td>
<td>Various chronic wounds: 47 diabetic foot wounds, 20 pressure ulcers, and 89 venous ulcers; 28 had failed prior treatment with advanced biologic therapies (Apligraf, Dermagraft, or Regranex)</td>
<td>Biovance</td>
</tr>
<tr>
<td>(2015)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frykberg et al</td>
<td>Prospective multicenter single-arm study</td>
<td>31 patients with chronic complex diabetic foot wounds with exposed tendon or bone</td>
<td>Grafix weekly until closure or 16 weeks</td>
</tr>
<tr>
<td>(2016)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Summary of Prospective Single-arm Studies or Registry Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Wounds Closed</th>
<th>Mean Time to Closure</th>
<th>Number of Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smiell et al (2015)</td>
<td>Biovance</td>
<td>41.6%</td>
<td>8 weeks</td>
<td>2.4</td>
</tr>
<tr>
<td>Frykberg et al (2016)</td>
<td>Grafix</td>
<td>59.3%</td>
<td>9 weeks</td>
<td>9</td>
</tr>
</tbody>
</table>

Section Summary: Diabetic Lower-Extremity Ulcers

For individuals who have non-healing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM or placental membrane (ie, AmnioBand Membrane, AmnioExcel, Biovance, Epicord, Epifix, Grafix), the evidence includes RCTs. The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing (<20% healing with ≥2 weeks of standard care) diabetic lower-extremity ulcers have compared HAM with standard care or with an established advanced wound care product. These trials used wound closure as the primary outcome measure, and some used power analysis, blinded assessment of wound healing, and ITT analysis. For the HAM products that have been sufficiently evaluated (ie, AmnioBand Membrane, Biovance, Epicord, Epifix, Grafix), results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries.

Lower-Extremity Ulcers due to Venous Insufficiency

Dehydrated Amniotic Membrane

Clinical Context and Therapy Purpose

The purpose of dehydrated amniotic membrane or placental membrane in patients who have lower-extremity ulcers due to venous insufficiency is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The question addressed in this evidence review is: does amniotic membrane or placental membrane improve the net health outcome in patients with venous ulcers?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest are patients with lower-extremity venous ulcers that have failed to heal with the SOC therapy.

**Interventions**

The therapy being considered is amniotic membrane or placental membrane applied every one to two weeks. It is applied in addition to the SOC.

**Comparators**

The following therapies are currently being used to make decisions about the healing of venous ulcers: SOC, which involves moist dressing, dry dressing, and compression therapy.

**Outcomes**

The primary endpoints of interest for trials of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds:

- Incidence of complete wound closure.
- Time to complete wound closure (reflecting accelerated wound closure).
- Incidence of complete wound closure following surgical wound closure.
- Pain control.

**Timing**

Complete ulcer healing with advanced wound therapies may be measured at 6 to 12 weeks.

**Setting**

The setting is outpatient care by a wound care specialist.

Two RCTs, both with EpiFix, were identified on amniotic membrane grafts for venous leg ulcers. Serena et al (2014) reported on an industry-sponsored multicenter open-label RCT that compared EpiFix d-HAM plus compression therapy with compression therapy alone for venous leg ulcers (see Table 7). The primary outcome in this trial was the proportion of patients with 40% wound closure at 4 weeks, which was achieved by about twice as many patients in the combined EpiFix group compared with the control group (see Table 8). However, a similar percentage of patients in the combined EpiFix group and the control group achieved complete wound closure during the four-week study. There was no significant difference in healing for wounds given 1 vs 2 applications of amniotic membrane (62% vs 63%, respectively). Strengths of this trial included adequate power and ITT analysis with last observation carried forward. Limitations included the lack of blinding for wound evaluation and use of 40% closure rather than complete closure. A 2015 retrospective study of 44 patients from this RCT (31 treated with amniotic membrane) found that wounds with at least 40% closure at 4 weeks (n=20) had a closure rate of 80% by 24 weeks; however, this analysis did not take into account additional treatments after the 4-week randomized trial period.
A second industry-sponsored multicenter open-label RCT, (Bianchi et al [2017]), evaluated the time to complete ulcer healing following weekly treatment with EpiFix d-HAM and compression therapy or compression therapy with standard dressing (see Table 7). Patients treated with EpiFix had a higher probability of complete healing by 12 weeks, as adjudicated by blinded outcome assessors (hazard ratio, 2.26; 95% CI, 1.25 to 4.10; p=0.01), and improved time to complete healing, as assessed by Kaplan-Meier analysis. Healing within 12 weeks was reported for 60% of patients in the EpiFix group and 35% of patients in the control group (see Table 8). There were several limitations of this trial. Nineteen (15%) patients were excluded from the analysis, and the proportion of patients excluded differed between groups (19% from the EpiFix group vs 11% from the control group). Also, the trial did not use the ITT analysis. Had all excluded patients been considered treatment failures, the difference between groups would have been 17% (48% wound healing for EpiFix vs 31% for controls). There was also a difference between the groups in how treatment failures at eight weeks were handled. Patients in the control group who did not have a 40% decrease in wound area at eight weeks were considered study failures and treated with advanced wound therapies. Although the trialists noted that only 1 patient from this group had healed by weeks 12 and 16, reporting is unclear about how many patients from the d-HAM group would have been considered treatment failures at 8 weeks using the same cutoff.

Table 7. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serena et al (2014)</td>
<td>U.S.</td>
<td>8</td>
<td>2012-2014</td>
<td>84 patients with a full-thickness chronic VLU treated for at least 14 d</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Active</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serena et al (2014)</td>
<td>1 (n=26) or 2 (n=27) applications of EpiFix plus compression (n=53)</td>
<td>Compression therapy alone (n=31)</td>
</tr>
<tr>
<td>Bianchi et al (2017)</td>
<td>Weekly EpiFix plus moist wound therapy plus compression (n=64; 52 analyzed)</td>
<td>Moist wound therapy plus compression (n=64; 57 analyzed)</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; VLU: venous leg ulcer.

Table 8. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent With 40% Wound Closure at 4 Weeks</th>
<th>Percent with Complete Wound Closure at 4 Weeks</th>
<th>Percent with Complete Wound Closure at 12 Weeks</th>
<th>Percent with Complete Wound Closure at 16 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>EpiFix</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>32</td>
<td>12.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bianchi et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EpiFix</td>
<td>60</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>35</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>0.013</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RCT: randomized controlled trial.

**Biovance**

As described above, Smiell et al. (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about half (n=89) were venous ulcers. Of the 179 treated, 28 (16%) ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of 8 weeks and a mean of 2.4 amniotic membrane applications. However, without a control group, the percentage of wounds that would have healed with the SOC is unknown.

**Section Summary: Lower-Extremity Ulcers due to Venous Insufficiency**

The evidence on HAM for the treatment of venous leg ulcers includes two multicenter RCTs with EpiFix. One RCT reported a larger percent wound closure at four weeks, but the percentage of patients with complete wound closure at four weeks did not differ between EpiFix and the SOC. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression. Although a significant difference in complete healing was reported, data interpretation is limited by the differential loss to follow-up and exclusions between groups and the lack of ITT analysis. Corroboration with well-designed and well-conducted RCTs evaluating wound healing is needed to demonstrate efficacy. The corroborating RCTs should report ITT analysis, with analysis of all patients, including those who were off treatment or had protocol deviations and exclusions. While per protocol analysis can supplement the results, it is not sufficient to determine the effect of the treatment on health outcomes.

**Osteoarthritis**

**ReNu**

A feasibility study (n=6) of cryopreserved (c-HAM) suspension with amniotic fluid–derived cells for the treatment of knee osteoarthritis was reported in 2016. A single intra-articular injection of the suspension was used, with follow-up at 1 and 2 weeks and at 3, 6, and 12 months posttreatment. Outcomes included the Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee scale, and a numeric pain scale. Statistical analyses were not performed for this small sample. No adverse events, aside from a transient increase in pain, were noted. RCTs are in progress.

**Section Summary: Osteoarthritis**

Current evidence is insufficient to support definitive conclusions on the utility of c-HAM in the treatment of knee osteoarthritis.

**Plantar Fasciitis**

**Clinical Context and Therapy Purpose**

The purpose of micronized amniotic membrane in patients who have plantar fasciitis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does injectable amniotic membrane improve the net health outcome in patients with plantar fasciitis?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are patients with plantar fasciitis that has failed to heal with the SOC therapy.

**Interventions**

The therapy being considered is micronized amniotic membrane. It is applied in addition to the SOC.

**Comparators**

The following therapies are currently being used to make decisions about the healing of plantar fasciitis: corticosteroid injections and SOC, which involves offloading, night-splinting, stretching, and orthotics.

**Outcomes**

The primary endpoints of interest for trials of plantar fasciitis are as follows: Visual Analog Score (VAS) for pain and function measured by the Foot Functional Index.

**Timing**

Acute effects of HAM injection may be measured at two to four weeks. The durability of treatment would be assessed at 6 to 12 months.

**Setting**

The setting is outpatient care by a primary care physician or foot specialist.

**Review of Evidence**

One systematic review and two randomized pilot studies were identified on the treatment of plantar fasciitis using an injection of micronized HAM.

**Systematic Review**

A 2016 network meta-analysis of 22 RCTs (total n=1216 patients) compared injection therapies for plantar fasciitis. In addition to c-HAM and micronized d-HAM/chorionic membrane, treatments included corticosteroids, botulinum toxin type A, autologous whole blood, platelet-rich plasma, nonsteroidal anti-inflammatory drugs, dry needling, dextrose prolotherapy, and polydeoxyribonucleotide. Placebo arms included normal saline, local anesthetic, sham dry needling, and tibial nerve block. Analysis indicated d-HAM had the highest probability for improvement in pain and composite outcomes in the short-term, however, this finding was based only on a single RCT. Outcomes at two to six months (seven RCTs) favored botulinum toxin for pain and patient recovery plan for composite outcomes.

**Randomized Controlled Trials**

Zelen et al (2013) reported a preliminary study with 15 patients per group (placebo, 0.5 cc, and 1.25 cc) and 8-week follow-up. A subsequent RCT by Cazell et al (2018) enrolled 145 patients and reported 3-month follow-up (see Table 9). In the Cazell et al (2018) RCT, amniotic membrane injection led to greater improvements in the VAS for pain and the Foot Functional Index between baseline and 3 months (see Table 10) compared to controls. VAS at 3 months had decreased to 17.1 in the AmnioFix group compared to 38.8 in the placebo control group, which would be considered a clinically significant difference.

**Table 9. Summary of Key RCT Characteristics**

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Active Intervention</th>
<th>Comparator Intervention</th>
</tr>
</thead>
</table>
MP 7.01.149
Amniotic Membrane and Amniotic Fluid

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cazzell et al (2018)\textsuperscript{16}; AIPF004 (NCT02427191)</td>
<td>US</td>
<td>14</td>
<td>2015-2018</td>
<td>Adult patients with plantar fasciitis with VAS for pain &gt; 45</td>
<td>n=73; Single injection of AmnioFix 40 mg/ml</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; VAS: visual analog score.

