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Origination: 4/2016
Last Review: 3/2019
Next Review: 3/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Amniotic Membrane and Amniotic Fluid when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products (AmnioBand® Membrane, Biovance®, Epifix®, Grafix™, GrafixPL Prime) may be considered medically necessary.

Sutured human amniotic membrane grafts may be considered medically necessary for the treatment of the following ophthalmic indications:
- Neurotrophic keratitis
- Corneal ulcers and melts
- Pterygium repair
- Stevens-Johnson syndrome
- Persistent epithelial defects.

When Policy Topic is not covered
Sutured human amniotic membrane grafts are considered investigational for the treatment of all other ophthalmic conditions including but not limited to dry eye syndrome, burns, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy.

Human amniotic membrane without suture (eg, Prokera®, AmbioDisk™) for ophthalmic indications is investigational.

Injection of microronized 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.

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

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 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 human amniotic membrane grafts (AMGs). An AMG requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in regarding treatments requiring multiple drops per day.

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

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

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

There are codes for the placement of amniotic membrane on the ocular surface:

65778: Placement of amniotic membrane on the ocular surface; without sutures
65779: single layer, sutured.

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals:  
  • With nonhealing diabetic lower-extremity ulcers | Interventions of interest are:  
  • Patch or flowable formulation of human amniotic membrane | Comparators of interest are:  
  • Standard wound care  
  • Advanced wound therapies | Relevant outcomes include:  
  • Symptoms  
  • Morbid events  
  • Functional outcomes  
  • Quality of life |
| Individuals:  
  • With lower-extremity ulcers | Interventions of interest are:  
  • Patch or flowable | Comparators of interest are:  
  • Compression | Relevant outcomes include:  
  • Symptoms |
<table>
<thead>
<tr>
<th>Individuals:</th>
<th>Interventions of interest are:</th>
<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>With knee osteoarthritis</td>
<td>Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid</td>
<td>Conservative therapy, Corticosteroid injections</td>
<td>Symptoms, Functional outcomes, Quality of life, Treatment-related morbidity</td>
</tr>
<tr>
<td>With plantar fasciitis</td>
<td>Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid</td>
<td>Medical therapy, Bandage contact lens</td>
<td>Symptoms, Morbid events, Functional outcomes, Quality of life</td>
</tr>
<tr>
<td>With neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects</td>
<td>Sutured human amniotic membrane graft</td>
<td>Medical therapy, Bandage contact lens</td>
<td>Symptoms, Morbid events, Functional outcomes, Quality of life</td>
</tr>
<tr>
<td>With ophthalmic disorders other than neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects</td>
<td>Sutured human amniotic membrane graft</td>
<td>Medical therapy, Bandage contact lens</td>
<td>Symptoms, Morbid events, Functional outcomes, Quality of life</td>
</tr>
<tr>
<td>With ophthalmic conditions</td>
<td>Human amniotic membrane without suture</td>
<td>Medical therapy, Bandage contact lens</td>
<td>Symptoms, Morbid events, Functional outcomes, Quality of life</td>
</tr>
</tbody>
</table>

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.
Diabetic Lower-Extremity Ulcers
For individuals who have nonhealing diabetic lower-extremity ulcers who receive patch or flowable formulation of HAM (AmnioBand Membrane, Biovance, Epifix, Grafix), the evidence includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on amniotic and placental membrane products for the treatment of nonhealing (<20% healing with ≥2 weeks of standard care) diabetic lower-extremity ulcers includes several RCTs that compared HAM to standard care or to an established advanced wound care product. These industry-sponsored studies used wound closure as the primary outcome measure, and some used power analysis, blinded assessment of wound healing, and intention-to-treat analysis. For the HAM products that have been sufficiently evaluated (AmnioBand Membrane, Biovance, Epifix, Grafix), results have shown improved outcomes compared to 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 patch or flowable formulation of HAM, the evidence includes two RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of venous lower extremity ulcers includes 2 multicenter RCTs with EpiFix. One RCT reported larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure did not differ between EpiFix and standard of care. A second multicenter RCT reported a significant difference in complete healing at 12 weeks, but interpretation is limited by methodologic concerns. Well designed and well conducted RCTs that compare HAM with standard care 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 injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid, the evidence includes a feasibility study. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The pilot study was in preparation for a larger RCT of HAM injection. Additional trials, which will have a larger sample sizes 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 injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes 2 small RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, 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**

For individuals who have neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects who receive sutured HAM graft, the evidence includes several RCTs and a technology assessment. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The most widely studied condition with a technology assessment of RCT evidence is the use of HAM following pterygium repair. The technology assessment concluded, based on 4 RCTs, that conjunctival or limbal autograft was more effective than HAM. An RCT evaluating HAM for refractory neurotrophic corneal ulcers found that outcomes following HAM graft were similar to conventional therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ophthalmic disorders other than neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects who receive sutured HAM graft, the evidence includes 2 RCTs and a systematic review that included 1 RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A 2012 Cochrane review found a single RCT on HAM graft for acute ocular burns. The trial suggested a benefit in the healing rate for ocular burns, but it was considered at high or uncertain risk of bias due to unequal baseline scores and the lack of masking of the treatment condition. A trial assessing HAM for the treatment of bullous keratopathy reported no difference in clinical outcomes between HAM and stromal puncture. RCTs are needed to evaluate the benefit of HAM for these other indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ophthalmic conditions who receive HAM without suture, the evidence includes 1 within-subject comparative study and case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Traditionally, amniotic membrane has been sutured onto the eye for a variety of severe ocular surface disorders. The Prokera device is novel because it has a ring around the cryopreserved HAM allograft that permits it to be inserted under topical anesthesia, similar to insertion of a contact lens, allowing for more widespread use. Use of Prokera has been reported for refractory ulcerative keratitis, neurotrophic keratitis, recurrent epithelial erosion, high-risk corneal grafts, acute chemical and thermal burns, acute Stevens-Johnson syndrome, necrotizing scleritis, and limbal stem cell deficiency. Current evidence on use of the Prokera device is limited. While the case series reported generally positive effects, the prospective comparative trial found no benefit of HAM compared to a bandage contact lens for healing a wound after photorefractive keratectomy. RCTs
are needed to determine whether HAM improves healing for the various ophthalmic disorders. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2017 supports that the following indications provide a clinically meaningful improvement in net health outcome and are consistent with generally accepted medical practice.

- Use of sutured human amniotic membrane (also described as amniotic membrane graft [AMG]) for individuals with:
  - Neurotrophic keratitis
  - Corneal ulcers and melts
  - Following pterygium repair
  - Stevens-Johnson syndrome, and
  - Persistent epithelial defects.

