Medical Policy

Title: Amniotic Membrane and Amniotic Fluid

See Also: Bio-Engineered Skin and Soft Tissue Substitutes

Professional
Original Effective Date: March 20, 2017
Revision Date(s): March 20, 2017; January 1, 2019
Current Effective Date: January 1, 2019

Institutional
Original Effective Date: March 20, 2017
Revision Date(s): March 20, 2017; January 1, 2019
Current Effective Date: January 1, 2019

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<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 due to venous insufficiency | Interventions of interest are:  
• Patch or flowable formulation of human amniotic membrane | Comparators of interest are:  
• Compression therapy  
• Advanced wound therapies | Relevant outcomes include:  
• Symptoms  
• Morbid events  
• Functional outcomes  
• Quality of life |
| Individuals:  
• With knee osteoarthritis | Interventions of interest are:  
• Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid | Comparators of interest are:  
• Conservative therapy  
• Corticosteroid injections | Relevant outcomes include:  
• Symptoms  
• Functional outcomes  
• Quality of life  
• Treatment-related morbidity |
<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals:  
• With plantar fasciitis | Interventions of interest are:  
• Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid | Comparators of interest are:  
• Conservative therapy  
• Corticosteroid injections | Relevant outcomes include:  
• Symptoms  
• Functional outcomes  
• Quality of life  
• Treatment-related morbidity |
| Individuals:  
• With neurotrophic keratitis, corneal ulcers and melts, pterygium repair, Stevens-Johnson, or persistent epithelial defects | Interventions of interest are:  
• Sutured human amniotic membrane graft | Comparators of interest are:  
• Medical therapy  
• Bandage contact lens | Relevant outcomes include:  
• Symptoms  
• Morbid events  
• Functional outcomes  
• Quality of life |
| Individuals:  
• With ophthalmic disorders other than keratitis, corneal ulcers and melts, pterygium repair, SJS, or epithelial defects | Interventions of interest are:  
• Sutured human amniotic membrane graft | Comparators of interest are:  
• Medical therapy  
• Bandage contact lens | Relevant outcomes include:  
• Symptoms  
• Morbid events  
• Functional outcomes  
• Quality of life |
| Individuals:  
• With ophthalmic conditions | Interventions of interest are:  
• Human amniotic membrane | Comparators of interest are:  
• Medical therapy  
• Bandage contact lens | Relevant outcomes include:  
• Symptoms  
• Morbid events  
• Functional outcomes  
• Quality of life |

**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.

**OBJECTIVE**

The objective of this evidence review is to evaluate whether various human amniotic membrane products improve the net health outcome for patients with various diabetic and venous ulcers, osteoarthritis, plantar fasciitis, and ophthalmic conditions.

**BACKGROUND**

**Human Amniotic Membrane**

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).

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.1 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, 1 dehydrated HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.2

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

Amniotic Fluid

Amniotic fluid surrounds the fetus during pregnancy and provides protection and nourishment. In the second half of gestation, most of the fluid is a result of micturition and secretion from the respiratory tract and gastrointestinal tract of the fetus, along with urea.1 The fluid contains proteins, carbohydrates, peptides, fats, amino acids, enzymes, hormones, pigments, and fetal cells. Use of human and bovine amniotic fluid for orthopedic conditions was first reported in 1927.3 Amniotic fluid has been compared with synovial fluid, containing hyaluronan, lubricant, cholesterol, and cytokines. Injection of amniotic fluid or amniotic fluid–derived cells is currently being evaluated for the treatment of osteoarthritis and plantar fasciitis.

Amniotic membrane and amniotic fluid are also being investigated as sources of pluripotent stem cells.1 Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type.
### Table 1. Amniotic Membrane and Amniotic Fluid Preparations: Preparation and Components

<table>
<thead>
<tr>
<th>Product (Supplier)</th>
<th>Preparation</th>
<th>Components</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cryopreserved, Dehydrated, or Extracted</td>
<td>Amnion</td>
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<tr>
<td><strong>Patch</strong></td>
<td></td>
<td></td>
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<tr>
<td>Affinity™ (NuTech Medical)</td>
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<tr>
<td>AlloWrap™ (AlloSource)</td>
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<tr>
<td>AmbioDisk® (IOP Ophthalmics)</td>
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<tr>
<td>PalinGen® SportFlow (Amnio ReGen Solutions)</td>
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Amniotic Membrane and Amniotic Fluid

<table>
<thead>
<tr>
<th>Product (Supplier)</th>
<th>Preparation</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProMatRX™ ACF (Amnio ReGen Solutions)</td>
<td>Cryopreserved, Dehydrated, or Extracted</td>
<td>C</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 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.