Table 10. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in VAS-Pain Between Baseline and 3 mo (95% CI)</th>
<th>Change in FFI-R Between Baseline and 3mo (95% CI)</th>
<th>Patients with Adverse Events up to 3 mo n(%)</th>
<th>Patients with Serious Adverse Events up to 3 mo n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cazzell et al (2018)\textsuperscript{16}; AIPF004</td>
<td>54.1 (48.3 to 59.9)</td>
<td>35.7 (30.5 to 41.0)</td>
<td>30 (41.1%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>AmnioFix</td>
<td>31.9 (24.8 to 39.1)</td>
<td>22.2 (17.1 to 27.4)</td>
<td>39 (54.2%)</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>22.2 (13.1 to 31.3)</td>
<td>13.5 (6.2 to 20.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI: confidence interval; FFI-R: Foot Function Index; RCT: randomized controlled trial; VAS: visual analog score.

Gaps in relevance and design and conduct of this publication are described in Tables 11 and 12. The major limitation of the study is the short-term follow-up, which the authors note is continuing to 12 months. The extended follow-up will be reported in a separate publication.

Table 11. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cazzell et al (2018)\textsuperscript{16}; AIPF004</td>
<td>3. Placebo injections were used. A control delivered at a similar intensity as the investigational treatment would be corticosteroid injections.</td>
<td>1, 2. Follow-up to 12 months will be reported in a subsequent publication.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cazzell et al</td>
<td>1. Single blinded trial, although outcomes</td>
<td></td>
<td></td>
<td>1. Only the first 3 months of 12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section Summary: Plantar Fasciitis

The evidence on injection of amniotic membrane for the treatment of plantar fasciitis includes preliminary studies and a larger (n=145) patient-blinded comparison of micronized injectable-HAM and placebo control. Injection of micronized amniotic membrane resulted in greater improvements in VAS for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is this is an interim report of three months results. The authors note that 12-month follow-up will be reported in a subsequent publication.

HAM for ophthalmologic conditions

Sutured and self-retained HAM has been evaluated for a variety of ophthalmologic conditions. Traditionally, the amniotic membrane has been fixed onto the eye with sutures or glue or placed under a bandage contact lens for a variety of ocular surface disorders. Several devices have been reported that use a ring around a HAM allograft that allows it to be inserted under topical anesthesia similar to insertion of a contact lens. Sutured HAM transplant has been used for many years for the treatment of ophthalmic conditions. Many of these conditions are rare, leading to difficulty in conducting RCTs. Therefore, clinical input was sought to determine the most appropriate use of sutured and non-sutured HAM. The following indications apply to both sutured and self-retained HAM unless specifically noted.

Neurotrophic Keratitis with Ocular Surface Damage or Inflammation that does not Respond to Conservative Treatment

Clinical Context and Therapy Purpose

The purpose of HAM in patients who have neurotrophic keratitis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does the use of sutured or self-retained HAM improve the net health outcome in patients who have neurotrophic keratitis?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are patients who have neurotrophic keratitis with ocular surface damage or inflammation that does not respond to conservative treatment.

Interventions
The therapy being considered is sutured or non-sutured HAM.

Comparators
The following therapies are currently being used: tarsorrhaphy or bandage contact lens.

Outcomes
The general outcomes of interest are eye pain and epithelial healing.

Timing
Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at one to three months.

Setting
The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

Review of Evidence
Khokhar et al (2005) reported on an RCT of 30 patients (30 eyes) with refractory neurotrophic corneal ulcers who were randomized to HAM transplantation (n=15) or conventional treatment with tarsorrhaphy or bandage contact lens. At the 3-month follow-up, 11 (73%) of 15 patients in the HAM group showed complete epithelialization compared with 10 (67%) of 15 patients in the conventional group. This difference was not significantly significant.

Suri et al (2013) reported on 11 eyes of 11 patients with neurotrophic keratopathy that had not responded to conventional treatment. The mean duration of treatment prior to Prokera insertion was 51 days. Five of the 11 patients (45.5%) were considered to have had a successful outcome.

Clinical input recommended HAM for neurotrophic keratitis that did not respond to conservative therapy. Input recommended non-sutured HAM as the preferred initial treatment "because it can be performed rapidly in an office setting, avoiding the delay associated with scheduling a procedure in an outpatient surgical facility."

Section Summary: Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy
An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.

Corneal Perforation When There is Active Inflammation After Corneal Transplant Requiring Adjunctive Treatment
Clinical Context and Therapy Purpose
The purpose of HAM in patients who have active inflammation after a corneal transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The question addressed in this evidence review is: does the use of sutured or self-retained HAM improve the net health outcome in patients who have corneal perforation when there is active inflammation after corneal transplant?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest are patients who have corneal perforation when there is active inflammation after a corneal transplant.

**Interventions**

The therapy being considered is sutured or non-sutured HAM.

**Comparators**

The following therapies are currently being used: medical therapy.

**Outcomes**

The general outcomes of interest are eye discomfort and reduction in inflammation.

**Timing**

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at one to three months.

**Setting**

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

**Review of Evidence**

No evidence was identified for this indication.

Clinical input indicated that "both sutured and non-sutured HAM reduces inflammation and promotes epithelial healing. It is, therefore, a useful adjunct in addition to corneal transplantation in those patients with active inflammation and perforation."

**Section Summary: Corneal Perforation When There is Active Inflammation After Corneal Transplant Requiring Adjunctive Treatment**

No evidence was identified for this indication. Clinical input supported the use of HAM to reduce inflammation and promote epithelial healing with active inflammation following corneal transplant.

**Bullous Keratopathy in Patients Who are not Candidates for a Curative Treatment (eg, endothelial or penetrating keratoplasty)**

**Clinical Context and Therapy Purpose**

The purpose of HAM in patients who have bullous keratopathy is to provide a treatment option that is an alternative to or an improvement on existing therapies. Bullous keratopathy is characterized by stromal edema and epithelial and subepithelial bulla formation.

The question addressed in this evidence review is: does the use of sutured or self-retained HAM improve the net health outcome in patients who have bullous keratopathy and are not candidates for a curative treatment?
The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are patients who have bullous keratopathy who are not candidates for curative treatment.

**Interventions**
The therapy being considered is sutured or non-sutured HAM.

**Comparators**
The following therapies are currently being used: stromal puncture.

**Outcomes**
The general outcomes of interest are eye discomfort and epithelial healing

**Timing**
Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at one to three months.

**Setting**
The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

**Review of Evidence**
Dos Santos Paris et al (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy. Forty patients with pain from bullous keratopathy who were either waiting for a corneal transplant or had no potential for sight in the affected eye were randomized to the two treatments. Symptoms had been present for approximately two years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with the use of HAM only if the pain did not resolve.

Clinical input recommended HAM as a palliative measure in patients who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) Input recommended HAM as a reasonable alternative to stromal puncture.

**Section Summary: Bullous Keratopathy in Patients Who are not Candidates for a Curative Treatment and Who are Unable to Remain Still for Stromal Puncture**
An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. Based on clinical input, non-sutured HAM could be used as an alternative to stromal puncture.

**Partial Limbal Stem Cell Deficiency with Extensive Diseased Tissue Where Selective Removal Alone is not Sufficient**

**Clinical Context and Therapy Purpose**
The purpose of HAM in patients who have LSCD is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The question addressed in this evidence review is: does the use of sutured or self-retained HAM improve the net health outcome in patients who have partial LSCD?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest are patients who have LSCD with extensive diseased tissue where selective removal alone is not sufficient.

**Interventions**

The therapy being considered is sutured or non-sutured HAM.

**Comparators**

The following therapies are currently being used: limbal stem cell transplants.

**Outcomes**

The general outcomes of interest are visual acuity and corneal epithelial healing.

**Timing**

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at one to three months.

**Setting**

**Review of Evidence**

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

No RCTs were identified on HAM for LSCD. Keirkhah et al (2008) reported on the use of HAM in 11 eyes of 9 patients who had LSCD. Patients underwent superficial keratectomy to remove the conjunctivalized pannus followed by HAM transplantation using fibrin glue. An additional Prokera patch was used in seven patients. An improvement in visual acuity was observed in all but two patients. Pachigolla et al (2009) reported a series of 20 patients who received a Prokera implant for ocular surface disorders; 6 of the patients had limbal stem cell deficiency with a history of chemical burn. Following treatment with Prokera, 3 of the 6 patients had a smooth corneal surface and improved vision to 20/40. The other 3 patients had final visual acuity of 20/400, counting fingers, or light perception.

Clinical input recommended HAM for patients with LSCD in conjunction with superficial keratectomy, noting that due to the rarity of this disease, it is unlikely that RCTs will ever be performed. Input also noted that “comparisons to limbal stem cell transplants are unlikely to be performed because of the risks of systemic immune suppression.”

**Section Summary: Partial LSCD with Extensive Diseased Tissue Where Selective Removal Alone is not Sufficient**

No RCTs were identified on HAM for LSCD. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. Clinical input noted the limitations of performing an RCT and supported the use of HAM for this indication.

**Moderate or Severe Stevens-Johnson Syndrome**
Clinical Context and Therapy Purpose

The purpose of HAM in patients who have Stevens-Johnson syndrome is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does the use of sutured or self-retained HAM improve the net health outcome in patients who have moderate or severe Stevens-Johnson syndrome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are patients who have moderate or severe Stevens-Johnson syndrome.

Interventions

The therapy being considered is sutured or non-sutured HAM.

Comparators

The following therapies are currently being used: medical therapy alone (antibiotics, steroids, or lubricants).

Outcomes

The general outcomes of interest are visual acuity, tear function, and corneal clarity.

Timing

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at one to three months.

Setting

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

Review of Evidence

One RCT from India by Sharma et al (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or medical therapy alone. The c-HAM was prepared locally and applied with fibrin glue rather than sutures. Application of c-HAM in the early stages of Stevens-Johnson syndrome resulted in improved visual acuity (p=0.042), better tear breakup time (p=0.015), improved Schirmer test results (p<0.001), and less conjunctival congestion (p=0.03). In the c-HAM group at 180 days, there were no cases of corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. These outcomes are dramatically better than those in the medical therapy alone group, which had 11 (44%) cases with corneal haze (p=0.001), 6 (24%) cases of corneal vascularization and conjunctivalization (p=0.03), and 6 (24%) cases of trichiasis and metaplastic lashes. Clinical input recommended HAM for moderate-to-severe Stevens-Johnson noting that “the severity of the disease and its infrequency makes it unlikely that a large RCT will be performed.” Sutured HAM would be preferred to prevent lid-related complications, but non-sutured HAM “is still helpful in emergency settings when the patient condition does not allow for surgical intervention.”

Section Summary: Moderate or Severe Stevens-Johnson Syndrome
The evidence on HAM for the treatment of Stevens-Johnson syndrome includes 1 RCT with 25 patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone. Clinical input indicated that large RCTs are unlikely due to the severity and rarity of the disease, supported the use of HAM for moderate or severe Stevens-Johnson.

**Persistent Epithelial Defects and Ulcerations That does not Respond to Conservative Therapy**

**Clinical Context and Therapy Purpose**

The purpose of HAM in patients who have persistent epithelial defects and ulcerations is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does the use of sutured or self-retained HAM improve the net health outcome in patients who have persistent epithelial defects and ulcerations that do not respond to conservative therapy?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest are patients who have persistent epithelial defects that do not respond to conservative therapy.

**Interventions**

The therapy being considered is sutured or non-sutured HAM.