Thus, the above indications may be considered medically necessary considering the suggestive evidence and clinical input support.

However, the clinical input does not support whether the following indications provide a clinically meaningful improvement in the net health outcome or are consistent with generally accepted medical practice.

- Use of sutured AMG for individuals with
  - Corneal perforation
  - Bullous keratopathy
  - Limbus stem cell deficiency, and
  - Severe dry eye.

Thus, the above indications may be considered investigational.

The clinical input also does not support whether the following indication provides a clinically meaningful improvement in the net health outcome or is consistent with generally accepted medical practice:

- Use of sutureless AMG (eg, Prokera) instead of sutured AMG.

Thus, the above indication may be considered investigational.

**Background**

Human amniotic membrane (HAM) consists of 2 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).

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 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, 1 d-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, proteins and 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, lubrican, cholesterol, and cytokines. Injection of amniotic fluid or amniotic fluid–derived cells is currently being evaluated for the treatment of osteoarthritis and plantar fasciitis.

Amniotic membrane and amniotic fluid are also being investigated as sources of pluripotent stem cells. 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 separate policy.

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

<table>
<thead>
<tr>
<th>Product (Supplier)</th>
<th>Preparation</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cryopreserved, Amnion</td>
<td>Chorion Amniotic Umbilical</td>
</tr>
<tr>
<td>Product (Supplier)</td>
<td>Preparation</td>
<td>Components</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>Dehydrated, or Extracted</td>
<td>Fluid</td>
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<tr>
<td><strong>Patch</strong></td>
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</tr>
<tr>
<td>Affinity™ (NuTech Medical)</td>
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<td>X</td>
</tr>
<tr>
<td>AlloWrap™ (AlloSource)</td>
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<td>X</td>
</tr>
<tr>
<td>AmbioDisk® (IOP Ophthalmics)</td>
<td>D</td>
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</tr>
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<td>AmbioDry5® (IOP Ophthalmics)</td>
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<td></td>
</tr>
<tr>
<td>AmnioBand® Membrane (MTF Wound Care)</td>
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</tr>
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<td>AmnioClear™ (Liventa Bioscience)</td>
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<td>X</td>
</tr>
<tr>
<td>AmnioExcel® (Derma Sciences)</td>
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</tr>
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<td>AmnioFix® (MiMedx)</td>
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<td>AmnioGraft® (BioTissue)</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Artacent® Wound (Tides Medical)</td>
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</tr>
<tr>
<td>BioDDryFlex® (BioD)</td>
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<td>BioDfence™ (BioD)</td>
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<td>BioRenew 200 (HRT)a</td>
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</tr>
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<td>BioSkin (thin - 45 microns, HRT)a</td>
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</tr>
<tr>
<td>BioSkin (thick - 200 microns, HRT)a</td>
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</tr>
<tr>
<td>Biovance® (Aliqual Biomedical)</td>
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</tr>
<tr>
<td>Clarix® (Amniox Medical)</td>
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<tr>
<td>Cygnus (Vivex Biomedical)</td>
<td>D</td>
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<td>Cygnus Max (Vivex Biomedical)</td>
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<td>EpiCord™ (MiMedx)</td>
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<td>EpiFix® (MiMedx)</td>
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<td>Dermavest™ (Aedicell)a</td>
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<td>Grafix® (Osiris)</td>
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<td>Guardian/AmnioBand® (MTF Wound Care)</td>
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<td>Neox® 100 (Amniox Medical)</td>
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<td>Neox® Cord (Amniox Medical)</td>
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<td>Neox® Wound Allograft (Amniox Medical)</td>
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<td>Prokera® (Bio-Tissue)</td>
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</tr>
<tr>
<td>Revitalon™ (Medline Industries)</td>
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<tr>
<td>WoundEx® 45 (Skye Biologics)a</td>
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<td>WoundEx® 200 (Skye Biologics)a</td>
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<td><strong>Suspension, particulate, or extraction</strong></td>
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<td>AmnioBand® Particulate (MTF Wound Care)</td>
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<td>AmnioMatrix® (Derma Sciences)</td>
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<tr>
<td>AmnioVisc™ (Lattice Biologics)</td>
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<td>X</td>
</tr>
<tr>
<td>BioSkin® Flow (HRT)b</td>
<td>E</td>
<td>X</td>
</tr>
<tr>
<td>Clarix® Flo (Amniox Medical)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>Interfyl™ (Alliqua Biomedical)</td>
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</tr>
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<td>Neox® Flo (Amniox Medical)</td>
<td>C</td>
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</tr>
<tr>
<td>OrthoFlo™ (MiMedx)</td>
<td>D</td>
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<tr>
<td><strong>Addendum</strong></td>
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<td>Product (Supplier)</td>
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<td>Components</td>
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</tr>
<tr>
<td>PalinGen® Flow (Amnio ReGen Solutions)</td>
<td>C</td>
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<tr>
<td>PalinGen® SportFlow (Amnio ReGen Solutions)</td>
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<td>X</td>
</tr>
<tr>
<td>ProMatrX™ ACF (Amnio ReGen Solutions)</td>
<td>C</td>
<td>X</td>
</tr>
<tr>
<td>ReNu™ (NuTech Medical)</td>
<td>D</td>
<td>X</td>
</tr>
<tr>
<td>WoundEx® Flow (Skye Biologics)</td>
<td>E</td>
<td>X</td>
</tr>
</tbody>
</table>

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

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

AmnioClip (FORTECH GmbH) is a ring designed to hold 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.

**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 (CFR) title 21, parts 1270 and 1271. Human amniotic membrane and amniotic fluid are included in these regulations.

In 2003, Prokera™ was cleared for marketing by FDA through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). FDA 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.”

**Rationale**

This evidence review was created in April 2015 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through December 11, 2017.

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

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

For conditions in which subjective measures are the primary outcomes, randomized controlled trials (RCTs) are particularly important due to the expected placebo effect and variable natural history. RCTs are also important because there may be numerous confounders of outcomes, and nonrandomized comparisons are prone to selection bias. For these reasons, RCTs are essential to demonstrate the clinical effectiveness of amniotic membrane and amniotic membrane injections compared with alternatives such as continued medical management or other established treatments (eg, Apligraf). Therefore, the products assessed in this review are those that have RCT evidence. For indications where treatment with some amniotic membrane products has been established, nonrandomized studies that include patients with similar characteristics and have similar magnitude of benefit may be considered sufficient evidence.

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

1. Incidence of complete wound closure.
2. Time to complete wound closure (reflecting accelerated wound closure).
3. Incidence of complete wound closure following surgical wound closure.
4. Pain control.

