Treatment of nonhealing diabetic lower-extremity ulcers using any of the following human amniotic membrane products may be considered medically necessary:

- **AmnioBand® Membrane**
- **Biovance®**
- **EpiCord®**
- **EpiFix®**
- **Grafix™**

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 (e.g., 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 algorithms (see Policy Guidelines)
- 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
- 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.
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 (e.g., 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 (e.g. tarsorrhaphy, salivary gland transplantation)

Table PG1. Dry Eye Severity Grading Scheme

<table>
<thead>
<tr>
<th>Dry Eye Severity Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discomfort, severity &amp; frequency</strong></td>
<td>Mild and/or episodic; occurs under environmental stress</td>
<td>Moderate episodic or chronic, stress or no stress</td>
<td>Severe frequent or constant without stress</td>
<td>Sever and/or disabling and constant</td>
</tr>
<tr>
<td><strong>Visual Symptoms</strong></td>
<td>None or episodic mild fatigue</td>
<td>Annoying and/or activity-limiting episodic</td>
<td>Annoying, chronic and/or constant, limiting activity</td>
<td>Constant and/or possibly disabling</td>
</tr>
<tr>
<td><strong>Conjunctival injection</strong></td>
<td>None to mild</td>
<td>None to mild</td>
<td>+/−</td>
<td>+/++</td>
</tr>
<tr>
<td><strong>Conjunctival staining</strong></td>
<td>None to mild</td>
<td>Variable</td>
<td>Moderate to marked</td>
<td>Marked</td>
</tr>
<tr>
<td><strong>Corneal staining (severity/location)</strong></td>
<td>None to mild</td>
<td>Variable</td>
<td>Marked central</td>
<td>Severe punctate erosions</td>
</tr>
<tr>
<td><strong>Corneal/tear signs</strong></td>
<td>None to mild</td>
<td>Mild debris, decrease meniscus</td>
<td>Filamentary keratitis, mucus clumping, increased tear debris</td>
<td>Filamentary keratitis, mucus clumping, increased tear debris, ulceration</td>
</tr>
<tr>
<td><strong>Lid/meibomian glands</strong></td>
<td>MGD variably present</td>
<td>MGD variably present</td>
<td>Frequent</td>
<td>Trichiasis, keratinization, symblepharon</td>
</tr>
<tr>
<td><strong>TFBUT (sec)</strong></td>
<td>Variable</td>
<td>≤ 10</td>
<td>≤ 5</td>
<td>Immediate</td>
</tr>
<tr>
<td><strong>Schirmer score (mm/5min)</strong></td>
<td>Variable</td>
<td>≤ 10</td>
<td>≤ 5</td>
<td>≤ 2</td>
</tr>
</tbody>
</table>

*Must have signs and symptoms. TBUT: fluorescein tear break-up time. MGD: meibomian gland disease

Coding
The following HCPCS codes are for specific products:
- **Q4132**: Grafix Core and GrafixPL Core, per sq cm
- **Q4133**: Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq cm
- **Q4137**: AmnioExcel, AmnioExcel Plus or BioDExcel, per sq cm
- **Q4138**: BioDfence DryFlex, pers sq cm
- **Q4139**: AmnioMatrix or BioDMatrix, injectable, 1 cc
- **Q4140**: BioDfence, per sq cm
- **Q4145**: EpiFix, injectable, 1 mg
- **Q4148**: Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per sq cm
- **Q4150**: AlloWrap DS or dry, per sq cm
- **Q4151**: AmnioBand or Guardian, per sq cm
- **Q4153**: Dermavest and Plurivest, per sq cm
- **Q4154**: Biovance, per sq cm
- **Q4155**: Neox Flo or Clarix Flo 1 mg
- **Q4156**: Neox 100 or Clarix 100, per sq cm
- **Q4157**: Revitalon, per sq cm
- Q4159: Affinity, per sq cm
- Q4160: Nushield, per sq cm
- Q4162: WoundEx Flow, BioSkin Flow, 0.5 cc
- Q4163: WoundEx, BioSkin, per sq cm
- Q4168: AmnioBand, 1 mg
- Q4169: Artacent wound, persq cm
- Q4170: Cygnus, per sq cm
- Q4171: Interfyl, 1 mg
- Q4173: PalinGen or PalinGen XPlus, per sq cm
- Q4174: PalinGen or ProMatrX, 0.36 mg per 0.25 cc
- Q4176: NeoPatch, per sq cm
- Q4177: FlowerAmnioFlo, 0.1 cc
- Q4178: FlowerAmnioPatch, per sq cm
- Q4180: Revita, per sq cm
- Q4181: Amnio Wound, per sq cm