**Comparators**

The following therapies are currently being used for persistent epithelial defects and ulceration: medical therapy alone (eg topical lubricants, topical antibiotics, therapeutic contact lens, or patching).

**Outcomes**

The general outcomes of interest are epithelial closure

**Timing**

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at one to three months.

**Setting**

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

**Review of Evidence**

Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease. They noted that c-HAM has been available since 1995, and has become an established treatment for persistent epithelial defects and ulceration refractory to conventional therapy. However, there was a lack of controlled studies due to the rarity of the diseases and the absence of standard therapy. They identified 661 reported cases in the peer-reviewed literature. Most cases reported assessed the conjunctival indications of pterygium, scars and symblepharon, and corneal indications of acute chemical injury and postinfectious keratitis. Clinical input recommended HAM for persistent epithelial defects that do not respond to conservative therapy (eg, topical lubricants and/or antibiotics, therapeutic contact lens, or patching), noting that “the
uncommon nature of the diseases associated with persistent epithelial defects and the lack of a standard therapeutic regimen account for the lack of RCTs.”

**Section Summary: Persistent Epithelial Defects and Ulceration That does not Respond to Conservative Therapy**

No RCTs were identified on persistent epithelial defects and ulceration. Clinical input noted the difficulty in conducting RCTs for this indication and supported the use of amniotic membrane for persistent epithelial defects and ulceration that does not respond to conservative therapy.

**Severe Dry Eye Disease with Ocular Surface Damage and Inflammation that does not Respond to Conservative Therapy**

**Clinical Context and Therapy Purpose**

The purpose of HAM in patients who have severe dry eye is to provide a treatment option that is an alternative to or an improvement on existing therapies. Dry eye disease involves tear film insufficiency with the involvement of the corneal epithelium. Inflammation is common in dry eye disease, which causes additional damage to the corneal epithelium.

The question addressed in this evidence review is: does the use of sutured or self-retained HAM improve the net health outcome in patients who have severe dry eye with ocular surface damage and inflammation?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest are patients who have severe dry eye with ocular surface damage and inflammation.

**Interventions**

The therapy being considered is sutured or non-sutured HAM.

**Comparators**

The following therapies are currently being used: medical management consisting of artificial tears, cyclosporine A, serum tears, antibiotics, steroids, and nonsteroidal anti-inflammatory medications.

**Outcomes**

The general outcomes of interest are the pain, corneal surface regularity, and vision, which may be measured by the Report of the International Dry Eye WorkShop score (DEWS). The DEWS assess nine domains with a score of one to four including discomfort, visual symptoms, tear breakup time, corneal signs and corneal staining. Corneal staining with fluorescein or Rose Bengal indicates damaged cell membranes or gaps in the epithelial cell surface. A DEWS of two to four indicates moderate-to-severe dry eye disease.

**Timing**

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at one to three months.

**Setting**

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.
Review of Evidence

John et al (2017) reported on an RCT with 20 patients with moderate-to-severe dry eye disease who were treated with Prokera c-HAM or maximal conventional treatment. The c-HAM was applied for an average of 3.4 days (range, 3-5 days), while the control group continued treatment with artificial tears, cyclosporine A, serum tears, antibiotics, steroids, and nonsteroidal anti-inflammatory medications. The primary outcome was an increase in corneal nerve density. Signs and symptoms of dry eye disease improved at both one-month and three-month follow-ups in the c-HAM group but not in the conventional treatment group. For example, pain scores decreased from 7.1 at baseline to 2.2 at 1 month and 1.0 at 3 months in the c-HAM group. In vivo confocal microscopy, reviewed by masked readers, showed a significant increase in corneal nerve density in the study group at three months, with no change in nerve density in the controls. Corneal sensitivity was similarly increased in the c-HAM group but not in controls.

The treatment outcomes in the DRY Eye Amniotic Membrane study (McDonald et al [2018]) was a retrospective series of 84 patients (97 eyes) with severe dry eye despite maximal medical therapy who were treated with Prokera self-retained c-HAM. A majority of patients (86%) had superficial punctate keratitis. Other patients had filamentary keratitis (13%), exposure keratitis (19%), neurotrophic keratitis (2%), and corneal epithelial defect (7%). Treatment with Prokera for a mean of 5.4 days (range, 2 to 11) resulted in an improved ocular surface and reduction in the DEWS score from 3.25 at baseline to 1.44 at 1 week, 1.45 at 1 month and 1.47 at 3 months (p=0.001). Ten percent of eyes required repeated treatment. There was no significant difference in the number of topical medications following c-HAM treatment.

Clinical input recommended HAM in cases of severe dry eye with ocular surface damage and inflammation.

Section Summary: Severe Dry Eye with Ocular Surface Damage and Inflammation that does not Respond to Conservative Therapy

The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. Clinical input supported the use of HAM in cases of severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy.

Moderate or Severe Acute Ocular Chemical Burns

Clinical Context and Therapy Purpose

The purpose of HAM in patients who have acute ocular burns is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does the use of sutured or self-retained HAM improve the net health outcome in patients who have moderate or severe acute ocular chemical burns? The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are patients who have moderate or severe acute ocular chemical burn.

Interventions
The therapy being considered is sutured or non-sutured HAM.

Comparators
The following therapies are currently being used: medical therapy (eg topical antibiotics, lubricants, steroids and cycloplegics, oral vitamin C, doxycycline)

Outcomes
The general outcomes of interest are visual acuity, corneal epithelialization, corneal clarity, and corneal vascularization.

Timing
Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at one to three months.

Setting
The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

Review of Evidence
An RCT of 100 patients with chemical or thermal ocular burns was published by Tandon et al (2011).28 Half of the patients (n=50) had moderate ocular burns and the remainder (n=50) had severe ocular burns. All but eight of the patients had alkali or acid burns. Patients were randomized to HAM transplantation plus medical therapy or medical therapy alone. Epithelial healing, which was the primary outcome, was improved in the group treated with HAM, but there was no significant difference between the two groups for the final visual outcome, symblepharon formation, corneal clarity or vascularization.

Use of the Prokera self-retained implant was reported by Kheirkhah et al (2008) in a series of 5 patients with acute alkaline burns.29 Clinical input recommended HAM for acute ocular chemical burn, noting that “ocular chemical burns represent a diverse array of clinical conditions and severity, making high-quality RCTs difficult or impossible to perform.”

Section Summary: Moderate or Severe Acute Ocular Chemical Burns
Evidence includes an RCT of 100 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Patients in the HAM group had a faster rate of epithelial healing, without a significant benefit for other outcomes. Clinical input was in support of HAM for acute ocular chemical burn.

Corneal Perforation When Corneal Tissue is not Immediately Available
Clinical Context and Therapy Purpose
The purpose of HAM in patients who have corneal perforation when corneal tissue is not immediately available is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does the use of sutured HAM improve the net health outcome in patients who have corneal perforation?

The following PICOTS were used to select literature to inform this review.
Patients
The relevant population of interest are patients who have corneal perforation when corneal tissue is not immediately available.

Interventions
The therapy being considered is sutured HAM.

Comparators
The following therapies are currently being used: conservative management.

Outcomes
The general outcomes of interest are eye pain.

Timing
Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at one to three months.

Setting
The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

Review of Evidence
No RCTs were identified on corneal perforation.

Clinical input noted that multiple layers of HAM have been shown to promote healing of corneal perforation and recommended sutured HAM for tectonic support when corneal tissue is not immediately available.

Section Summary: Corneal Perforation When Corneal Tissue is not Immediately Available
The standard treatment for corneal perforation is corneal transplantation. Based on clinical input, sutured HAM may be used as a temporary measure when corneal tissue is not immediately available.

Following Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft

Clinical Context and Therapy Purpose
The purpose of HAM in patients who have pterygium repair is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: does the use of sutured or glued HAM improve the net health outcome in patients who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft (eg, extensive, double, or recurrent pterygium)?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are patients who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

Interventions
The therapy being considered is sutured or glued HAM.

**Comparators**

The following therapies are currently being used: conjunctival autograft.

**Outcomes**

The general outcomes of interest are a recurrence of pterygium.

**Timing**

Pterygium recurrence would be measured at one to three months.

**Setting**

The setting is in a surgical suite for pterygium repair.

**Review of Evidence**

RCTs have been reported on the use of amniotic membrane following pterygium repair. The American Academy of Ophthalmology (2013) published a technology assessment on options and adjuvants for pterygium surgery. Reviewers identified four RCTs comparing conjunctival or limbal autograft procedure with amniotic membrane graft, finding that conjunctival or limbal autograft was more effective than HAM graft in reducing the rate of pterygium recurrence. A 2016 Cochrane review of 20 RCTs (total n=1866 patients) arrived at the same conclusion. Clinical input recommended sutured or glued HAM for pterygium repair when there was insufficient healthy tissue to create a conjunctival autograft (eg, extensive, double, or recurrent pterygium).

**Section Summary: Following Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft**

Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence. Based on clinical input, sutured or glued HAM may be considered when there is insufficient healthy tissue to create a conjunctival autograft (eg, extensive, double, or recurrent pterygium).

**Summary of Evidence**

**Diabetic Lower-Extremity Ulcers**

For individuals who have non-healing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM (ie, AmnioBand Membrane, Biovance, EpiFix, Grafix), the evidence includes RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing (<20% healing with ≥2 weeks of standard care) diabetic lower-extremity ulcers have compared HAM with standard care or with an established advanced wound care product. These trials used wound closure as the primary outcome measure, and some used power analysis, blinded assessment of wound healing, and ITT analysis. For the HAM products that have been sufficiently evaluated (ie, AmnioBand Membrane, Biovance, Epicord, EpiFix, Grafix), results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Lower-Extremity Ulcers due to Venous Insufficiency**
For individuals who have lower-extremity ulcers due to venous insufficiency who receive a patch or flowable formulation of HAM, the evidence includes two RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for the treatment of lower-extremity venous ulcers includes two multicenter RCTs with EpiFix. One RCT reported larger percent wound closure at four weeks but the percentage of patients with complete wound closure did not differ between EpiFix and the SOC. A second multicenter RCT reported a significant difference in complete healing at 12 weeks, but the interpretation is limited by methodologic concerns. Well-designed and well-conducted RCTs that compare HAM with the SOC for venous insufficiency ulcers are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Osteoarthritis

For individuals who have knee osteoarthritis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes a feasibility study. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. The pilot study assessed the feasibility of a larger RCT evaluating HAM injection. Additional trials, which will have a larger sample size and longer follow-up, are needed to permit conclusions on the effect of this treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

Plantar Fasciitis

For individuals who have plantar fasciitis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes two small RCTs. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. Research on HAM injections for plantar fasciitis is at an early stage. The evidence includes a small (n=23) double-blind comparison with corticosteroid and a patient-blinded (n=45) comparison of 2 different doses of dehydrated HAM with saline. Additional controlled trials with larger sample sizes and longer follow-up are needed to permit conclusions on the effect of HAM and amniotic fluid injections on plantar fasciitis pain. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ophthalmic Conditions

Neurotrophic Keratitis with Ocular Surface Damage and Inflammation That does not Respond to Conservative Therapy

For individuals who have neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Corneal Ulcers and Melts That does not Respond to Initial Medical Therapy

For individuals who have corneal ulcers and melts, that does not respond to initial medical therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a
delay in treatment associated with scheduling a surgical treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Corneal Perforation When There is Active Inflammation After Corneal Transplant Requiring Adjunctive Treatment**