**DIABETIC LOWER-EXTREMITY ULCERS**

**Dehydrated Amniotic Membrane or Placental Membrane**

**AmnioBand vs Standard Care**

AmnioBand Membrane was compared with standard of care (SOC) for the treatment of nonhealing (minimum 4 weeks) diabetic foot ulcers in an industry-sponsored, multicenter trial by DiDomenico et al (2016).(5) Forty patients were randomized to SOC or to SOC plus weekly applications of the dehydrated placental allograft for up to 12 weeks. Healing was determined by the principal investigator at each institution and confirmed by an independent and blinded panel of 6 physicians. This study was adequately powered to detect a difference of 45% between groups in the primary outcome (the proportion of wounds healed at 6 weeks). Complete healing by 6 weeks was observed for 70% (14/20) of wounds treated with the dehydrated placental matrix compared with 15% (3/20) of
wounds treated by SOC alone (p=0.001). The odds ratio for healing was 17 (95% confidence interval [CI], 3.1 to 93; p=0.001). At 12 weeks, complete healing was observed for 85% (17/20) of wounds in the AmnioBand group compared with 25% (5/20) in the SOC group. Mean time to heal for wounds treated with amniotic membrane was 36 days (95% CI, 27 to 46 days) compared to 70 days (95% CI, 59 to 81 days; p<0.001) with standard care. The number needed to treat to achieve healing at 12 weeks was 1.7 (95% CI, 1.2 to 2.8). Strengths of this study included power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and intention-to-treat (ITT) analysis.

**AmnioExcel vs Standard Care**

AmnioExcel dehydrated human amniotic membrane (d-HAM) was compared with standard care in an industry-sponsored, open-label multicenter RCT (N=29) by Snyder et al (2016).(6) Randomization was performed by computer module and stratified by site and wound area. The primary outcome was the percentage of patients with complete wound closure at 6 weeks. The per protocol population included 11 patients in the AmnioExcel group and 10 in the SOC group. For the ITT population, 33% (95% CI, 25.0% to 46.4%) of patients in the AmnioExcel group achieved wound closure by 6 weeks compared to 0% of the SOC group (p=0.017). In the per protocol analysis, 45.5% of patients treated with AmnioExcel achieved wound closure by 6 weeks compared to 0% in the SOC arm (p=0.008) with a 95% confidence interval of the responder ratio of 32.9% to 58.0% (p=0.014). Power analysis was not described and 8 patients withdrew early (4 in each group), raising questions about the reliability of the effect size.

**Biovance Registry**

In 2015, Smiell et al reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types, including 47 diabetic foot wounds, 20 pressure ulcers, and 89 venous ulcers.(7) This study showed the effectiveness of d-HAM in a real-world setting. The size of the wounds at baseline ranged from less than 2 cm² (35.4% of wounds) to over 25 cm² (9.0% of wounds). Ninety-eight percent were on the lower extremities. Twenty-eight ulcers had failed prior treatment with advanced biologic therapies (Apligraf, Dermagraft, or Regranex), including 10 diabetic foot wounds. For all wound types, 41.6% closed, with a mean time to closure of 8 weeks and a mean of 2.4 amniotic membrane applications. In the subgroup of 112 patients who practiced good wound care, including offloading or compression therapy as indicated, 49.6% of wounds closed by a mean of 7.4 weeks. Wounds that had not closed during the observation period decreased in size by a mean of 46.6%.

**EpiFix vs Standard Care**

In 2013, Zelen et al reported an industry-sponsored, nonblinded, RCT comparing use of EpiFix d-HAM (n=13) with SOC (n=12) for diabetic foot ulcers of at least 4 weeks in duration.(8) EpiFix was applied every 2 weeks if the wound had not healed, with weekly dressing changes comprised of nonadherent dressing, moisture retentive dressing, and a compression dressing. Standard moist wound dressing was changed daily. After 4 weeks of treatment, EpiFix-treated wounds
had reduced in size by a mean of 97% compared with 32% for the SOC group. Healing rate, defined as complete epithelialization of the open area of the wound, was 77% for EpiFix compared with 0% for SOC. After 6 weeks of treatment, wound sizes were reduced by 98.4% with EpiFix treatment compared with -1.8% for SOC. The healing rate was 92% with EpiFix compared with 8% with SOC alone. At trial conclusion, unhealed wounds from the control group were treated with EpiFix.(9) The mean duration of foot ulcers at the beginning of treatment was 19.4 weeks (range, 6.0-54 weeks) for the combined group. Follow-up was available at 9 to 12 months after primary healing in 18 of 22 eligible patients. Examination of these 18 patients found that 17 (94.4%) wounds remained fully healed.

_EpiFix vs Apligraf_

EpiFix d-HAM was compared with Apligraf (living cell therapy) in a multicenter RCT published by Zelen et al (2015).(10) Sixty patients with less than 20% wound reduction during a 2 week run-in period were randomized to treatment with EpiFix, Apligraf, or standard wound care. Although patients and site investigators could not be blinded due to differences in products, wound healing was verified by 3 independent physicians who evaluated photographic images. Median wound size was 2.0 cm² (range, 1.0-9.0 cm²) and median duration of the index ulcer was 11 weeks (range, 5-54 weeks). After 6 weekly treatments, the mean percent wound area healed was 97.1% for EpiFix, 80.9% for Apligraf, and 27.7% for SOC; 95% of wounds had healed completely in the EpiFix group compared with 45% treated with Apligraf and 35% who received standard wound care (p=0.003). The estimated median time to wound closure, based on Kaplan-Meier analysis, was 13 days for EpiFix compared with 49 days for both Apligraf and SOC (p<0.001).

In 2015, Kirsner et al reported an industry-sponsored observational study comparing the effectiveness of Apligraf and EpiFix in a real-world setting.(11) Data were obtained from a wound care–specific database from 3000 wound care facilities. The database included 1458 diabetic ulcers treated for the first time in 2014 with Apligraf (n=994) or EpiFix (n=464). Using the same criteria as the 2015 study by Zelen (described above), data were included on the treatment of 226 diabetic foot ulcers from 99 wound care centers. Selection criteria for foot wounds included size between 1 cm² and 25 cm², duration of 1 year or less, and wound reduction of 20% or less in the 14 days prior to treatment. Although wounds for the 2 groups were comparable at baseline, the rationale for using a particular product was not reported. One hundred sixty-three wounds were treated with Apligraf (mean, 2.5 applications) and 63 were treated with EpiFix (mean, 3.5 applications, p=0.003). By week 24, 72% of wounds treated with Apligraf and 47% of wounds treated with EpiFix had closed (p=0.01). Median time to closure was 13.3 weeks for Apligraf and 26.0 weeks for EpiFix (p=0.01). This study is at risk of selection bias in determining treatment assignment.