**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.”

**POLICY**

A. Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered medically necessary.
   1. AmnioBand Membrane (Q4151, Q4168)
   2. Biovance (Q4154)
   3. Epifix (Q4145, Q4186)
   4. Grafix (Q4132, Q4133)

B. FDA-approved sutured and non-sutured human amniotic membrane grafts may be considered medically necessary for the treatment of the following ophthalmic indications:
   1. Neurotrophic keratitis
   2. Corneal ulcers and melts
   3. Pterygium repair
   4. Stevens-Johnson syndrome
   5. Persistent epithelial defects (with documented pain for ≥5 days)
   6. Acid or alkaline burn
C. FDA approved sutured and non-sutured human amniotic membrane grafts are considered experimental / 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.

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

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

F. All other indications not listed above are considered experimental / investigational, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency.

Policy Guidelines
1. 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).
2. 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.
3. 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. An amniotic membrane graft requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in regard to treatments requiring multiple drops per day.

Rationale
This evidence review has been updated 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 (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.

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 the industry in developing products for the 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 of 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).³ 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 trial 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 with 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 trial 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 of Care**

AmnioExcel dehydrated human amniotic membrane (d-HAM) was compared with SOC 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 with 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 with 0% in the SOC arm (p=0.008) with a 95% CI 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**

Smiell et al (2015) 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. 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 of Care**

Zelen et al (2013) reported on 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. 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. The 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 the trial conclusion, unhealed wounds from the control group were treated with EpiFix. 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. In a subsequent report by Zelen et al (2014), weekly application of EpiFix resulted in significantly faster healing (n=20; mean, 2.4 weeks) compared with biweekly application (n=20; mean, 4.1 weeks; p=0.039). All wounds treated weekly had healed by week 8 compared with 75% of wounds treated biweekly (p=0.047).

**EpiFix vs Apligraf**

EpiFix d-HAM was compared with Apligraf (living cell therapy) in a multicenter RCT published by Zelen et al (2015, 2016). 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). This study was extended to 12 weeks with 100 patients who were treated with either EpiFix (n=32), Apligraf (n=33), or standard wound care (n=35).12 Patients whose wound failed to heal by at least 50% by 6 weeks exited the study; this included 4 patients in the Apligraf group and 13 in the SOC group. An additional 5 SOC patients withdrew from the study. Patients treated with EpiFix had a higher probability of wound healing (hazard ratio, 5.66; 95% CI, 3.03 to 10.57; p<0.001) compared with SOC and required fewer weekly treatments (3.4) compared with wounds treated with Apligraf (5.9; p=0.003).

Kirsner et al (2015) reported on an industry-sponsored observational study comparing the effectiveness of Apligraf and EpiFix in a real-world setting.13 Data were obtained from a wound care-specific database from 3000 wound care facilities. The database included profiles of 1458 diabetic ulcers treated for the first time in 2014 with Apligraf (n=994) or EpiFix (n=464). Using the same criteria as the study by Zelen (2015; 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 before 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 was found to be at risk of selection bias in determining treatment assignment.

Cryopreserved Placental Membrane

Grafix vs Standard of Care

Grafix cryopreserved placental membrane was compared with standard wound care in a 2014 multicenter RCT.14 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 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 the 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 comparing HAM with SOC or with 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 with SOC, and outcomes that are at least as good as the advanced wound care product Apligraf. Also, 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**

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 2).15 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 3). However, a similar percentage of patients in the combined EpiFix group and the control group achieved complete wound closure during the 4 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.16

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 2).17 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 3). 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 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 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 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>
<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)15</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>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Compression therapy alone (n=31)</td>
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### Table 3. 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>Serena et al (2014)15</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>0.005</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bianchi et al (2017)17</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>EpiFix</td>
<td></td>
<td>60</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>35</td>
<td>44</td>
<td></td>
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<tr>
<td>p</td>
<td></td>
<td>0.013</td>
<td>0.007</td>
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</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 SOC is unknown.