For individuals who have corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No comparative evidence was identified for this indication. Clinical input supported the use of HAM to reduce inflammation and promote epithelial healing with active inflammation following corneal transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Bullous Keratopathy as a Palliative Measure in Patients Who are not Candidates for a Curative Treatment (eg, endothelial or penetrating keratoplasty)**

For individuals who have bullous keratopathy and who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. Based on clinical input, non-sutured HAM could be used as an alternative to stromal puncture. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Partial LSCD with Extensive Diseased Tissue Where Selective Removal Alone is not Sufficient**

For individuals who have partial LSCD with extensive diseased tissue where selective removal alone is not sufficient who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No RCTs were identified on HAM for LSCD. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. Clinical input noted the limitations of performing an RCT and supported the use of HAM for this indication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Moderate or Severe Stevens-Johnson Syndrome**

For individuals who have moderate or severe Stevens-Johnson syndrome who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for the treatment of Stevens-Johnson includes one RCT with 25 patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone. Clinical input indicated that large RCTs are unlikely due to the severity and rarity of the disease, supported the use of HAM for moderate or severe Stevens-Johnson. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Persistent Epithelial Defects and Ulceration That does not Respond to Conservative Therapy**

For individuals who have persistent epithelial defects that does not respond to conservative therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No RCTs were identified on persistent epithelial defects and ulceration. Clinical input noted the difficulty in conducting RCTs for this indication and supported the use of amniotic membrane for persistent epithelial defects and ulcerations that does not respond to conservative therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Severe Dry Eye with Ocular Surface Damage and Inflammation That does not Respond to Conservative Therapy

For individuals who have severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy, who receive HAM, the evidence includes an RCT and a large case series. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. Clinical input supported HAM in cases of severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Moderate or Severe Acute Ocular Chemical Burns

For individuals who have moderate or severe acute ocular chemical burn who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Evidence includes an RCT of 100 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Patients in the HAM group had a faster rate of epithelial healing, without a significant benefit for other outcomes. Clinical input was in support of HAM for acute ocular chemical burn. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Corneal Perforation When Corneal Tissue is not Immediately Available

For individuals who have corneal perforation when corneal tissue is not immediately available who receive sutured HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The standard treatment for corneal perforation is corneal transplantation. Based on clinical input, sutured HAM may be used as a temporary measure when corneal tissue is not immediately available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft

For individuals who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft who receive HAM, the evidence includes RCTs and systematic reviews of RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence. Based on clinical input, sutured or glued HAM may be considered when there is insufficient healthy tissue to create a conjunctival autograft (eg, extensive, double, or recurrent pterygium). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

CLINICAL INPUT

Objective

In 2019, clinical input was sought to help determine whether the use of human amniotic membrane graft either without or with suture fixation for several ophthalmic conditions would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

Respondents
Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Academy of Ophthalmology (AAO)
- Mark Latina, MD, Ophthalmology, Tufts University School of Medicine, identified by Massachusetts Society of Eye Physicians and Surgeons

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide a review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.
### Clinical Input Responses

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<td>Corneal ulcers and melts</td>
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<td>Acute ocular chemical burn</td>
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**Additional Comments**

**Neuropathic keratitis**

- “Sutured and non-sutured human amniotic membrane HAM are both accepted and effective treatments for neurotrophic keratopathy that does not respond to conservative therapy in patients with corneal staining or an epithelial defect that (1) has failed to completely close after
5 days of conservative treatment, or (2) has failed to demonstrate a decrease in size after 2 days of conservative treatment. Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. Failure of multiple modalities should not be required prior to moving to HAM. HAM requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in that regard over treatments that require multiple drops per day. Non-sutured HAM is the preferred initial treatment because it can be performed rapidly in an office setting, bypassing the delay associated with scheduling a procedure in an outpatient facility. It also avoids the facility fees associated with the sutured HAM procedure. Patients that are responding to non-sutured HAM may need a second or third application if healing is not yet complete. Those who show a poor response or poorly tolerate a non-sutured HAM device are candidates for sutured HAM.” (AAO)

- “In my opinion and based on the literature, the use of AM (with or without sutures) for treating neurotrophic keratoconjunctivitis is medically necessary when the standard therapy fails. It interrupts the disease process by controlling inflammation, preventing further damage and restoring ocular surface integrity. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

Corneal ulcers and melts

- “Corneal ulcers and melts comprise a wide range of disorders with varying etiologies. Common to many of these are an underlying inflammatory component. HAM has been shown to reduce inflammation and promote epithelial healing. These properties make HAM an effective adjunct in treating these conditions while the primary etiology is addressed with targeted therapy (e.g. corticosteroids, antibiotics, biologic immunomodulators). HAM is typically employed when there is a lack of response to initial medical treatment or where HAM can offer some degree of tectonic support in cases where there is significant stromal tissue loss. The varied and uncommon nature of the etiology of ulcers and melts makes it unlikely that there will ever be significantly-sized RCTs comparing HAM to conventional therapy or sutured vs. non-sutured HAM. There are numerous small series and case reports without controls showing improvement after HAM placement in cases that were not responding to conventional therapy.” (AAO)

- “Based on my experience, the use of AM at an early stage of the disease would prevent any unexpected complications such as infection, scarring, melt and perforation. Particularly, using AM without suture for this indication provides the advantage of in-office treatment without any delay. Furthermore, it avoids potential sight-threatening complications and achieves a clinically meaningful improvement in net visual outcome.” (Dr. Latina)

Corneal perforation

- “Multilayered sutured HAM has been performed in some cases of corneal perforation. While it offers some tectonic support, corneal tissue is the preferred graft material in these cases. HAM alone may be a reasonable temporizing alternative when corneal tissue is not immediately available. Non-sutured HAM would not offer significant tectonic support in these cases. Both sutured and non-sutured HAM reduces inflammation and promotes epithelial healing. It is therefore a useful adjunct in addition to corneal transplantation in those patients with active inflammation and perforation.” (AAO)

- “Depending on the size and location of the corneal perforation, treatment options include gluing, amniotic membrane transplantation, and corneal transplantation. The success rate of using AM to repair corneal perforation is reported to be as high as 93%. [1-7] Kim et al [11] used multiple layers of AM with tissue glue in 10 patients with large corneal perforations up to 5 mm
and noted 90% success in complete closure of perforation. AM offers the advantage of avoiding potential corneal graft rejection and postoperative astigmatism of tectonic corneal grafts.” (Dr. Latina)

Bullous Keratopathy

- “HAM is one of several modalities for treatment of bullous keratopathy due to corneal endothelial dysfunction. HAM does not address the underlying endothelial disease, so it is considered palliative rather than curative therapy. It is a reasonable alternative for patients who are not candidates for curative endothelial or penetrating keratoplasty. Sutured HAM has been shown to be as effective for bullous keratopathy as anterior stromal puncture (Paris F. Br J Ophthalmol 2013;97:980. PMID 23723410) and phototherapeutic keratectomy (Chawla B. Cornea 2010;29:976. PMID 20517149). Non-sutured HAM is a reasonable alternative to anterior stromal puncture as it is faster and simpler to perform. Sutured HAM in an operating room setting and non-sutured HAM in the office are of particular value in patients who have difficulty holding still for office procedures such as anterior stromal puncture in which there is a risk of increased corneal scarring or globe perforation with patient movement. HAM typically offers long-lasting pain relief in these cases, obviating the need for corneal transplantation with its associated increased risks (rejection, infection) and costs.” (AAO)
- “Based on the literature, AM is considered as a longer-term treatment for bullous keratopathy patients with poorer visual prognosis. AM without sutures may also be used as an interim measure for patients awaiting corneal transplant. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

Pterygium repair

- “While HAM is more effective at preventing recurrences than bare sclera technique, and subject to fewer serious complications than mitomycin C, conjunctival autograft has been shown to be more effective than HAM in terms of reducing recurrences. However, there are patients with extensive, double, or recurrent pterygia in which there is insufficient healthy tissue to create a conjunctival autograft. In these patients, sutured or non-sutured (glued) HAM is the material of choice for covering the conjunctival defect left after removal of the pterygium as the recurrence rate is lower than if the sclera is left bare. Sutured and glued HAM should be covered for these cases” (AAO)
- “The most daunting challenge of pterygium surgery is the high rate of recurrence, as high as 88%. Surgical techniques in more recent years, in which scleral defects are covered with conjunctival autograft or cryopreserved amniotic membrane (AM) with or without mitomycin C (MMC), have resulted in much better outcomes, with less recurrence rates and minimal complications....In my opinion, AM is as effective as conjunctival autograft in preventing pterygium recurrence, and can be considered as a preferred grafting procedure for pterygium repair. The use of AM provide the following benefits: save donor conjunctiva, minimize surgical trauma, reduce surgery time, reduce postoperative pain, reduce inflammation, facilitate faster recovery and healing. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

Limbal stem cell deficiency

- “Limbal stem cell deficiency is an uncommon, serious disorder leading to conjunctivalization, irregularity, and opacity of the corneal surface. Total limbal stem cell deficiency typically requires a limbal stem cell transplant to restore the ocular surface. These vascularized
transplants require prolonged systemic immunosuppression and the attendant risks to support graft survival and prevent recurrence of the disease. Partial limbal stem cell deficiency may respond to selective removal of the diseased tissue without a transplant when a limited portion of the ocular surface is involved. In more extensive cases where selective removal alone is not sufficient, HAM in conjunction with superficial keratectomy to remove the diseased tissue can provide long-term restoration of a smooth and transparent ocular surface and improved visual acuity without having to resort to a transplant (Kheirkhah AV. Am J Ophthalmol 2008;145:787. PMID 18329626). Due to the rarity of this disease, it is unlikely that RCTs will ever be performed. Comparisons to limbal stem cell transplants are unlikely to be performed because of the risks of systemic immune suppression. HAM should be covered in conjunction with superficial keratectomy for cases of limbal stem cell deficiency.” (AAO)

• “Patients with Limbal stem cell deficiency (LSCD) suffer from severe loss of vision due to vascularized cornea scarring and non-healing epithelial defect. Their vision cannot be corrected by conventional penetrating keratoplasty. Previous studies have shown that in eyes with partial LSCD, AM promotes expansion of remaining limbal epithelial stem cells.” (Dr. Latina)

Stevens-Johnson

• “Sutureless or sutured HAM, depending on the severity of the disease, in conjunction with medical therapy has become the accepted management technique for the treatment of moderate or severe Stevens-Johnson. Both should be covered for this indication. The severity of the disease and its infrequency makes it unlikely that a large RCT will be performed.” (AAO)

• “In my opinion, and based on the literature, the use of AM with sutures is preferred to prevent long term lid related complications. The use of AM without suture is still helpful in emergency settings when the patient condition does not allow for surgical intervention. Collectively, the use of AM for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

Persistent epithelial defects

• “HAM is an effective treatment for persistent epithelial defects due to a number of underlying causes. While not a first-line treatment, both sutured and non-sutured HAM are appropriate in patients with epithelial defects that fail to show a response within 2 days of initiation of conservative therapy. Conservative therapy is considered to be any one or more of the following: topical lubricants and/or antibiotics, therapeutic contact lens, or patching. If there is a failure to respond to any one of these modalities, HAM is an appropriate second step...The uncommon nature of the diseases associated with persistent epithelial defects and the lack of a standard therapeutic regimen account for the lack of RCTs.” (AAO)