_Cryopreserved Placental Membrane_

_Grafix vs Standard Care_

Grafix cryopreserved placental membrane was compared with standard wound care in a 2014 multicenter RCT.(12) Strengths of this trial included power analysis,
blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and ITT analysis. Ninety-seven patients with chronic diabetic foot ulcers were randomized to Grafix or to standard wound therapy, both administered once a week for up to 12 weeks. Power analysis indicated that 94 patients per arm would be needed. However, after prespecified interim analysis at 50% enrollment, the blinded review committee recommended that the trial be stopped due to efficacy of the treatment. ITT analysis from the blinded evaluation phase showed a significant increase in the proportion of patients achieving the primary outcome of wound closure by 12 weeks (62.0% vs 21.3%, p<0.001) and a decrease in the median time to complete wound closure (42.0 days vs 69.5 days, p=0.019). Safety evaluation found that fewer Grafix-treated patients experienced at least 1 adverse event (44.0% vs 66.0%, p=0.031) or had wound-related infections (18.0% vs 36.2%, p=0.044), with a trend toward fewer hospitalizations related to infections (6% vs 15%, p=0.15).

**Section Summary: Diabetic Lower-Extremity Ulcers**

The evidence on amniotic and placental membrane products for the treatment of diabetic lower-extremity ulcers includes several RCTs compared HAM to SOC or to an established advanced wound care product. All of these industry-sponsored studies included evaluation of wound closure as the primary outcome measure, and some included power analysis, blinded assessment of wound healing, and ITT analysis. For the amniotic membrane products evaluated in RCTs (eg, AmnioBand Membrane, EpiFix, Grafix), results indicated improved outcomes compared to SOC, and outcomes that are at least as good as the advanced wound care product Apligraf. In addition, a registry study for Biovance showed improved health outcomes, with a magnitude of benefit similar to that observed in the RCTs for other products.

**LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY**

**Dehydrated Amniotic Membrane**

**EpiFix**

In 2014, Serena et al reported on an industry-sponsored multicenter open-label RCT that compared EpiFix d-HAM plus compression therapy to compression therapy alone for venous leg ulcers (see Table 1).(13) The primary outcome in this study 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 groups compared to the control group (see Table 2). However, a similar percentage of patients in the combined EpiFix group the control group achieved complete wound closure during the 4 week study. There was no significant difference in healing for wounds given 1 versus 2 applications of amniotic membrane (62% vs 63%, respectively). Strengths of this study 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.\(^{(14)}\)

A second industry-sponsored multicenter open-label RCT of EpiFix d-HAM (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 1).\(^{(15)}\) Patients treated with EpiFix had a higher probability of complete healing by 12 weeks adjudicated by blinded outcome assessors (HR=2.26; 95% CI, 1.25 to 4.10; \(p=0.01\)) and improved time to complete healing 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 2). There were several limitations of this study. Nineteen (15\%) patients were excluded from analysis and the proportion of patients excluded differed between the 2 groups. The 19 excluded patients comprised 19\% of patients from the EpiFix group and 11\% of patients from the control group. In addition, the study did not use ITT analysis. If all excluded patients had been considered treatment failures, the difference between groups would be reduced to 17\% (48\% wound healing for EpiFix vs 31\% for controls). There was also a difference between the groups in how treatment failures at 8 weeks were handled. Patients in the control group who did not have a 40\% decrease in wound area at 8 weeks were considered study failures and treated with advanced wound therapies. Although the authors 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 also have been considered treatment failures at 8 weeks.

Table 2. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participa tions</th>
<th>Active</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serena et al (2014)13</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 cm(^2) treated for at least 14 d</td>
<td>1 (n=26) or 2 (n=27) applications of EpiFix plus compression (n=53)</td>
<td>Compression therapy alone (n=31)</td>
</tr>
<tr>
<td>Bianchi et al (2017)15</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>
<td>Moist wound therapy plus compression (n=64; 57 analyzed)</td>
</tr>
</tbody>
</table>

VLU: venous leg ulcer.

Table 3. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent with 40% Wound Closure at 4</th>
<th>Percent With Complete Wound</th>
<th>Percent With Complete Wound Closure</th>
<th>Percent With Complete Wound Closure</th>
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<tbody>
<tr>
<td></td>
<td>Weeks</td>
<td>Closure at 4 Weeks</td>
<td>at 12 Weeks</td>
<td>at 16 Weeks</td>
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<td>----------------</td>
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<tr>
<td>Serena et al (2014)13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EpiFix</td>
<td>62%</td>
<td>11.3%</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</td>
<td></td>
<td>0.005</td>
<td></td>
<td></td>
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<tr>
<td>Bianchi et al (2017)15</td>
<td></td>
<td></td>
<td></td>
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</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</td>
<td>0.013</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR: not reported; VLU: venous leg ulcer.

**Biovance**

As described above, in 2015, Smiell et al 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.(7) 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 SOC is unknown.

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

Well designed and well conducted RCTs that compare HAM with standard care for venous lower extremity ulcers, that evaluate the outcome of complete wound closure, are needed to demonstrate efficacy. The evidence on HAM for the treatment of venous leg ulcers includes 2 multicenter RCTs with EpiFix. The 2014 RCT by Serena reported a larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure at 4 weeks did not differ between EpiFix and standard of care. A 2017 study by Bianchi et al evaluated complete wound closure at 12 weeks following weekly application of EpiFix or standard dressings with compression. Although a significant difference in complete healing was reported, interpretation is limited by the differential loss to follow-up and exclusions, and the lack of ITT analysis. Corroboration with well designed and well conducted RCTs that evaluate wound healing is needed to demonstrate efficacy. The corroborating RCTs should report intention-to-treat 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 human amniotic membrane (c-HAM) suspension with amniotic fluid-derived cells (ReNu) for the treatment of knee osteoarthritis was reported in 2016.(16) 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
Statistical analyses were not performed for this small sample. No adverse effects, aside from a transient increase in pain, were noted. An RCT is in progress.

**PLANTAR FASCIITIS**

One systematic review and 2 randomized pilot studies were identified on the treatment of plantar fasciitis using injection of micronized HAM.