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

Well-designed and well-conducted RCTs are comparing HAM with SOC for venous lower-extremity ulcers and evaluating 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 RCT by Serena (2014) 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 SOC. The study by Bianchi (2017) 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 human amniotic membrane (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. An RCT is 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
One systematic review and 2 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. The minimum clinically important difference was defined as -9 mm on a visual analog scale, which is substantially lower than the 30% (20-mm) decrease in visual analog scale score for pain more typically used. Secondary outcomes included total and subscores for the Foot Health Status Questionnaire (FHSQ), with a minimum clinically important difference defined as 7 on the FHSQ function and 9 on the FHSQ general foot health subscales. Overall, the 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 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. When the efficacy of d-HAM was compared with corticosteroid injections, the mean difference in visual analog scale 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 trial (2015) found similar improvements with an injection of c-HAM (Clarix Flo) and corticosteroid injection. Another industry-sponsored, patient-blinded study by Zelen et al (2013; N=45) compared injection of saline with d-HAM (AmnioFix) 0.5 mL or 1.25 mL in patients who had symptoms recalcitrant to conservative treatment. In the 2 d-HAM groups, scores on the American Orthopaedic Foot and Ankle Society hindfoot scale improved by about 50 points over 8 weeks 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).
**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 did not provide sufficient evidence 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**
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.

**Following Pterygium Repair**
A number of RCTs have been reported on the 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 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.

**Persistent Epithelial Defects and Ulceration**
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.

**Ocular Burns**
A 2012 Cochrane review evaluated the evidence on HAM graft for acute ocular burns.27 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 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 eyes treated with amniotic membrane transplantation 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 eyes treated with amniotic membrane transplantation and 1 (6.7%) of 15 control eyes were epithelialized by day 21. There was no significant difference in final visual acuity (1.77 logMAR in eyes treated with amniotic membrane transplantation vs 1.64 in control eyes; p=0.79). 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 amniotic membrane transplantation was lacking.

**Bullous Keratopathy**
Bullous keratopathy is characterized by stromal edema and epithelial and subepithelial bulla formation. 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.28 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 the 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 the 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 with medical therapy alone. A 2012 Cochrane review found an 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 on an RCT with 20 patients with moderate-to-severe dry eye disease who were treated with Prokera c-HAM or maximal conventional treatment.\textsuperscript{29} 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 also evaluated in a series by Cheng et al (2016).\textsuperscript{30} The senior author of the study 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, 0.3-6.8 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**

Vlasov et al (2016) reported on a prospective, nonrandomized controlled trial evaluating the effect of sutureless amniotic membrane (Prokera) on corneal wound healing after PRK.\textsuperscript{31} 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 after that. The primary outcome was re-epithelialization, which was assessed daily with slit lamp examination, fluorescein staining, and photography. The time to complete reepithelialization 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 in the eyes treated with the amniotic membrane graft and bandage contact lens.

Other Indications
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.30

Section Summary: HAM Without Suture for Ophthalmic Conditions
Current evidence on the use of the Prokera device includes an RCT with 20 patients, a within-subject comparative study, and case series. 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 with a bandage contact lens when used for wound healing after PRK. While the studies reported generally positive effects, high-quality RCTs are needed to determine the effect of sutureless self-contained HAM on corneal healing.

SUMMARY OF EVIDENCE
Diabetic Lower-Extremity Ulcers
For individuals who have nonhealing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM (ie, AmnioBand Membrane, Biovance, EpiFix, Grafix), the evidence includes 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 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 intention-to-treat analysis. For the HAM products that have been sufficiently evaluated (ie, AmnioBand Membrane, Biovance, 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 2 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of lower-extremity venous 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 the interpretation is limited by methodologic concerns. Well-designed and well-conducted RCTs that compare HAM with the standard of 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 an 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 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 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 a systemic review article and RCTs. 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 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 (N=20), 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 its use is limited. While the small RCT and case series reported generally positive effects, the prospective comparative trial found no benefit of HAM compared with a bandage contact lens for healing a wound after photorefractive keratectomy. RCTs are needed to determine whether sutureless HAM improves healing for the various ophthalmic disorders. The evidence is insufficient to determine the effects of the technology on health outcomes.

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2017 Input

In response to requests, clinical input on use of human amniotic membrane for ophthalmic disorders was received from 1 specialty society while this policy was under review in 2017.

Based on the evidence and independent clinical input, the clinical input supports that the following indications provide a clinically meaningful improvement in the 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.

Based on the evidence and independent clinical input, 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.

Based on the evidence and independent clinical input, the clinical input 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.

PRACTICE GUIDELINES AND POSITION STATEMENTS

No guidelines or statements were identified.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.
ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 4.