• “Persistent epithelial defect (PED) is often caused by microtrauma, neurotrophic keratopathy and exposure. Conventional treatment includes correcting the underlying condition, suppressing the inflammation, and promoting the healing process using tears. If conventional treatment fails after 2 weeks, these patients are prone to further complications and corneal scarring and haze. Because PED also be ‘neurotrophic’, please refer to Neurotrophic keratitis indication. As stated above, conventional treatments usually fail to promote prompt healing in these conditions and the eyes are prone to delayed healing, corneal ulceration, scarring, and infection. These complications in turn result in poor patient outcomes, visual detriment, and a greater frequency of office visits and associated costs...Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)
Severe dry eye

- “Traditional dry eye therapy typically consists of frequent application of lubricants, hot compresses, and environmental controls to increase humidity. Patients may not respond to traditional dry eye therapy due to the severity of the disease or due to inability to control the environment or administer drops frequently. Topical drugs such as cyclosporine and lifitegrast may be helpful in these cases but they may take months to take effect. If the patient’s daily activities are significantly affected by dry eye signs and symptoms, HAM may provide rapid relief while waiting for long-term medications to take effect. HAM is unlikely to be of benefit for mild dry eye disease or disease that responds to conservative therapy. Because HAM limits acuity it is only viable as a short-term therapy. Sutured HAM is not typically used for severe dry eye alone but may be necessary in the face of one or more concomitant diseases discussed in the other sections. Our recommendation is that non-sutured HAM be covered in patients with persistent symptoms or persistent corneal staining that does not respond to traditional dry eye therapy.” (AAO)

- “Dry eye disease (DED) is a multifactorial disease comprised of tear film insufficiency and associated ocular surface disorder such as superficial epithelial defect. Treatment of DED depends on the etiology and the level of severity. Although artificial tears, immunosuppressants and punctalocclusion are commonly used for tear film insufficiency, ocular surface involvement with a defect are usually refractory and may require eye protection devices and/ or surgical intervention... In my practice, a single placement of Amniotic Membrane (non-sutured) was also effective in reducing signs and symptoms of DED for a period lasting more than three months. Therefore, amniotic membrane without sutures should be considered for severe dry eye with ocular surface damage and inflammation.” (Dr. Latina)

Acute ocular chemical burn

- “Ocular chemical burns represent a diverse array of clinical conditions and severity, making high quality RCTs difficult or impossible to perform. The Cochrane review cited in the BCBS review (Clare G. Cochrane Database Syst Rev 2012;9:CD009379. PMID 22972141) reflects this difficulty. However, it is clear that there are subsets of patients that respond to either sutured or non-sutured HAM based in its ability to reduce inflammation and promote epithelial healing. Particularly in moderate and severe burns where the prognosis with traditional therapy is poor, sutured and non-sutured HAM are important alternatives that should be covered. There are multiple reports of good outcomes in these cases.” (AAO)

- “In my opinion, and based on the literature, the use of AM without sutures is preferred to prevent surgical trauma and suture related complications in such compromised eyes. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

SUPPLEMENTAL INFORMATION

2019

In response to requests while this policy was under review in 2018-2019, clinical input on the use of human amniotic membrane graft either without or with suture fixation for several ophthalmic conditions was received from 2 respondents, including 1 specialty society-level response and 1 physician-level response identified through specialty societies including physicians with academic medical center affiliations.
Evidence from clinical input is integrated within the Rationale section summaries and the Summary of Evidence.

Practice Guidelines and Position Statements

Tear Film and Ocular Surface Society

The Tear Film and Ocular Surface Society (2017) published the DEWS [Dry Eye Workshop] II management and therapy report. The report evaluated the evidence on treatments for dry eye and provided the following treatment algorithm for dry eye disease management:

Step 1:
- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if meibomian gland dysfunction is present, then consider lipid containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:
If above options are inadequate consider:
- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands
- In-office intense pulsed light therapy for meibomian gland dysfunction
- Prescription drugs to manage dry eye disease
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited-duration)
- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3:
If above options are inadequate consider:
- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
- Soft bandage lenses
- Rigid scleral lenses
Step 4:
If above options are inadequate consider:

- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (eg tarsorrhaphy, salivary gland transplantation)

**Society for Vascular Surgery et al**

The Society for Vascular Surgery (2016) in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine made the following recommendation: "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amniotic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 4.

**Table 13. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03441607a</td>
<td>Safety &amp; Efficacy of Micronized Human Amnion Chorion Membrane Biologic (mHACMb) FloGraft (Micronized Human Amnion Chorion Membrane)® in Adults With Pain Due to Osteoarthritis of the Knee</td>
<td>320</td>
<td>Mar 2019</td>
</tr>
<tr>
<td>NCT02318511a</td>
<td>An Investigation of ReNu™ Knee Injection: Monitoring the Response of Knee Function and Pain in Patients With Osteoarthritis</td>
<td>200</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT03414255a</td>
<td>A Phase 3, Prospective, Double-Blinded, Randomized Controlled Trial Of The Micronized dHACM Injection As Compared To Saline Placebo Injection In The Treatment Of Achilles Tendonitis</td>
<td>158</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT03414268a</td>
<td>A Phase 3, Prospective, Double-Blinded, Randomized Controlled Trial of the Micronized dHACM Injection As Compared To Saline Placebo Injection In The Treatment Of Plantar Fasciitis</td>
<td>164</td>
<td>Oct 2019</td>
</tr>
</tbody>
</table>
Amniotic Membrane and Amniotic Fluid

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03379324a</td>
<td>A Prospective, Randomized Study Comparing Outcomes Following Arthroscopic Double-row Rotator Cuff Repair With and Without the Addition of a Cryopreserved, Liquid, Injectable Amnion Allograft</td>
<td>260</td>
<td>Sep 2019</td>
</tr>
<tr>
<td>NCT02322554</td>
<td>The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers</td>
<td>50,000</td>
<td>Jan 2020</td>
</tr>
<tr>
<td>NCT03390920</td>
<td>Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions</td>
<td>200</td>
<td>Jun 2022</td>
</tr>
<tr>
<td>NCT02609594a</td>
<td>A Multi-center Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Amnioband Dehydrated Human Amniotic Membrane and Standard of Care vs. Standard of Care Alone in the Treatment of Venous Leg Ulcers</td>
<td>240</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02838784a</td>
<td>The Efficacy and Safety of Artacent™ for Treatment Resistant Lower Extremity Venous and Diabetic Ulcers: A Prospective Randomized Study</td>
<td>134</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02880592a</td>
<td>A Multi-center, Randomized Controlled Clinical Trial Evaluating the Effect of Fresh Amniotic Membrane in the Treatment of Diabetic Foot Ulcers</td>
<td>100</td>
<td>Jan 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial.

ESSENTIAL HEALTH BENEFITS

The Affordable Care Act (ACA) requires fully insured non-grandfathered individual and small group benefit plans to provide coverage for ten categories of Essential Health Benefits (“EHBs”), whether the benefit plans are offered through an Exchange or not. States can define EHBs for their respective state.

States vary on how they define the term small group. In Idaho, a small group employer is defined as an employer with at least two but no more than fifty eligible employees on the first day of the plan or contract year, the majority of whom are employed in Idaho. Large group employers, whether they are self-funded or fully insured, are not required to offer EHBs, but may voluntary offer them.

The Affordable Care Act requires any benefit plan offering EHBs to remove all dollar limits for EHBs.

REFERENCES


32. Cazzell, SS, Stewart, JJ, Agnew, PP, Senatore, JJ, Walters, JJ, Murdoch, DD, Reyzelman, AA, Miller, SS. Randomized Controlled Trial of Micronized Dehydrated Human Amnion/Chorion Membrane (dHACM) Injection Compared to Placebo for the Treatment of Plantar Fasciitis. NA. PMID 30058377.

**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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</thead>
<tbody>
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<td>CPT</td>
<td>No specific code</td>
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</tr>
<tr>
<td>HCPCS</td>
<td>Q4132</td>
<td>Grafix core, per square centimeter</td>
</tr>
<tr>
<td>Q4133</td>
<td>Grafix prime, per square centimeter</td>
<td></td>
</tr>
<tr>
<td>Q4137</td>
<td>Amnioexcel or BioDExCel, per square centimeter</td>
<td></td>
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<tr>
<td>Q4138</td>
<td>Biodfence Dryflex, per square centimeter</td>
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</tr>
<tr>
<td>Q4139</td>
<td>AmnioMatrix or BioDMatrix, injectable, 1 cc.</td>
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<tr>
<td>Q4140</td>
<td>Biodfence, per square centimeter</td>
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</tr>
<tr>
<td>Q4145</td>
<td>Epifix, injectable, 1 mg</td>
<td></td>
</tr>
<tr>
<td>Q4148</td>
<td>Neox 1k, per square centimeter</td>
<td></td>
</tr>
<tr>
<td>Q4150</td>
<td>AlloWrap DS or dry, per square centimeter</td>
<td></td>
</tr>
<tr>
<td>Q4151</td>
<td>AmnioBand or Guardian, per square centimeter</td>
<td></td>
</tr>
<tr>
<td>Q4153</td>
<td>Dermavest and Plurivest, per square centimeter</td>
<td></td>
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<tr>
<td>Q4154</td>
<td>Biovance, per square centimeter</td>
<td></td>
</tr>
<tr>
<td>Q4155</td>
<td>Neoxflo or Clarixflo, 1 mg</td>
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<td>Q4156</td>
<td>Neox 100, per square centimeter</td>
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<td>Q4157</td>
<td>Revitalon, per square centimeter</td>
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<tr>
<td>Q4159</td>
<td>Affinity, per square centimeter</td>
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<tr>
<td>Q4160</td>
<td>NuShield, per square centimeter</td>
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<tr>
<td>Q4162</td>
<td>AmnioPro Flow, BioSkin Flow, BioRenew Flow, WoundEx Flow, AmnioGen-A, AmnioGen-C, 0.5 cc</td>
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<tr>
<td>Q4163</td>
<td>AmnioPro, BioSkin, BioRenew, WoundEx, AmnioGen-45, AmnioGen-200, per square centimeter</td>
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<tr>
<td>Q4168</td>
<td>Amnioband, 1 mg</td>
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<tr>
<td>Q4169</td>
<td>Artacent wound, per square centimeter</td>
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</tr>
<tr>
<td>Q4170</td>
<td>Cygnus, per square centimeter</td>
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<tr>
<td>Q4171</td>
<td>Interfyl, 1 mg</td>
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<tr>
<td>Q4173</td>
<td>Palingen or palingen xplus, per square centimeter</td>
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<tr>
<td>Q4174</td>
<td>Palingen or promatrix, 0.36 mg per 0.25 cc</td>
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</tr>
<tr>
<td>Q4183</td>
<td>Surgigraft, per square centimeter</td>
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<tr>
<td>Q4184</td>
<td>Cellesta, per square centimeter</td>
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<tr>
<td>Q4185</td>
<td>Cellesta flowable amnion (25 mg per cc); per 0.5 cc</td>
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<tr>
<td>Q4186</td>
<td>Epifix, per square centimeter</td>
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<td>Q4187</td>
<td>Epicord, per square centimeter</td>
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<td>Q4188</td>
<td>Amnioarmor, per square centimeter</td>
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<tr>
<td>Q4189</td>
<td>Artacent ac, 1 mg</td>
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<tr>
<td>Q4190</td>
<td>Artacent ac, per square centimeter</td>
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</tr>
<tr>
<td>Q4191</td>
<td>Restorigin, per square centimeter</td>
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</tr>
<tr>
<td>Q4192</td>
<td>Restorigin, 1 cc</td>
<td></td>
</tr>
<tr>
<td>Q4194</td>
<td>Novachor, per square centimeter</td>
<td></td>
</tr>
<tr>
<td>Q4198</td>
<td>Novachor, per square centimeter</td>
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<tr>
<td>Q4201</td>
<td>Matrion, per square centimeter</td>
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<td>Q4204</td>
<td>Xwrap, per square centimeter</td>
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<td>ICD-10-CM</td>
<td>E08.621-E08.622; E09.621-E09.622; E10.621-E10.622; E11.621-E11.622; E13.621-E13.622</td>
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<tr>
<td>Type of Service</td>
<td>Medicine</td>
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</table>