**Systematic Review**

A 2016 network meta-analysis of 22 RCTs (total N=1216 patients) compared injection therapies for plantar fasciitis.(17) In addition to c-HAM and micronized d-HAM/chorionic membrane, treatments included corticosteroids, botulinum toxin type A, autologous whole blood, platelet-rich plasma (PRP), nonsteroidal anti-inflammatory drugs, dry needling, dextrose prolotherapy, and polydeoxynucleotide. Placebo arms included normal saline, local anesthetic, sham dry needling, and tibial nerve block. The minimum clinically important difference (MCID) was defined as \(-9\) mm on a visual analog scale (VAS), which is substantially lower than the 30% or 20-mm decrease in VAS score for pain more typically used. Secondary outcomes included total and subscores for the Foot Health Status Questionnaire (FHSQ), with an MCID defined as 7 on the FHSQ function and 9 on the FHSQ general foot health subscales. Overall, risk of bias was low for randomization and blinding of participants, high for blinding of personnel, and uncertain for allocation concealment and outcome reporting. Analysis found d-HAM had the highest probability for improvement in pain and composite outcomes in the short term. However, this finding was based only on 1 RCT. When the efficacy of d-HAM was compared to corticosteroid injections, the mean difference in VAS score was a modest at \(-7.32\) out of 100 (95% CI, \(-11.2\) to \(-3.38\)) and the mean difference in the FHSQ score was 31.2 (95% CI, 13.9 to 48.6). Outcomes at 2-to-6 months (7 RCTs) favored botulinum toxin for pain and PRP for composite outcomes.

**Clarix Flo**

One small (N=23), industry-sponsored, double-blind study (2015) found similar improvements with injection of c-HAM (Clarix Flo) compared with corticosteroid injection.(18) Another industry-sponsored, patient-blinded study (2013) by Zelen et al (N=45) compared injection of saline to d-HAM (AmnioFix) 0.5 mL or 1.25 mL in patients with symptoms recalcitrant to conservative treatment.(19) In the 2 d-HAM groups, scores on the American Orthopaedic Foot and Ankle Society hindfoot scale improved by about 50 points over the 8 weeks of the study compared with 10 points for controls (p<0.001). FACES pain scores decreased from 8.7 out of 10 at baseline to 0.8 at 8 weeks with d-HAM, compared with a decrease from 8.0 to 4.6 for controls (p<0.001). Longer follow-up is ongoing.

**Section Summary: Plantar Fasciitis**

The evidence on injection of particulated amniotic membrane and amniotic fluid for the treatment of plantar fasciitis is limited. Evidence includes a small (N=23) double-blind comparison with corticosteroid and a patient-blinded (N=45) comparison of 2 different doses of d-HAM with saline. Power analyses were not reported. A network meta-analysis, which identified only the Zelen et al trial,
concluded that d-HAM was more effective than corticosteroid. However, these 2 small trials are not sufficient to demonstrate an improvement in health outcomes for this common condition. Additional study in a larger number of patients is needed to demonstrate consistency in results.

SUTURED HAM GRAFT FOR OPHTHALMOLOGIC CONDITIONS
Sutured HAM graft has been evaluated for a variety of ophthalmologic conditions.

**Neurotrophic Keratitis**
In 2005, Khokhar and Natung reported on an RCT of 30 patients (30 eyes) with refractory neurotrophic corneal ulcers who were randomized to HAM transplantation (n=15) or to conventional treatment with tarsorrhaphy or bandage contact lens. At the 3-month follow-up, 11 (73.3%) of 15 patients in the HAM group showed complete epithelialization compared to 10 (66.7%) of 15 in the conventional group. This difference was not significantly significant.

**Following Pterygium Repair**
A number of RCTs have been reported on use of amniotic membrane following pterygium repair. In 2013, the American Academy of Ophthalmology published a technology assessment on options and adjuvants for pterygium surgery. Reviewers identified 4 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.

**Stevens-Johnson Syndrome**
One RCT from India (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or to 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), tear breakup time (p=0.015), 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 compared dramatically with the medical therapy alone group, which had 11 (44%) of 25 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.

**Persistent Epithelial Defects and Ulceration**
In 2004, Bouchard and John wrote a review 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 rarity of the diseases and the absence of a 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.

**Ocular Burns**
A 2012 Cochrane review evaluated the evidence on HAM graft for acute ocular burns.(25) Included in the review was a single RCT from India of 68 patients with acute ocular burns who were randomized to c-HAM plus medical therapy or to medical therapy alone. In the subset of 36 patients with moderate ocular burns treated within 7 days, 13 (65.0%) of 20 control eyes and 14 (87.5%) of 16 AMT-treated eyes had complete epithelialization by 21 days. There was a trend (p=0.09) toward a reduced relative risk of failure of epithelization in the treatment group. Mean logarithm of the minimum angle of resolution (logMAR) final visual acuities were 0.06 in the treatment group and 0.38 in the control group. In the subset of patients with severe ocular burns treated within 7 days, 1 (5.9%) of 17 AMT-treated eyes and 1 (6.7%) of 15 control eyes were epithelialized by day 21. There was no significant difference in final visual acuity, which was 1.77 logMAR in the treated eyes and 1.64 in the control group (p=NS). The risk of bias was considered high because of differences between the groups at baseline and because outcome assessors could not be masked to treatment. Reviewers determined that conclusive evidence supporting the treatment of acute ocular surface burns with AMT is lacking.

**Bullous Keratopathy**
Bullous keratopathy is characterized by stromal edema and epithelial and subepithelial bulla formation. In 2013, Dos Santos Paris et al published an RCT that compared fresh HAM to stromal puncture for the management of pain in patients with bullous keratopathy.(26) 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 2 treatments. Symptoms had been present for approximately 2 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 use of HAM only if pain did not resolve.

**Dry Eye Syndrome, Corneal Perforation, and Limbus Stem Cell Deficiency**
No RCTs were identified on these other ophthalmic indications.

**Section Summary: Sutured HAM Graft for Ophthalmic Conditions**
The most widely studied condition with a technology assessment evaluating RCT evidence is use of HAM following pterygium repair. The assessment concluded, based on 4 RCTs, that conjunctival or limbal autograft was more effective than HAM. An RCT on HAM for refractory neurotrophic corneal ulcers found that outcomes following HAM graft were similar to those for conventional therapy. One RCT has shown that application of c-HAM in the early stages of Stevens-Johnson syndrome leads to clinically significant improvement compared to medical therapy alone. A 2012 Cochrane review found 1 RCT evaluating HAM graft for acute ocular
burns. The trial suggested a benefit for HAM in the healing rate for ocular burns, but it was considered at high or uncertain risk of bias due to unequal baseline scores and lack of masking to treatment condition. A trial on HAM for the treatment of bullous keratopathy reported that there was no difference in clinical outcomes between HAM and stromal puncture. Other indications have been studied only in case series.