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>
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<td>NCT02318511a</td>
<td>An Investigation of ReNu™ Knee Injection: Monitoring the Response of Knee Function and Pain in Patients With Osteoarthritis</td>
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<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>
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<td>Nov 2018</td>
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<td>A Multi-center, Randomized Controlled Clinical Trial Evaluating the Effect of Fresh Amniotic Membrane in the Treatment of Diabetic Foot Ulcers</td>
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<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>
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<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>
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<td>Dec 2018</td>
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<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>
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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>NCT03390920</td>
<td>Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions Musculoskeletal Conditions</td>
<td>200</td>
<td>Jun 2022</td>
</tr>
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</table>

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

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

CPT/HCPCS

65778 Placement of amniotic membrane on the ocular surface; without sutures
65779 Placement of amniotic membrane on the ocular surface; single layer, sutured
Q4100 Skin substitute, not otherwise specified
Q4132 Grafix Core and GrafixPL Core, per sq cm
Q4133 Grafix Prime and GrafixPL Prime, Stravix and StravixPL, per sq cm
Q4137 AmnioExcel, AmnioExcel Plus or BioDExCel, per sq cm
Q4138 BioDFence DryFlex, per 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, 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
Q4183 Surgigraft, per square centimeter
Q4184 Cellesta, per square centimeter
Q4185 Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4186 Epifix, per square centimeter
Q4187 Epicord, per square centimeter
Q4188 Amnioarmor, per square centimeter
Q4189 Artacent ac, 1 mg
Q4190 Artacent ac, per square centimeter
Q4191 Restorigin, per square centimeter
Q4192 Restorigin, 1 cc
Q4194 Novachor, per square centimeter
Q4198 Genesis amniotic membrane, per square centimeter
Q4201 Matrion, per square centimeter
Q4204 Xwrap, per square centimeter

- There are specific HCPCS codes for some of these products. If no specific HCPCS code exists for the product, an unlisterd code such as Q4100 would be used.
- There are no specific codes for AmnioFix or OrthoFlo. It might be reported using the code for another MiMedx product such as Q4145 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.

**ICD-10 Diagnoses**

E08.621 Diabetes mellitus due to underlying condition with foot ulcer
E08.622 Diabetes mellitus due to underlying condition with other skin ulcer
(Use additional code to identify site of ulcer limited to the ICD-10 L codes listed in this policy.)

E09.621  Drug or chemical induced diabetes mellitus with foot ulcer
E09.622  Drug or chemical induced diabetes mellitus with other skin ulcer
(Use additional code to identify site of ulcer limited to the ICD-10 L codes listed in this policy.)

E10.621  Type 1 diabetes mellitus with foot ulcer
E10.622  Type 1 diabetes mellitus with other skin ulcer
(Use additional code to identify site of ulcer limited to the ICD-10 L codes listed in this policy.)

E11.621  Type 2 diabetes mellitus with foot ulcer
E11.622  Type 2 diabetes mellitus with other skin ulcer
(Use additional code to identify site of ulcer limited to the ICD-10 L codes listed in this policy.)

E13.621  Other specified diabetes mellitus with foot ulcer
E13.622  Other specified diabetes mellitus with other skin ulcer
(Use additional code to identify site of ulcer limited to the ICD-10 L codes listed in this policy.)