Diabetes codes with foot ulcer or other skin ulcer
### Place of Service

<table>
<thead>
<tr>
<th>Place of Service</th>
<th>Description</th>
</tr>
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<tbody>
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### ICD-10-PCS

<table>
<thead>
<tr>
<th>Code Range</th>
<th>Description</th>
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<tbody>
<tr>
<td>H11.001-H11.069</td>
<td>Pterygium of eye code range</td>
</tr>
<tr>
<td>H16.001-H16.079</td>
<td>Corneal ulcer code range</td>
</tr>
<tr>
<td>H16.231-H16.239</td>
<td>Neurotrophic keratoconjunctivitis code range</td>
</tr>
<tr>
<td>H18.831-H18.839</td>
<td>Recurrent erosion of cornea code range</td>
</tr>
<tr>
<td>L51.1</td>
<td>Stevens-Johnson syndrome</td>
</tr>
</tbody>
</table>

ICD-10-PCS codes are only used for inpatient services. There is no specific ICD-10-PCS code for this procedure.

### Type of service

<table>
<thead>
<tr>
<th>Type of service</th>
<th>Description</th>
</tr>
</thead>
</table>

### Place of service

<table>
<thead>
<tr>
<th>Place of service</th>
<th>Description</th>
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</thead>
</table>

### POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/23/15</td>
<td>New Policy – Add to Surgery section</td>
<td>Policy created with literature review through February 5, 2015; considered investigational.</td>
</tr>
<tr>
<td>02/11/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through December 14, 2015; reference 4 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>01/12/17</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 7, 2016; material on patch formulations of amniotic membrane moved from policy 7.01.113 (Bioengineered Skin and Soft Tissue Substitutes); references 7-8, 15, 18, 20, and 22-23 added. AmnioBand®, Biovance®, Epifix®, Grafix™ considered medically necessary for diabetic foot ulcers; all other products and indications are investigational.</td>
</tr>
<tr>
<td>06/01/17</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 27, 2017; references 7 and 21-28 added. Clinical input reviewed. Sutured amniotic membrane grafts considered medically necessary for neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Ophthalmic products added and discontinued product names removed from Table 1.</td>
</tr>
<tr>
<td>07/13/17</td>
<td>Replace policy – Coding update</td>
<td>ICD-10-CM codes added to code table for ophthalmic indications.</td>
</tr>
<tr>
<td>02/26/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes to policy as noted. Policy updated with literature review through December 11, 2017; references 10, 12, 17, 24, and 29 added. Specific indications added to the investigational policy statements.</td>
</tr>
<tr>
<td>04/18/19</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 07/15/2019.</td>
</tr>
</tbody>
</table>
Policy updated with literature review through November 27, 2018; references added. Clinical input reviewed. EpiCord add to medically necessary statement for diabetic lower extremity ulcers. Sutured and non-sutured amniotic membrane may be considered medically necessary for specified ophthalmic conditions.
APPENDIX

Respondent Profile

<table>
<thead>
<tr>
<th>Specialty Society</th>
<th>Clinical Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Ophthalmology</td>
<td>Ophthalmology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#</th>
<th>Name of Organization</th>
<th>Clinical Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>American Academy of Ophthalmology</td>
<td>Ophthalmology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physician</th>
<th>#</th>
<th>Name</th>
<th>Degree</th>
<th>Institutional Affiliation</th>
<th>Clinical Specialty</th>
<th>Board Certification and Fellowship Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identified by Mass Society of Eye Physicians and Surgeons</td>
<td>2</td>
<td>Mark Latina</td>
<td>MD</td>
<td>Tufts University School of Medicine</td>
<td>Ophthalmology</td>
<td>Ophthalmology, Glaucoma Fellowship trained</td>
</tr>
</tbody>
</table>

Respondent Conflict of Interest Disclosure

<table>
<thead>
<tr>
<th>#</th>
<th>1) Research support related to the topic where clinical input is being sought</th>
<th>2) Positions, paid or unpaid, related to the topic where clinical input is being sought</th>
<th>3) Reportable, more than $1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought</th>
<th>4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES/NO</td>
<td>Explanation</td>
<td>YES/NO</td>
<td>Explanation</td>
<td>YES/NO</td>
</tr>
<tr>
<td>1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response. NR = not reported

Clinical Input Responses

Objective

Clinical input is sought to help determine whether the use of a particular technology for a population would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice.

The following PICO applies to this indication.

Original Policy Date: April 2015
Amniotic Membrane and Amniotic Fluid

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>- With neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson, or persistent epithelial defects</td>
<td>- Sutured human amniotic membrane graft</td>
<td>- Medical therapy</td>
<td>- Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Bandage contact lens</td>
<td>- Morbid events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Functional outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Quality of life</td>
</tr>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>- With ophthalmic disorders other than keratitis, corneal ulcers and melts, pterygium repair, SJS, or epithelial defects</td>
<td>- Sutured human amniotic membrane graft</td>
<td>- Medical therapy</td>
<td>- Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Bandage contact lens</td>
<td>- Morbid events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Functional outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Quality of life</td>
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<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>- With ophthalmic conditions</td>
<td>- Human amniotic membrane without suture</td>
<td>- Medical therapy</td>
<td>- Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Bandage contact lens</td>
<td>- Morbid events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Functional outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Quality of life</td>
</tr>
</tbody>
</table>

Responses

1. We are seeking your opinion on whether using human amniotic membrane graft either without or with suture fixation for the below indications provide a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:
   a. Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
   b. Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals who may be appropriate for human amniotic membrane graft with versus without suture fixation for this indication;
   c. Supporting evidence from the authoritative scientific literature (please include PMID).

<table>
<thead>
<tr>
<th>#</th>
<th>Indications</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neurotrophic keratitis</td>
<td>Sutured and non-sutured human amniotic membrane HAM are both accepted and effective treatments for neurotrophic keratopathy that does not respond to conservative therapy in patients with corneal staining or an epithelial defect that (1) has failed to completely close after 5 days of conservative treatment, or (2) has failed to demonstrate a decrease in size after 2 days of conservative treatment. Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. Failure of multiple</td>
</tr>
</tbody>
</table>
modalities should not be required prior to moving to HAM. HAM requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in that regard over treatments that require multiple drops per day. Non-sutured HAM is the preferred initial treatment because it can be performed rapidly in an office setting, bypassing the delay associated with scheduling a procedure in an outpatient facility. It also avoids the facility fees associated with the sutured HAM procedure. Patients that are responding to non-sutured HAM may need a second or third application if healing is not yet complete. Those who show a poor response or poorly tolerate a non-sutured HAM device are candidates for sutured HAM.

Khokhar (Cornea 2005;24:654. PMID 16015082) found an increased but nonsignificant rate of epithelial healing with sutured HAM compared to more invasive interventions such as tarsorrhaphy for neurotrophic corneal ulceration in a small randomized clinical trial (RCT). A larger trial might have demonstrated a significant difference but the disease is uncommon enough to make such a trial difficult to perform. For the same reason, there have been no trials directly comparing sutured and non-sutured HAM for neurotrophic keratopathy. This reflects not only the uncommon nature of the disease but also the lack of interest in subjecting patients to the more invasive and expensive sutured HAM procedure when clinical experience indicates that non-sutured HAM is effective in a significant number of patients.

Other uncontrolled series and case reports supporting effectiveness of HAM for neurotrophic keratopathy:
Chen HJ. Br J Ophthalmol 2000;84:63. PMID 10906085
Ivekovic B. Coll Anthropol 2002;26:47. PMID 12137322
Suri K. Eye Contact Lens 2013;39:341. PMID 23945524
Uhlig CE. Acta Ophthalmol 2015;93:e481. PMID 25773445

Neuorthrophic keratitis

Neuorthrophic keratitis is a degenerative corneal disease induced by an impairment of corneal innervation and often manifested by corneal persistent epithelial defects (PED). Neuorthrophic PED is characterized by painless epithelial breakdown, inflammation of the underlying stroma, and poor healing. The disease progression often leads to spontaneous corneal melting and perforation. In my practice, conventional treatments including topical medications, bandage contact lens, eye patching, and tarsorrhaphy usually fail to promote healing. If delayed healing was achieved, there is still a high risk of corneal scarring.

Cryopreserved amniotic membrane (AM) has successfully been used to enhance the healing in patients with Neuorthrophic keratitis. [1-8] Besides the known actions of the AM in controlling inflammation and promoting healing, it is also rich in nerve growth factors that facilitate the recovery of the corneal nerves and enhancement of corneal wound healing.

In my opinion and based on the literature, the use of AM (with or without sutures) for treating neuorthrophic keratoconjunctivitis is medically necessary when the standard therapy fails. It interrupts the disease process by...
controlling inflammation, preventing further damage and restoring ocular surface integrity. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.


1 Corneal ulcers and melts

Corneal ulcers and melts comprise a wide range of disorders with varying etiologies. Common to many of these are an underlying inflammatory component. HAM has been shown to reduce inflammation and promote epithelial healing. These properties make HAM an effective adjunct in treating these conditions while the primary etiology is addressed with targeted therapy (e.g. corticosteroids, antibiotics, biologic immunomodulators). HAM is typically employed when there is a lack of response to initial medical treatment or where HAM can offer some degree of tectonic support in cases where there is significant stromal tissue loss.

The varied and uncommon nature of the etiology of ulcers and melts makes it unlikely that there will ever be significantly-sized RCTs comparing HAM to conventional therapy or sutured vs. non-sutured HAM. There are numerous small series and case reports without controls showing improvement after HAM placement in cases that were not responding to conventional therapy. A number of these were summarized in a review by Bouchard (Ocul Surf 2004;2:201. PMID 17216092).
Cited below are selected reports supporting the efficacy of HAM for the treatment of corneal ulcers and melts, including several published since Bouchard’s review:

Kruse FE. Ophthalmology 1999;106:1504. PMID: 10442895
Chen HC. Cornea 2006;25:564. PMID 16783145
Sheha H. Cornea 2009;28:1118. PMID 19770726
Tok OY. Int J Ophthalmol 2015;18:938. PMID 26558205
Sharma N. Indian J Ophthalmol 2018;66:816. PMID 2978990
Prabhasawat P. Br J Ophthalmol 2001;85:1455. PMID 11734521

Corneal ulcers and melts
Cryopreserved amniotic membrane (AM) has successfully been used to control inflammation and promote healing in corneal ulcers of varying etiology. [1-9] Based on my experience, the use of AM at an early stage of the disease would prevent any unexpected complications such as infection, scarring, melt and perforation. Particularly, using AM without suture for this indication provides the advantage of in-office treatment without any delay. Furthermore, it avoids potential sight-threatening complications and achieves a clinically meaningful improvement in net visual outcome.