**HAM WITHOUT SUTURE FOR OPHTHALMIC CONDITIONS**

Traditionally, 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 c-HAM allograft that allows it to be inserted under topical anesthesia similar to insertion of a contact lens. The easier insertion may lead to more widespread use, such as dry eye disease and for healing after photorefractive keratectomy (PRK). The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

**Dry Eye Disease**

John et al (2017) reported an RCT with 20 patients with moderate to severe dry eye disease who were treated with Prokera c-HAM or maximal conventional treatment.(27) 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 1-month and 3-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 3 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 Prokera c-HAM device was evaluated in a 2016 series by Cheng et al.(28) The senior author of the study (S.C.G. Tseng) holds the patent on Prokera. This retrospective review assessed 10 patients treated with the self-retained device for moderate-to-severe dry eye disease. In this study, these 10 patients had moderate-to-severe dry eye syndrome despite conventional medical treatment. The c-HAM device was placed in 15 eyes (1 eye at a time) for a mean of 4.9 days (range, 2-8 days), after which the c-HAM was either dissolved or cloudy. Treatment resulted in symptomatic relief for a mean of 4.2 months (range, 0.3 to 6.8 months) after a single treatment. Symptomatic improvement was accompanied by statistically significant reductions of Ocular Surface Disease Index scores, use of topical medications, conjunctival hyperemia, corneal staining (all p<0.001), and a trend toward improved visual acuity (p=0.06).

**Photorefractive Keratectomy**

In 2016, Vlasov et al reported on a prospective, nonrandomized controlled trial evaluating the effect of sutureless amniotic membrane (Prokera) on corneal wound
healing after PRK.(29) Forty patients (80 eyes) had PRK for myopia. After surgery, a high-oxygen-transmissible bandage contact lens was applied on the dominant eye and cryopreserved amniotic membrane on the nondominant eye. Patients were assessed daily until complete corneal re-epithelialization occurred in both eyes and then at 2 weeks and 1, 3, 6, and 12 months thereafter. The primary outcome was re-epithelialization, which was assessed daily with slitlamp examination, fluorescein staining, and photography. The time to complete reepithelization was faster in eyes treated with a bandage contact lens (3.7 days; range, 3-7 days) than with the amniotic membrane product (4.6 days; range, 3-16 days). Initially, patients reported greater discomfort and dryness with amniotic membrane. Visual and clarity and optical quality of the cornea were similar between the amniotic membrane graft eyes and bandage contact lens eyes.

Other
Use of Prokera has also been reported for refractory ulcerative keratitis, neurotrophic keratitis, recurrent epithelial erosion, high-risk corneal grafts, acute chemical and thermal burns, acute Stevens-Johnson syndrome, necrotizing scleritis, and limbal stem cell deficiency (referenced in Cheng et al, 2016).28

Section Summary: HAM Without Suture for Ophthalmic Conditions
Current evidence on use of the Prokera device includes an RCT with 20 patients, a within-subject comparative study, and case series. While the studies reported generally positive effects, high-quality RCTs are needed to determine the effect of sutureless self-contained HAM on corneal healing. The RCT with 20 patients found a benefit of Prokera in patients with dry eye disease, but the prospective comparative trial identified found no benefit of HAM compared to a bandage contact lens when used for wound healing after PRK. Larger RCTs are needed to determine whether HAM improves healing for these various disorders.

SUMMARY OF EVIDENCE
Diabetic Lower-Extremity Ulcers
For individuals who have nonhealing diabetic lower-extremity ulcers who receive patch or flowable formulation of HAM (AmnioBand Membrane, Biovance, Epifix, Grafix), the evidence includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The RCTs evaluating amniotic and placental membrane products for the treatment of nonhealing (<20% healing with ≥2 weeks of standard care) diabetic lower-extremity ulcers have compared HAM to standard care or to 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 intention-to-treat analysis. For the HAM products that have been sufficiently evaluated (AmnioBand Membrane, Biovance, Epifix, Grafix), results have shown improved outcomes compared to 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 patch or flowable formulation of HAM, the evidence includes two RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of venous lower extremity ulcers includes 2 multicenter RCTs with EpiFix. One RCT reported larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure did not differ between EpiFix and standard of care. A second multicenter RCT reported a significant difference in complete healing at 12 weeks, but interpretation is limited by methodologic concerns. Well designed and well conducted RCTs that compare HAM with standard care 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 injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes a feasibility study. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The pilot study was for a precursor to a larger RCT of HAM injection. Additional trials, which will have a larger sample sizes 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 injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes 2 small RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, 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**
For individuals who have neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects who receive sutured HAM graft, the evidence includes several RCTs and a technology assessment. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The most widely studied condition with a technology assessment of RCT evidence is the use of HAM following pterygium repair. The technology assessment concluded, based on 4 RCTs, that conjunctival or limbal autograft was more effective than HAM. An RCT evaluating HAM for refractory neurotrophic corneal ulcers found that outcomes following HAM graft were similar
to conventional therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ophthalmic disorders other than neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, or persistent epithelial defects who receive sutured HAM graft, the evidence includes 2 RCTs and a systematic review that included 1 RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A 2012 Cochrane review found a single RCT on HAM graft for acute ocular burns. The trial suggested a benefit in the healing rate for ocular burns, but it was considered at high or uncertain risk of bias due to unequal baseline scores and the lack of masking of the treatment condition. A trial assessing HAM for the treatment of bullous keratopathy reported no difference in clinical outcomes between HAM and stromal puncture. RCTs are needed to evaluate the benefit of HAM for these other indications. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have ophthalmic conditions who receive HAM without suture, the evidence includes an RCT with 20 patients, a within-subject comparative study, and case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Traditionally, amniotic membrane has been sutured onto the eye for a variety of severe ocular surface disorders. The Prokera device is novel because it has a ring around the cryopreserved HAM allograft that permits it to be inserted under topical anesthesia, similar to insertion of a contact lens, allowing for more widespread use. Use of Prokera has been reported for refractory dry eye syndrome, ulcerative keratitis, neurotrophic keratitis, recurrent epithelial erosion, high-risk corneal grafts, acute chemical and thermal burns, acute Stevens-Johnson syndrome, necrotizing scleritis, and limbal stem cell deficiency. Current evidence on use of the Prokera device is limited. While the small RCT and case series reported generally positive effects, the prospective comparative trial found no benefit of HAM compared to a bandage contact lens for healing a wound after photorefractive keratectomy. RCTs are needed to determine whether HAM improves healing for the various ophthalmic disorders. The evidence is insufficient to determine the effects of the technology on health outcomes.