**Effective January 1, 2019**, the following HCPCS codes are for specific products:
- Q4183: Surgigraft, per square cm
- Q4184: Cellesta or cellesta duo per square cm *(Code revision effective 10/1/2019)*
- Q4185: Cellesta flowable amnion (25 mg per cc); per 0.5 cc
- Q4186: Epifix, per square cm
- Q4187: Epicord, per square cm
- Q4188: Amnioarmor, per square cm
- Q4189: Artacent ac, 1 mg
- Q4190: Artacent ac, per square cm
- Q4191: Restorigin, per square cm
- Q4192: Restorigin, 1 cc
- Q4194: Novachor, per square cm
- Q4198: Genesis amniotic membrane, per square cm
- Q4201: Matrion, per square cm
- Q4204: Xwrap, per square cm

**Effective October 1, 2019**, the following HCPCS codes are for specific products:
- Q4208: Novafix, persq cm
- Q4209: SurGraft, persq cm
- Q4210: Axolotl Graft or Axolotl DualGraft, persq cm
- Q4211: Amnion Bio or AxoBioMembrane, persq cm
- Q4212: AlloGen, per cc
- Q4213: Ascent, 0.5 mg
- Q4214: Cellesta Cord, persq cm
- Q4215: Axolotl Ambient or Axolotl Cryo, 0.1 mg
- Q4216: Artacent Cord, per sq cm
- Q4217: WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, persq cm
- Q4218: SurgICORD, persq cm
- Q4219: SurgiGRAFT-DUAL, persq cm
- Q4221: Amnio Wrap2, per sq cm

If no specific HCPCS code exists for the product, an unlisted code such as the following would be used:
- Q4100: Skin substitute, not otherwise specified

There are no specific codes for AmnioFix or OrthoFlo. It might be reported using the code for another MiMedx product such as the following:
- Q4145: EpiFix, injectable, 1 mg
- Q4100: Skin substitute, not otherwise specified
Effective **October 1, 2019**, the following HCPCS code is for a human amniotic allograft membrane used to repair tissue deficits and to reduce healing time for chronic and post-surgical wounds:

- **Q4205**: Membrane Graft or Membrane Wrap, per sq cm

Effective **October 1, 2019**, the following HCPCS code is for a human amniotic flowable allograft that is intended for homologous use to support the repair of soft tissue injury:

- **Q4206**: Fluid Flow or Fluid GF, 1 cc

There is no specific code for this type of injection. It might be reported with one of the musculoskeletal system injection codes or the subcutaneous or intramuscular code:

- **20550**: Injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar “fascia”)
- **20999**: Unlisted procedure, musculoskeletal system, general
- **96372**: Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular

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**: Placement of amniotic membrane on the ocular surface; single layer, sutured

**Description**

Several commercially available forms of human amniotic membrane (HAM) and amniotic fluid can be administered by patches, topical application, or injection. Amniotic membrane and amniotic fluid are being evaluated 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.

**Related Policies**

- Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions
- Bioengineered Skin and Soft Tissue Substitutes
- Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow)

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**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**

**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 that 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 that these properties are retained in cryopreserved HAM and dehydrated HAM products, resulting in a readily available tissue with regenerative potential. In support, one 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.

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. 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. 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. Amniotic fluid has been compared with synovial fluid, containing hyaluronan, lubricant,
cholsterol, 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. 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 Blue Shield of California Medical Policy: Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow).