Corneal perforation

Multilayered sutured HAM has been performed in some cases of corneal perforation. While it offers some tectonic support, corneal tissue is the preferred graft material in these cases. HAM alone may be a reasonable temporizing alternative when corneal tissue is not immediately available. Non-sutured HAM would not offer significant tectonic support in these cases.

Both sutured and non-sutured HAM reduces inflammation and promotes epithelial healing. It is therefore a useful adjunct in addition to corneal transplantation in those patients with active inflammation and perforation.

The rare nature of these cases guarantees that there will be no large RCTs performed for this indication. A number of clinical series and case reports supporting the efficacy of HAM for corneal perforation are cited here:

1. Prabhasawat P. Br J Ophthalmol 2001;85:1455. PMID 11734521
4. Hick S. Cornea 2005;24:369. PMID 15829790

Depending on the size and location of the corneal perforation, treatment options include gluing, amniotic membrane transplantation, and corneal transplantation. The success rate of using AM to repair corneal perforation is reported to be as high as 93%. [1-7] Kim et al [7] used multiple layers of AM with tissue glue in 10 patients with large corneal perforations up to 5 mm and noted 90% success in complete closure of perforation. AM offers the advantage of avoiding potential corneal graft rejection and postoperative astigmatism of tectonic corneal grafts. I personally did not use AM for this indication, but based on the literature, multiple layers of AM for this indication provides a clinically meaningful improvement in net health outcome.

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<td>2</td>
<td><strong>Bullous keratopathy</strong>&lt;br&gt;Cryopreserved amniotic membrane (AM) is recommended for Bullous keratopathy with poor visual potential. AM achieves immediate pain relief, reduced inflammation, and complete healing. [1-12] Chansanti et al [4] noted postoperative relief of pain in 14 eyes (82.4%) and complete corneal epithelial healing in 15 eyes (88.2%) after</td>
</tr>
</tbody>
</table>
AMT. Sonmez et al. [5] performed anterior stromal micropuncture and AMT in five eyes with painful bullous keratopathy [40]. All showed an intact, smooth corneal epithelial surface 1 month after the procedure, and there were no patients that developed recurrent bullae formation during an average follow-up period of 21 months. Siu et al [12] reported a long term symptomatic relief of bullous keratopathy with amniotic membrane transplant in a total of 21 eyes of 20 patients. The majority of eyes experienced pain reduction (94%), with a significant mean pain score difference of 6.8 ± 2.6, 2-tail p < 0.001 (99% CI 4.9-8.7). The mean preoperative and postoperative pain scores were 7.3 ± 2.9 and 0.5 ± 1.0, respectively. 16 eyes (76%) were completely pain free, and 10 eyes (47%) remained symptom free after a mean follow-up of 39.0 ± 36.3 months (range 5-171 months). The median epithelial healing time was 2 weeks (range 1-20 weeks). Based on the literature, AM is considered as a longer-term treatment for bullous keratopathy patients with poorer visual prognosis. AM without sutures may also be used as an interim measure for patients awaiting corneal transplant. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.


|   | Limbal stem cell deficiency | Limbal stem cell deficiency is an uncommon, serious disorder leading to conjunctivalization, irregularity, and opacity of the corneal surface. Total limbal stem cell deficiency typically requires a limbal stem cell transplant to restore the ocular surface. These vascularized transplants require prolonged systemic immunosuppression and the attendant risks to support graft survival and prevent recurrence of the disease. Partial limbal stem cell deficiency may respond to selective removal of the diseased tissue without a transplant when a limited portion of the ocular surface is involved. In more extensive cases where selective removal alone is not sufficient, HAM in conjunction with superficial keratectomy to remove the diseased tissue can provide long-term restoration of a smooth and transparent ocular surface and improved visual acuity without having to resort to a transplant (Kheirkhah AV. Am J Ophthalmol 2008;145:787. PMID 18329626). Due to the rarity of this disease, it is unlikely that RCTs will ever be performed. Comparisons to limbal stem cell transplants are unlikely to be performed because of the risks of systemic immune suppression.

HAM should be covered in conjunction with superficial keratectomy for cases of limbal stem cell deficiency. |
|   | Patients with Limbal stem cell deficiency (LSCD) suffer from severe loss of vision due to vascularized cornea scarring and non-healing epithelial defect. Their vision cannot be corrected by conventional penetrating keratoplasty. Previous studies have shown that in eyes with partial LSCD, AM promotes expansion of remaining limbal epithelial stem cells [1-4]. To avoid suture-related disadvantages and complications, Kheirkhah et al. [5] recently reported successful reconstruction of the corneal surface in nine patients with nearly total LSCD using fibrin glue. Kheirkhah et al. [56] further reported successful use of minimal conjunctival limbal autograft in conjunction with AM for total limbal stem cell deficiency.

5. Kheirkhah A, V. Casas V. Raju K et al. Sutureless amniotic membrane transplantation for partial limbal stem cell... |
Amniotic Membrane and Amniotic Fluid

| 1 | Stevens-Johnson | Sutureless HAM plus medical therapy has been demonstrated in a small RCT to be more effective than medical therapy alone in treatment of Stevens-Johnson syndrome (Sharma N. Ophthalmology 2016;123:484. PMID 26686968). Sutureless or sutured HAM, depending on the severity of the disease, in conjunction with medical therapy has become the accepted management technique for the treatment of moderate or severe Stevens-Johnson. Both should be covered for this indication. The severity of the disease and its infrequency makes it unlikely that a large RCT will be performed. Additional literature demonstrating good visual outcomes with both sutured and sutureless HAM in a disease that prior to introduction of HAM was typically blinding includes:

Shammas MC. Am J Ophthalmol 2010;149:203. PMID 20005508  
Gregory DM. Ocular Surf 2008;6:40. PMID 18418506  
Shay E. Surv Ophthalmol 2009;54:468. PMID 19699503  
Gregory DM. Ophthalmology 2011;118:908. PMID 21440941  
Shay E. Cornea 2010;29:359. PMID 20098313  
Tomlins PJ. Cornea 2013;32:365. PMID 22677638  
Kolomeyer AM. Eye Contact Lens 2013;39:e7. PMID 22683916  
Ma KN. Ocular Surf 2016;14:31. PMID 26387869 |

| 2 | Stevens-Johnson | Amniotic membrane with sutures has been used to suppress inflammation, promote healing, and prevent scarring in patients with acute Stevens Johnson Syndrome (SJS) with or without toxic epidermal necrolysis (TEN) [1-6]. The conventional management at intensive care and burn units are usually reserved for life-threatening problems, and thus are frequently inadequate to address ocular inflammation and ulceration. As a result, patients suffering are frequently left with a blinding disease owing to scarring-induced late complications. Gregory et al. [7] and Shay et al. [8] have reviewed the literature and found that AMT performed within 2 weeks after the onset of disease effectively aborts inflammation and facilitates rapid healing in AM-covered areas, thus preventing pathogenic cicatricial complications at the chronic stage in 12 eyes. Several case reports and cases series [6-12] demonstrated the effectiveness of AM without sutures (ProKera) at the acute stage of SJS/ TEN, and noted restoration of normal vision. Gregory et al [9] further reported restoration of vision in 10 consecutive cases using AM with and without sutures. However, because this devastating ocular surface disease usually elicits inflammation and ulceration in such hidden areas as the lid margin, the tarsus and the fornix, AM extended to cover the entire ocular surface is necessary.[10] Ma et al [13] developed a novel technique for using large AM graft without suture to cover the entire ocular surface in patients with acute SJS. In my opinion, and based on the literature, the use of AM with sutures is preferred to prevent long term lid related complications. The use of AM without suture is still helpful in
Amniotic Membrane and Amniotic Fluid

emergency settings when the patient condition does not allow for surgical intervention. Collectively, the use of AM for this indication provides a clinically meaningful improvement in net health outcome.


1 Persistent epithelial defects

HAM is an effective treatment for persistent epithelial defects due to a number of underlying causes. While not a first-line treatment, both sutured and non-sutured HAM are appropriate in patients with epithelial defects that
fail to show a response within 2 days of initiation of conservative therapy. Conservative therapy is considered to be any one or more of the following: topical lubricants and/or antibiotics, therapeutic contact lens, or patching. If there is a failure to respond to any one of these modalities, HAM is an appropriate second step.

Persistent epithelial defects are often a precursor to corneal stromal melting and ulceration. Many of the comments and citations in the above "Section b. corneal ulcers and melts" are applicable here. The uncommon nature of the diseases associated with persistent epithelial defects and the lack of a standard therapeutic regimen account for the lack of RCTs. However, the following publications demonstrate the effectiveness of HAM for this indication.

Prabhasawat P. Br J Ophthalmol 2001;85:1455. PMID 11734521
Lee SH. Am J Ophthalmol 97;123:303. PMID 9063239
Letko E. Arch Ophthalmol 2001;119:659. PMID 11346392
Gris O. Cornea 2002;21:22. PMID 11805502
Seitz B. Eye (London) 2009;23:840. PMID 18535612
Dekaris I. Coll Antropol 2010;34 Suppl 2:15. PMID 21305721

Persistent epithelial defects (PED) is often caused by microtrauma, neurotrophic keratopathy and exposure. Conventional treatment includes correcting the underlying condition, suppressing the inflammation, and promoting the healing process using tears. If conventional treatment fails after 2 weeks, these patients are prone to further complications and corneal scarring and haze. Because PED also be ‘neurotrophic’, please refer to Neurotrophic keratitis indication. As stated above, conventional treatments usually fail to promote prompt healing in these conditions and the eyes are prone to delayed healing, corneal ulceration, scarring, and infection. These complications in turn result in poor patient outcomes, visual detriment, and a greater frequency of office visits and associated costs. The following publications [1-6] show the effectiveness of AM with and without sutures in promoting healing in PEDs. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.

### Severe dry eye

As noted in the BCBS review, non-sutured HAM has been demonstrated in an RCT to be more effective than conservative therapy in patients with moderate to severe dry eye disease (John T. J Ophthalmol 2017;2017:6404918. PMID 28894606). Also noted in the review was a small series of 10 patients with moderate to severe dry eye that were non-responsive to conventional therapy (Cheng AM. Ocul Surf 2016;14:56. PMID 26387870). These patients improved with placement of non-sutured HAM. A more recent, larger retrospective review of patients with severe dry eye disease unresponsive to traditional therapy and then treated with non-sutured HAM showed that 88% of subjects demonstrated significant improvement of symptoms extending beyond the period of treatment with HAM (McDonald MD. Clin Ophthalmol 2018;12:677. PMID 29670328).