H11.001  Unspecified pterygium of right eye
H11.002  Unspecified pterygium of left eye
H11.003  Unspecified pterygium of eye, bilateral
H11.011  Amyloid pterygium of right eye
H11.012  Amyloid pterygium of left eye
H11.013  Amyloid pterygium of eye, bilateral
H11.021  Central pterygium of right eye
H11.022  Central pterygium of left eye
H11.023  Central pterygium of eye, bilateral
H11.031  Double pterygium of right eye
H11.032  Double pterygium of left eye
H11.033  Double pterygium of eye, bilateral
H11.041  Peripheral pterygium, stationary, right eye
H11.042  Peripheral pterygium, stationary, left eye
H11.043  Peripheral pterygium, stationary, bilateral
H11.051  Peripheral pterygium, progressive, right eye
H11.052  Peripheral pterygium, progressive, left eye
H11.053  Peripheral pterygium, progressive, bilateral
H11.061  Recurrent pterygium of right eye
H11.062  Recurrent pterygium of left eye
H11.063  Recurrent pterygium of eye, bilateral
H16.011  Central corneal ulcer, right eye
H16.012  Central corneal ulcer, left eye
H16.013  Central corneal ulcer, bilateral
H16.021  Ring corneal ulcer, right eye
H16.022  Ring corneal ulcer, left eye
H16.023  Ring corneal ulcer, bilateral
H16.031  Corneal ulcer with hypopyon, right eye
H16.032  Corneal ulcer with hypopyon, left eye
H16.033  Corneal ulcer with hypopyon, bilateral
H16.041  Marginal corneal ulcer, right eye
H16.042  Marginal corneal ulcer, left eye
H16.043  Marginal corneal ulcer, bilateral
H16.051  Mooren's corneal ulcer, right eye
H16.052  Mooren's corneal ulcer, left eye
H16.053  Mooren's corneal ulcer, bilateral
H16.061  Mycotic corneal ulcer, right eye
H16.062  Mycotic corneal ulcer, left eye
H16.063  Mycotic corneal ulcer, bilateral
H16.121  Filamentary keratitis, right eye
H16.122  Filamentary keratitis, left eye
H16.123  Filamentary keratitis, bilateral
H16.231  Neurotrophic keratoconjunctivitis, right eye
H16.232  Neurotrophic keratoconjunctivitis, left eye
H16.233  Neurotrophic keratoconjunctivitis, bilateral
H18.831  Recurrent erosion of cornea, right eye
H18.832  Recurrent erosion of cornea, left eye
H18.833  Recurrent erosion of cornea, bilateral
L97.212  Non-pressure chronic ulcer of right calf with fat layer exposed
L97.213  Non-pressure chronic ulcer of right calf with necrosis of muscle
L97.214  Non-pressure chronic ulcer of right calf with necrosis of bone
L97.222  Non-pressure chronic ulcer of left calf with fat layer exposed
L97.223  Non-pressure chronic ulcer of left calf with necrosis of muscle
L97.224  Non-pressure chronic ulcer of left calf with necrosis of bone
L97.312  Non-pressure chronic ulcer of right ankle with fat layer exposed
L97.313  Non-pressure chronic ulcer of right ankle with necrosis of muscle
L97.314  Non-pressure chronic ulcer of right ankle with necrosis of bone
L97.322  Non-pressure chronic ulcer of left ankle with fat layer exposed
L97.323  Non-pressure chronic ulcer of left ankle with necrosis of muscle
L97.324  Non-pressure chronic ulcer of left ankle with necrosis of bone
L97.412  Non-pressure chronic ulcer of right heel and midfoot with fat layer exposed
L97.413  Non-pressure chronic ulcer of right heel and midfoot with necrosis of muscle
L97.414  Non-pressure chronic ulcer of right heel and midfoot with necrosis of bone
L97.422  Non-pressure chronic ulcer of left heel and midfoot with fat layer exposed
L97.423  Non-pressure chronic ulcer of left heel and midfoot with necrosis of muscle
L97.424  Non-pressure chronic ulcer of left heel and midfoot with necrosis of bone
L97.512  Non-pressure chronic ulcer of other part of right foot with fat layer exposed
L97.513  Non-pressure chronic ulcer of other part of right foot with necrosis of muscle
L97.514  Non-pressure chronic ulcer of other part of right foot with necrosis of bone
L97.522  Non-pressure chronic ulcer of other part of left foot with fat layer exposed
L97.523  Non-pressure chronic ulcer of other part of left foot with necrosis of muscle
L97.524  Non-pressure chronic ulcer of other part of left foot with necrosis of bone
L97.812  Non-pressure chronic ulcer of other part of right lower leg with fat layer exposed
L97.813  Non-pressure chronic ulcer of other part of right lower leg with necrosis of muscle
L97.814  Non-pressure chronic ulcer of other part of right lower leg with necrosis of bone
L97.822  Non-pressure chronic ulcer of other part of left lower leg with fat layer exposed
L97.823  Non-pressure chronic ulcer of other part of left lower leg with necrosis of muscle
L97.824  Non-pressure chronic ulcer of other part of left lower leg with necrosis of bone
T26.11XA Burn of cornea and conjunctival sac, right eye, initial encounter
T26.11XD Burn of cornea and conjunctival sac, right eye, subsequent encounter
T26.11XS Burn of cornea and conjunctival sac, right eye, sequela
T26.12XA Burn of cornea and conjunctival sac, left eye, initial encounter
T26.12XD Burn of cornea and conjunctival sac, left eye, subsequent encounter
T26.12XS Burn of cornea and conjunctival sac, left eye, sequela
T26.31XA Burns of other specified parts of right eye and adnexa, initial encounter
T26.31XD Burns of other specified parts of right eye and adnexa, subsequent encounter
T26.31XS Burns of other specified parts of right eye and adnexa, sequela
T26.32XA Burns of other specified parts of left eye and adnexa, initial encounter
T26.32XD Burns of other specified parts of left eye and adnexa, subsequent encounter
T26.32XS Burns of other specified parts of left eye and adnexa, sequela
T26.51XA Corrosion of right eyelid and periocular area, initial encounter
T26.51XD Corrosion of right eyelid and periocular area, subsequent encounter
T26.51XS Corrosion of right eyelid and periocular area, sequela
T26.52XA Corrosion of left eyelid and periocular area, initial encounter
T26.52XD Corrosion of left eyelid and periocular area, subsequent encounter
T26.52XS Corrosion of left eyelid and periocular area, sequela
T26.61XA Corrosion of cornea and conjunctival sac, right eye, initial encounter
T26.61XD Corrosion of cornea and conjunctival sac, right eye, subsequent encounter
T26.61XS Corrosion of cornea and conjunctival sac, right eye, sequela
T26.62XA Corrosion of cornea and conjunctival sac, left eye, initial encounter
T26.62XD Corrosion of cornea and conjunctival sac, left eye, subsequent encounter
T26.62XS Corrosion of cornea and conjunctival sac, left eye, sequela
T26.81XA Corrosions of other specified parts of right eye and adnexa, initial encounter
T26.81XD Corrosions of other specified parts of right eye and adnexa, subsequent encounter
T26.81XS Corrosions of other specified parts of right eye and adnexa, sequela
T26.82XA Corrosions of other specified parts of left eye and adnexa, initial encounter
T26.82XD Corrosions of other specified parts of left eye and adnexa, subsequent encounter
T26.82XS Corrosions of other specified parts of left eye and adnexa, sequela

REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>03-20-2017</td>
<td>Policy added to the bcbksks.com web site.</td>
</tr>
<tr>
<td>01-01-2019</td>
<td>Updated Description section.</td>
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<tr>
<td></td>
<td>In Policy section:</td>
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<tr>
<td></td>
<td>▪ In Item A 1, added &quot;Q4168&quot;.</td>
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<tr>
<td></td>
<td>▪ In Item A 3, removed &quot;Q4131&quot; and added &quot;Q4145, Q4186&quot;.</td>
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<td>▪ Added new Item B, &quot;FDA-approved sutured and non-sutured human amniotic</td>
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<td>membrane grafts may be considered medically necessary for the treatment</td>
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<td>of the following ophthalmic indications: 1. Neurotrophic keratitis 2.</td>
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<tr>
<td></td>
<td>Corneal ulcers and melts</td>
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<td>epithelial defects (with documented pain for ≥5 days) 6. Acid or</td>
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<td></td>
<td>alkaline burn.</td>
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<td>▪ Added new Item C, &quot;FDA-approved sutured and non-sutured human amniotic</td>
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<tr>
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<td>membrane grafts are considered experimental / investigational for the</td>
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<td>treatment of all other ophthalmic conditions including but not limited</td>
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<td>to dry eye syndrome, corneal perforation, bullous keratopathy, limbus</td>
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<tr>
<td></td>
<td>stem cell deficiency, and after photorefractive keratectomy.&quot;</td>
</tr>
</tbody>
</table>
In Item D (previous Item B), added "including but not limited to treatment of osteoarthritis and plantar fasciitis" to read "Injection of micronized or particulated human amniotic membrane is considered experimental / investigational for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis."

In Item F (previous Item D), removed "human amniotic membrane products and" and added "including but not limited to treatment of lower-extremity ulcers due to venous insufficiency" to read "All other human amniotic membrane products and indications not listed above are considered experimental / investigational, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency."

Updated Policy Guidelines.

Updated Rationale section.

In Coding section:
- Added CPT codes: 65778, 65779.
- Added new HCPCS codes: Q4183, Q4184, Q4185, Q4186, Q4187, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4201, Q4204.
- Removed deleted HCPCS code: Q4131.
- Revised nomenclature to HCPCS codes: Q4132, Q4133, Q4137, Q4148, Q4156, Q4162, Q4163.

Updated References section.

REFERENCES


Other References
1. Blue Cross and Blue Shield of Kansas Ophthalmology / Optometry Liaison Committee Consent Ballot, November 2018.
2. Blue Cross and Blue Shield of Kansas Ophthalmology / Optometry Liaison Committee, May 2018.