<table>
<thead>
<tr>
<th>Product (Supplier)</th>
<th>Preparation, Dehydrated, or Extracted</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affinity™ (NuTech Medical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AlloWrap™ (AlloSource)</td>
<td>D</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™ (Livента Bioscience)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>AmnioExcel® (Dema 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>
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</tr>
<tr>
<td>Artacent® Wound (Tides Medical)</td>
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</tr>
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<td>BioDDryFlex® (BioD)</td>
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<td>BioDfence™ (BioD)</td>
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</tr>
<tr>
<td>BioSkin (HRT)α</td>
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<td>X</td>
</tr>
<tr>
<td>Biovance® (Alliqua Biomedical)</td>
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<td>X</td>
</tr>
<tr>
<td>Clarix® (Amnio Medical)</td>
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<td>X</td>
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<tr>
<td>Cygnus (Vivex Biomedical)</td>
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</tr>
<tr>
<td>Cygnus Max (Vivex Biomedical)</td>
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<td>X</td>
</tr>
<tr>
<td>Epicord™ (MiMedx)</td>
<td>D</td>
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</tr>
<tr>
<td>Epifix® (MiMedx)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Demavest® (Aedicell)α</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 (Amnio Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Neox® Cord (Amnio Medical)</td>
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<td>Neox® Wound Allograft (Amnio Medical)</td>
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<td>NuShield™ (NuTech Medical)</td>
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<td>PalinGen® Membrane (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Plurivest® (Aedicell)α</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Prokera® (Bio-Tissue)</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Revitalon™ (Medline Industries)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>WoundEx® (Skye Biologics)α</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>Suspension, particulate, or extraction</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioBand® Particulate (MTF Wound Care)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>AmnioMatrix® (Dema 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)β</td>
<td>E</td>
<td>X</td>
</tr>
<tr>
<td>Clarix® Flo (Amnio Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>InterfyI® (Alliqua Biomedical)</td>
<td>NS</td>
<td>X</td>
</tr>
<tr>
<td>Neox® Flo (Amnio Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Orthoflo® (MiMedx)</td>
<td>D</td>
<td>X</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Product (Supplier)</th>
<th>Preparation</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>PalinGen® Flow (Amnio ReGen Solutions)</td>
<td>C X X</td>
<td></td>
</tr>
<tr>
<td>PalinGen® SportFlow (Amnio ReGen Solutions)</td>
<td>C X X</td>
<td></td>
</tr>
<tr>
<td>ProMatrX™ ACF (Amnio ReGen Solutions)</td>
<td>C X X</td>
<td></td>
</tr>
<tr>
<td>ReNu™ (NuTech Medical)</td>
<td>D X X X</td>
<td></td>
</tr>
<tr>
<td>WoundEx® Flow (Skye Biologics)</td>
<td>E X X X X</td>
<td></td>
</tr>
</tbody>
</table>

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

a,b Processed by HRT and marketed by under different tradenames.

**Literature Review**

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 everyone 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>Zelen et al (2015, 2016)⁸,⁹.</td>
<td>US</td>
<td>60</td>
<td>2015-2016</td>
<td>60 patients with less than 20% wound healing in a 2 week run-in period</td>
<td>EpiFix</td>
<td>Apligraf or SOC with collagen-alginate dressing</td>
</tr>
</tbody>
</table>
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Lavery et al (2014)\textsuperscript{10}, 97 patients with chronic diabetic foot ulcers

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>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>Ananian et al (2018)\textsuperscript{4}</td>
<td>8 Weeks (PP) n (%)</td>
<td></td>
<td></td>
<td>Patients with Index Ulcer Related Adverse Events n (%)</td>
</tr>
<tr>
<td>N</td>
<td>62</td>
<td>15 (48.4%)</td>
<td>1 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Grafix</td>
<td>12</td>
<td>12 (38.7%)</td>
<td>4 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Diff (95% CI)</td>
<td>9.68%</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)\textsuperscript{11}</td>
<td>12 Weeks (PP) n (%)</td>
<td>12 Weeks (ITT) n (%)</td>
<td>Patients with Adverse Events (% of total)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>134</td>
<td>155</td>
<td>155</td>
<td></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)\textsuperscript{11}</td>
<td>n (%)</td>
<td></td>
<td>Mean (95% CI)</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>AmnioBand</td>
<td>14 (70%)</td>
<td>17 (85%)</td>
<td>36 (27 to 46)</td>
<td></td>
</tr>
<tr>
<td>SOC</td>
<td>3 (15%)</td>
<td>5 (25%)</td>
<td>70 (59 to 81)</td>
<td></td>
</tr>
<tr>
<td>OR/NNT (95% CI)</td>
<td>OR: 17 (3.1 to 93)</td>
<td>NNT: 1.7 (1.2 to 2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>0.001</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Snyder et al (2016)\textsuperscript{11}</td>
<td>Mean (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AmnioExcel</td>
<td>33% (25.0% to 46.4%)</td>
<td>45.5% (32.9% to 58.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOC</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>0.017</td>
<td>0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zelen et al (2015, 2016)\textsuperscript{8,9}</td>
<td>n (%)</td>
<td>Wounds Healed at 12 Weeks</td>
<td>Weekly Treatments</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>60</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EpiFix</td>
<td>19 (95%)</td>
<td>NR</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>Apligraf</td>
<td>9 (45%)</td>
<td>NR</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>SOC</td>
<td>7 (35%)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>5.66; (3.03 to 10.57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>0.003</td>
<td>&lt;0.001 vs SOC</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Lavery et al (2014)\textsuperscript{10}</td>
<td>Wounds Healed at 12 Weeks</td>
<td>Patients With Adverse Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>97a</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grafix</td>
<td>62.0%</td>
<td>42.0</td>
<td>44.0%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Allocation</td>
<td>Blinding</td>
<td>Selective Reporting</td>
<td>Data Completeness</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>----------</td>
<td>---------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Tettelbach et al (2018)¹¹.</td>
<td>1, 2, 3. No blinding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DiDomenico et al (2016)¹¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snyder et al (2016)¹¹.</td>
<td></td>
<td></td>
<td></td>
<td>1. There was high loss to follow-up with discontinuation of 8 of 29 participants</td>
</tr>
<tr>
<td>Zelen et al (2015, 2016)⁸,⁹.</td>
<td></td>
<td></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>
</tr>
</tbody>
</table>