Traditional dry eye therapy typically consists of frequent application of lubricants, hot compresses, and environmental controls to increase humidity. Patients may not respond to traditional dry eye therapy due to the severity of the disease or due to inability to control the environment or administer drops frequently. Topical drugs such as cyclosporine and lifitegrast may be helpful in these cases but they may take months to take effect. If the patient's daily activities are significantly affected by dry eye signs and symptoms, HAM may provide rapid relief while waiting for long-term medications to take effect. HAM is unlikely to be of benefit for mild dry eye disease or disease that responds to conservative therapy. Because HAM limits acuity it is only viable as a short-term therapy.

Sutured HAM is not typically used for severe dry eye alone, but may be necessary in the face of one or more concomitant diseases discussed in the other sections.

Our recommendation is that non-sutured HAM be covered in patients with persistent symptoms or persistent corneal staining that does not respond to traditional dry eye therapy.

### Dry eye disease (DED)

Dry eye disease (DED) is a multifactorial disease comprised of tear film insufficiency and associated ocular surface disorder such as superficial epithelial defect. Treatment of DED depends on the etiology and the level of severity. Although artificial tears, immunosuppressants and punctal occlusion are commonly used for tear film insufficiency, ocular surface involvement with a defect are usually refractory and may require eye protection devices and/or surgical intervention.

In fact, Prokera has been reported to manage ocular signs and symptoms of DED. In a retrospective study by Cheng et al,[1] Prokera was placed for 5 days (Range: 2-8 days) in 15 eyes of 10 patients with moderate to severe DED. The dry eye severity ranged from Grade 1 to 4 according to the Report of the International Dry Eye Work...
MP 7.01.149
Amniotic Membrane and Amniotic Fluid

Amniotic Membrane and Amniotic Fluid Shop (DEWS) 2007.[2] All patients experienced symptomatic relief for a mean period of 4.2 months (Range: 0.3-6.8). Such improvement was accompanied by reduction of Ocular Surface Disease Index (OSDI) symptom scores, the use of topical medications, conjunctival hyperemia, and corneal staining as well as improvement in the quality of vision.11 In a single site prospective, randomized, and controlled study conducted by John et al [3], Prokera together with standard of care was placed in 10 patients for 3.4 ± 0.7 days (Range: 3-5 days) while standard of care was instituted in another 10 patients as the control. All 20 patients presented with moderate to severe DED with DEWS Grade 2-4. Compared to the control arm of 10 patients receiving standard of care, the treatment arm of 10 patients receiving Prokera together with standard of care resulted in reduction of symptoms based on SPEED score and signs such as superficial punctate keratitis (SPK) measured by fluorescein staining, leading to an overall reduction of the mean DEWS severity score from 2.9 ± 0.3 at baseline to 1.1 ± 0.3 at 1 month and 1.0 ± 0.0 at 3 months, respectively (both p ≤ 0.001). These palliative benefits are correlated with an increase of corneal nerve density measured by in vivo confocal microscopy from 12,241 ± 5,083 µm/mm² at baseline to 16,364 ±3,734 µm/mm² at 1 month, and 18,827 ±5,453 µm/mm² at 3 months (both p=0.015). The increase of corneal nerve density is also correlated with an increase of corneal sensitivity measured by a monofilament in the Bonnet-Crochet esthesiometer. A lasting benefit for more than 3 months after one placement of Prokera was also demonstrated in a retrospective study by McDonald et al [4] in 97 eyes of 84 of patients with moderate to severe DED (DEWS 2-4), of which the majority presented with symptoms of ocular discomfort, blurry vision, ocular pain, redness, and light sensitivity. Most of the cases manifested the ocular sign of SPK due to exposure keratitis, filamentary keratitis, epithelial defect, and neurotrophic keratitis. A single placement of Prokera for 5.4 ± 2.8 days leads to notable improvement of DED symptoms and reduction of ocular signs in 74 subjects (88%) as evidenced by notable reduction of the mean DEWS severity score from 3.25 to 1.44 at 1 week, 1.45 at 1 month, and 1.47 at 3 months.

In my practice, a single placement of Amniotic Membrane (non-sutured) was also effective in reducing signs and symptoms of DED for a period lasting more than three months. Therefore, amniotic membrane without sutures should be considered for severe dry eye with ocular surface damage and inflammation.

<table>
<thead>
<tr>
<th></th>
<th>Acute ocular chemical burn</th>
<th>Previous studies have demonstrated the importance of early intervention with cryopreserved amniotic membrane (AM) in mild and moderate chemical burns. [1-10] Specifically, Miller et al [7] used AM as a patch graft with sutures in 13 eyes of patients with acute chemical burn grade II-IV (within 2 weeks of the injury) and epithelial healing occurred within 2-5 weeks. Prabhasawat et al [8] also showed that AM as a patch graft performed within 5 days of grades II and III chemical burns promoted faster epithelial healing and less corneal haze than if performed after 5 days. These results were confirmed by Tandon et al [9] who demonstrated the efficacy of sutured AM in eyes with acute ocular burns in a prospective, randomized, controlled clinical trial of 100 patients with grade II to IV acute ocular burns. Patients were randomized to receive AM or conventional medical treatment. The rate of epithelial healing was significantly better in the AM group than the group with standard medical therapy alone. Kheirkhah et al [10] noted a similar positive outcome when AM without sutures (Prokera) was used within 8 days of chemical burn injury. Based on the above, the use of AM with or without sutures in acute chemical burn is considered a medical necessity to control inflammation, prevent further damage, reduce scarring and restore visual function. In my opinion, and based on the literature, the use of AM without sutures is preferred to prevent surgical trauma and suture related complications in such compromised eyes. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.</th>
</tr>
</thead>
</table>
|   |   | Westekemper H. Br J Ophthalmol 2017;101:103. PMID 27150827
|   |   | Meller D. Ophthalmology 2000;107:980. PMID 10811094
|   |   | Ucakhan OO. Cornea 2002;21:169. PMID 11862088
|   |   | Arora R. Eye 2005;19:273. PMID 15286672
|   |   | Tejwani S. Cornea 2007;26:21. PMID 17198009
|   |   | Prabhasawat P. J Med Assoc Thai 2007;90:319. PMID 17375638
|   |   | Kheirkhah A. Arch Ophthalmol 2008;126:1059. PMID 18695099
|   | Acute ocular chemical burn | Ocular chemical burns represent a diverse array of clinical conditions and severity, making high quality RCTs difficult or impossible to perform. The Cochrane review cited in the BCBS review (Clare G. Cochrane Database Syst Rev 2012;9:CD009379. PMID 22972141) reflects this difficulty. However, it is clear that there are subsets of patients that respond to either sutured or non-sutured HAM based in its ability to reduce inflammation and promote epithelial healing. Particularly in moderate and severe burns where the prognosis with traditional therapy is poor, sutured and non-sutured HAM are important alternatives that should be covered. There are multiple reports of good outcomes in these cases. Though control groups are lacking, several of these reports are fairly large series and were not addressed directly in the BCBS review:|
|   |   | Westekemper H. Br J Ophthalmol 2017;101:103. PMID 27150827
|   |   | Meller D. Ophthalmology 2000;107:980. PMID 10811094
|   |   | Ucakhan OO. Cornea 2002;21:169. PMID 11862088
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|   |   | Tejwani S. Cornea 2007;26:21. PMID 17198009
|   |   | Prabhasawat P. J Med Assoc Thai 2007;90:319. PMID 17375638
|   |   | Kheirkhah A. Arch Ophthalmol 2008;126:1059. PMID 18695099

NR = not reported

2. Based on the evidence and your clinical experience for using human amniotic membrane with suture fixation for the clinical indications described below:
   a. Respond YES or NO for each clinical indication whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND
   b. Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

<table>
<thead>
<tr>
<th>#</th>
<th>Indications</th>
<th>YES / NO</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
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<td>2</td>
<td>3</td>
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<tr>
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Original Policy Date: April 2015
### Amniotic Membrane and Amniotic Fluid

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NR = not reported

3. Based on the evidence and your clinical experience for using [human amniotic membrane with suture fixation](#) for the clinical indications described below:
   a. Respond YES or NO for each clinical indication whether this intervention is consistent with generally accepted medical practice; AND
   b. Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

<table>
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<td>Corneal perforation</td>
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</table>
Based on the evidence and your clinical experience for using human amniotic membrane without suture fixation for the clinical indications described below:

a. Respond YES or NO for each clinical indication whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND

b. Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

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<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Bullous keratopathy</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR = not reported

4. Based on the evidence and your clinical experience for using human amniotic membrane without suture fixation for the clinical indications described below:

- Respond YES or NO for each clinical indication whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND
- Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.
5. Based on the evidence and your clinical experience for using **human amniotic membrane without suture fixation** for the clinical indications described below:
   a. Respond YES or NO for each clinical indication whether this intervention is consistent with generally accepted medical practice;
      AND
   b. Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

<table>
<thead>
<tr>
<th>#</th>
<th>Indications</th>
<th>YES / NO</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neurothrophic keratitis</td>
<td>Yes</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Neurothrophic keratitis</td>
<td>Yes</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td>Corneal ulcers and melts</td>
<td>Yes</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>Corneal ulcers and melts</td>
<td>Yes</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td>Corneal perforation</td>
<td>No</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>Corneal perforation</td>
<td>No</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td>Bullous keratopathy</td>
<td>Yes</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>Bullous keratopathy</td>
<td>Yes</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td>Pterygium repair</td>
<td>Yes</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>Pterygium repair</td>
<td>No</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td>Limbal stem cell deficiency</td>
<td>Yes</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
### Additional narrative rationale or comments regarding clinical pathway and/or any relevant scientific citations (including the PMID) supporting your clinical input on this topic.

**#** | **Additional Comments**
---|---
1 | Specific citations are included above in the comments for each of the individual indications.
2 | Amniotic Membrane is available either as an outpatient clinic based onlay protective bandage contact lens AM patch, or as an ASC or hospital based operating room surgical inlay tissue substitute and is an established treatment for several severe ocular surface diseases. It is most commonly used in patients whose condition is refractory to conventional therapies, such as Corneal Ulcers and Melts, Neurotrophic Keratitis, severe anterior basement membrane dystrophy, and especially difficult-to-heal Persistent Epithelial Defects (PED). I use Prokera (BioTissue) to treat ocular surface diseases because, based on the clinical presentation and the failure of conventional therapy, it is medically necessary in order to achieve the best clinical outcome. Prokera is a cryopreserved (not dehydrated) sutureless AM and is the only such AM cleared by the FDA (2003). It is indicated for use “where the ocular surface is damaged, or the underlying corneal stroma is inflamed.” The Prokera self-retaining ring makes it possible to non-surgically insert AM into the eye like a very large contact lens and thereby secure the membrane in place. As such, Prokera represents a significant improvement over the use of AM grafts that require the more invasive, time consuming, and costly suturing procedure. Clinically, use of amniotic membranes serve two primary roles: reduction of...
Amniotic Membrane and Amniotic Fluid

7. Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

<table>
<thead>
<tr>
<th>#</th>
<th>YES / NO</th>
<th>Citations of Missing Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>See specific citations in above comments on each of the individual indications.</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>In general- amniotic membrane is an important Therapy for ocular surface disease which is unresponsive to conventional therapies. In my experience Amniotic membrane grafts have significantly improved the clinical course of many patients, that would have otherwise resulted in vision loss and saved patients from more extensive surgical procedures.</td>
</tr>
</tbody>
</table>