A review of the literature has shown that amniotic membrane has been used for nearly 2 decades for ophthalmic disorders, although RCT evidence is limited. Therefore, clinical input was requested in 2017 on the specific disorders for which amniotic membrane would be expected to improve health outcomes and use is consistent with generally accepted medical practice. Input supported the use of sutured or glued amniotic membrane for neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Those providing input had low confidence that sutureless amniotic membrane performed as well or better than sutured amniotic membrane.
CLINICAL INPUT

OBJECTIVE
In 2017, clinical input was sought to help determine the appropriate use in clinical practice of human amniotic membrane (also referred to as amniotic membrane graft [AMG]) for ophthalmic disorders.

RESPONDENTS
Clinical input was provided on behalf of the American Academy of Ophthalmology (AAO) by Dr. David Glasser, Chair of AAO’s Health Policy Committee.

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

With regard to the 9 indications listed above, there was lower range confidence that there is adequate evidence demonstrating that sutureless fixation HAM (also called amniotic membrane graft [AMG]) (eg, Prokera, AmbioDisk) performs as well as or better than sutured or glued AMG.

Use of AMG would be expected to improve health outcomes and is considered consistent with generally accepted medical practice for:

- “patients with an epithelial defect that (1) has failed to completely close after 5 days of conservative treatment (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 AMG. AMG 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.”
- “We are in agreement that larger controlled studies are needed to show benefit of AMG in dry eye disease, where the disease is common and such studies should be easy to perform.”
SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS
No guidelines or statements were identified.

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 2.

Table 4. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02318511a</td>
<td>An Investigation of ReNu™ Knee Injection: Monitoring the Response of Knee Function and Pain in Patients With Osteoarthritis</td>
<td>200</td>
<td>Mar 2018</td>
</tr>
<tr>
<td>NCT02609594a</td>
<td>A Multi-center Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Amnioband Dehydrated Human Amniotic Membrane and Standard of Care vs. Standard of Care Alone in the Treatment of Venous Leg Ulcers</td>
<td>240</td>
<td>Nov 2018</td>
</tr>
<tr>
<td>NCT02880592a</td>
<td>A Multi-center, Randomized Controlled Clinical Trial Evaluating the Effect of Fresh Amniotic Membrane in the Treatment of Diabetic Foot Ulcers</td>
<td>100</td>
<td>Nov 2018</td>
</tr>
<tr>
<td>NCT02427191a</td>
<td>A Prospective, Single-Blinded, Randomized Controlled Trial of the Micronized dHACM Injection as Compared to the Saline Placebo Injection in the Treatment of Plantar Fasciitis (AmnioFix Injectable)</td>
<td>146</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02838784a</td>
<td>The Efficacy and Safety of Artacent™ for Treatment Resistant Lower Extremity Venous and Diabetic Ulcers: A Prospective Randomized Study</td>
<td>134</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT03379324a</td>
<td>A Prospective, Randomized Study Comparing Outcomes Following Arthroscopic Double-row Rotator Cuff Repair With and Without the Addition of a Cryopreserved, Liquid, Injectable Amnion Allograft</td>
<td>260</td>
<td>Sep 2019</td>
</tr>
<tr>
<td>NCT02322554</td>
<td>The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers</td>
<td>50,000</td>
<td>Jan 2020</td>
</tr>
</tbody>
</table>
Amniotic Membrane and Amniotic Fluid 7.01.149

| NCT03390920 | Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions | 200 | Jun 2022 |

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

References:


**Billing Coding/Physician Documentation Information**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>65778</td>
<td>Placement of amniotic membrane on the ocular surface; without sutures</td>
</tr>
<tr>
<td>65779</td>
<td>Placement of amniotic membrane on the ocular surface; single layer, sutured</td>
</tr>
<tr>
<td>Q4131</td>
<td>EpiFix or Epicord, per sq cm (Code deleted 1/1/2019)</td>
</tr>
<tr>
<td>Q4132</td>
<td>Grafix Core, per sq cm</td>
</tr>
<tr>
<td>Q4133</td>
<td>Grafix Prime, per sq cm</td>
</tr>
<tr>
<td>Q4137</td>
<td>AmnioExcel or BioDExCel, per sq cm</td>
</tr>
<tr>
<td>Q4138</td>
<td>BioDFence DryFlex, per sq cm</td>
</tr>
<tr>
<td>Q4139</td>
<td>AmnioMatrix or BioDMatrix, injectable, 1 cc</td>
</tr>
<tr>
<td>Q4140</td>
<td>BioDFence, per sq cm</td>
</tr>
<tr>
<td>Q4145</td>
<td>EpiFix, injectable, 1 mg</td>
</tr>
<tr>
<td>Q4148</td>
<td>Neox 1k, per sq cm</td>
</tr>
<tr>
<td>Q4150</td>
<td>AlloWrap DS or dry, per sq cm</td>
</tr>
</tbody>
</table>
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, per sq cm
Q4157  Revitalon, per sq cm
Q4159  Affinity, per sq cm
Q4160  Nushield, per sq cm
Q4162  AmnioPro Flow, BioSkin Flow, BioRenew Flow, WoundEx Flow, Amniogen-A, Amniogen-C, 0.5 cc
Q4163  AmnioPro, BioSkin, BioRenew, WoundEx, Amniogen-45, Amniogen-200, per sq cm
Q4168  AmnioBand, 1 mg
Q4169  Artacent wound, per sq 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 (new code 1/1/2018)
Q4177  FlowerAmnioFlo, 0.1 cc (new code 1/1/2018)
Q4178  FlowerAmnioPatch, per sq cm (new code 1/1/2018)
Q4180  Revita, per sq cm (new code 1/1/2018)
Q4181  Amnio Wound, per sq cm (new code 1/1/2018)
Q4184  Cellesta, per sq cm (new code 1/1/2019)
Q4185  Cellesta Flowable Amnion (25 mg per cc); per 0.5 cc (new code 1/1/2019)
Q4186  Epifix, per sq cm (new code 1/1/2019)
Q4187  Epicord, per sq cm (new code 1/1/2019)
Q4188  AmnioArmor, per sq cm (new code 1/1/2019)
Q4189  Artacent AC, 1 mg (new code 1/1/2019)
Q4190  Artacent AC, per sq cm (new code 1/1/2019)
Q4191  Restorigin, per sq cm (new code 1/1/2019)
Q4192  Restorigin, 1 cc (new code 1/1/2019)
Q4194  Novachor, per sq cm (new code 1/1/2019)
Q4198  Genesis Amniotic Membrane, per sq cm (new code 1/1/2019)