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


⁷ 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).

⁸ Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

⁹ 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.11 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>Frykberg et al (2016)12.</td>
<td>Prospective multi-center 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>
</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)11.</td>
<td>Biovance</td>
<td>41.6%</td>
<td>8 weeks</td>
<td>2.4</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 (i.e., 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 (i.e., 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 everyone 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 between 2 and 20 cm² treated for at least 14 d</td>
<td>1 (n=26) or 2 (n=27) applications of EpiFix plus compression (n=53)</td>
</tr>
<tr>
<td>Bianchi et al (2017)</td>
<td>U.S.</td>
<td>15</td>
<td>2015-2017</td>
<td>128 patients with a full-thickness VLU of at least 30-d duration</td>
<td>Weekly EpiFix plus moist wound therapy plus compression (n=64; 52 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></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, a 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>
<tbody>
<tr>
<td>Cazzell et al (2018) [^{18}, \text{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>
<td>n = 72; Single injection of saline</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>AmnioFix</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>Placebo</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>Diff (95% CI)</td>
<td>22.2 (13.1 to 31.3)</td>
<td>13.5 (6.2 to 20.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
<td></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></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cazzell et al (2018) [^{18}, \text{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></td>
<td></td>
<td>1, 2. Follow-up to 12 months will be reported in a subsequent publication.</td>
<td></td>
</tr>
</tbody>
</table>

[^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.
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 (2018)</td>
<td>1. Single blinded trial, although outcomes were self-reported by blinded patients</td>
<td>1. Only the first 3 months of 12 month follow-up were reported.</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.

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 (e.g., 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 (e.g., 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 bum. 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 (e.g. 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 (e.g., 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 bum.

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

Comparators
The following therapies are currently being used: medical therapy (e.g. 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 (e.g., 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 (e.g., 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 (e.g., 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 (i.e., 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 (i.e., 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 do not Respond to Initial Medical Therapy
For individuals who have corneal ulcers and melts that do 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 (e.g., endothelial or penetrating keratoplasty)
For individuals who have bullous keratopathy and who are not candidates for a curative treatment (e.g., 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 do 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 (e.g., 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:
Clinical Input Responses

<table>
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<tr>
<th>Use of human amniotic membrane for following indications</th>
<th>Type of HAM</th>
<th>Respondent</th>
<th>Identified by</th>
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<th><strong>Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice</strong></th>
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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 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 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 from Blue Cross Blue Shield Association 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.32 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 (e.g. 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.”33

**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**

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<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 Achilles Tendonitis</td>
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<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>
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<td>NCT02322554</td>
<td>The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers</td>
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<td>Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions</td>
<td>200</td>
<td>Jun 2022</td>
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<td>NCT02609594a</td>
<td>A Multi-center Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Amnioband Dehydrated Human Amnion 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>
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<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>
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<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.

**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.
**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Reason/indication for human amniotic membrane/fluid product
  - Type and name of human amniotic membrane/fluid product

**Post Service**

- Procedure report including type and name of product used

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
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<td>Placement of amniotic membrane on the ocular surface; without sutures</td>
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<td>Placement of amniotic membrane on the ocular surface; single layer, sutured</td>
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<td>WoundEx, BioSkin, per sq cm</td>
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### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.
Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.