**ICD-10 Codes**

E08.621-  Diabetes codes with foot ulcer or other skin ulcer
E08.622;
E09.621-
E09.622;
E10.621-
E10.622;
E11.621-
E11.622:
E13.621-
E13.622
H11.001-  Pterygium of eye code range
H11.069
H16.001- Corneal ulcer code range
H16.079
H16.231- Neurotrophic keratoconjunctivitis code range
H16.239
H18.831- Recurrent erosion of cornea code range
H18.839
L51.1 Stevens-Johnson syndrome

Additional Policy Key Words
N/A

Policy Implementation/Update Information
4/1/16 New Policy; considered investigational.
3/1/17 Material on patch formulations of amniotic membrane moved from policy 7.01.113 (Bioengineered Skin and Soft Tissue Substitutes). AmnioBand® Membrane, Biovance®, Epifix®, Grafix™ considered medically necessary for diabetic foot ulcers; all other products and indications are investigational. Removed "Injections" from title.
3/1/18 Sutured amniotic membrane grafts considered medically necessary for neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Sutured human amniotic membrane grafts are considered investigational for the treatment of all other ophthalmic conditions including but not limited to dry eye syndrome, burns, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy. Human amniotic membrane without suture (eg, Prokera®, AmbioDisk™) for ophthalmic indications is investigational.
3/1/19 No policy statement changes. Updated HCPCS codes with 2019 codes.

Appendix

Appendix 1: Clinical Input 2017

Appendix Table 1. Respondent Profile

<table>
<thead>
<tr>
<th>Specialty Society</th>
<th>Clinical Specialty</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Name of Organization</td>
</tr>
<tr>
<td>1</td>
<td>American Academy of Ophthalmology</td>
</tr>
</tbody>
</table>

Appendix Table 2. Respondent Conflict of Interest Disclosure

| 1. Research support related to the topic where clinical input | 2. Positions, paid or unpaid, related to the topic where | 3. Reportable, more than $1,000, health care- | 4. Reportable, more than $350, gifts or travel |
is being sought clinical input is being sought related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought

<table>
<thead>
<tr>
<th>No.</th>
<th>Yes/No</th>
<th>Explanation</th>
<th>Yes/No</th>
<th>Explanation</th>
<th>Yes/No</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Individual physician respondents answered at individual level. Specialty society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the society-level response.

Appendix 2: Clinical Input Responses

Objective
Clinical input is sought to help determine the appropriate use in clinical practice of amniotic membrane graft (AMG) for ophthalmic disorders.

Responses
1. With regard to the use of AMG in each of the following ophthalmic disorders:
   a. Please use the 1 to 5 scale outlined below to indicate your level of confidence that there is adequate evidence demonstrating that this use will improve health outcomes.

<table>
<thead>
<tr>
<th>No.</th>
<th>Ophthalmic Disorder</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neurotrophic keratitis</td>
<td>1 2 3 4 5</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corneal ulcers and melts</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corneal perforation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bullous keratopathy</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Following pterygium repair</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limbal stem cell deficiency</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stevens-Johnson syndrome</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent epithelial defects</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe dry eye</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. With regard to the use of AMG in each of the following ophthalmic disorders:
   a. Please use the 1 to 5 scale outlined below to indicate your level of confidence that this clinical use is in accordance with generally accepted medical practice.

<table>
<thead>
<tr>
<th>No.</th>
<th>Ophthalmic Disorder</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neurotrophic keratitis</td>
<td>1 2 3 4 5</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corneal ulcers and melts</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corneal perforation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bullous keratopathy</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Following pterygium repair</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limbal stem cell deficiency</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stevens-Johnson syndrome</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent epithelial defects</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe dry eye</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. With regard to the use of AMG in each of the following ophthalmic disorders:

a. Please use the 1 to 5 scale outlined below to indicate your level of confidence that there is adequate evidence demonstrating that **sutureless fixation AMG** (eg, Prokera) performs as well as or better than sutured or glued AMG.

<table>
<thead>
<tr>
<th>No.</th>
<th>Ophthalmic Disorder</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neurotrophic keratitis</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corneal ulcers and melts</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corneal perforation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bullous keratopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Following pterygium repair</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Limbal stem cell deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stevens-Johnson syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent epithelial defects</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Severe dry eye</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. For individuals with **persistent epithelial defects**, what objective condition characteristics (ie, patient selection criteria) and management criteria (ie, regarding prior trial of standard treatment options) would describe use of AMG that improves health outcomes and is considered in accordance with generally accepted medical practice?

<table>
<thead>
<tr>
<th>No.</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patients with an epithelial defect that</td>
</tr>
<tr>
<td></td>
<td>1. has failed to completely close after 5 days of conservative treatment</td>
</tr>
<tr>
<td></td>
<td>2. has failed to demonstrate a decrease in size after 2 days of conservative treatment</td>
</tr>
<tr>
<td></td>
<td>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 AMG.</td>
</tr>
<tr>
<td></td>
<td>AMG requires less effort on the part of the patient to adhere to a treatment regimen and</td>
</tr>
</tbody>
</table>
has a significant advantage in that regard over treatments that require multiple drops per day.

5. For individuals with **severe dry eye**, what objective condition characteristics (ie, patient selection criteria) and management criteria (ie, regarding prior trial of standard treatment options) would describe use of AMG that improves health outcomes and is considered in accordance with generally accepted medical practice?

<table>
<thead>
<tr>
<th>No.</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AMG is a reasonable option when patients demonstrate persistent corneal staining despite conservative therapy. Conservative therapy in this case would include frequent preservative-free tears, hot compresses and efforts to control the environment. At times these may not work because the patient is unable to control the environment or administer drops frequently. Drugs such as cyclosporine or 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, AMG may provide rapid relief while waiting for long-term medications to take effect. However, it is unlikely to be of benefit for less-severe disease or disease that responds to conservative therapy. Because it limits acuity it is only viable as a short-term therapy.</td>
</tr>
</tbody>
</table>

6. Additional comments and/or any citations supporting your clinical input on the clinical use of AMG in patients with ophthalmic disorders.

<table>
<thead>
<tr>
<th>No.</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>We are in agreement that larger controlled studies are needed to show benefit of AMG in dry eye disease, where the disease is common and such studies should be easy to perform. It is unlikely that larger RCTs will be possible in less common conditions with multiple different underlying etiologies and severities such as corneal melts or perforations, persistent epithelial defects, Stevens-Johnson syndrome or neurotrophic keratitis. The limited clinical literature clearly supports the benefit of AMG in these cases, though sutured AMG is superior to Pro-Kera for the more severe diseases such as perforations and Stevens-Johnson.</td>
</tr>
</tbody>
</table>

7. Is there any evidence missing from the attached draft review of evidence?

<table>
<thead>
<tr>
<th>No.</th>
<th>Yes/No</th>
<th>Citations of Missing Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>