Medical Policy

BlueCross BlueShield Kansas
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Title: Amniotic Membrane and Amniotic Fluid

Related Policies:	▪ *Bio-Engineered Skin and Soft Tissue Substitutes* ▪ *Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)* ▪ *Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non–Orthopedic Conditions*

Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
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
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 with ocular surface damage and inflammation that does not respond to conservative treatment	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With corneal ulcers or melts that do not respond to initial medical therapy	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals:	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include:

Populations	Interventions	Comparators	Outcomes
• With bullous keratopathy as a palliative measure in patients who are not candidates for a curative treatment (e.g., endothelial or penetrating keratoplasty)	• Sutured or self-retained human amniotic membrane	• Medical therapy • Bandage contact lens	• Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With moderate or severe Stevens-Johnson syndrome	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With persistent epithelial defects that do not respond to conservative therapy	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With moderate or severe acute ocular chemical burn	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With corneal perforation when corneal tissue is not immediately available	Interventions of interest are: • Sutured human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals:	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include:

Populations	Interventions	Comparators	Outcomes
• With pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft	• Sutured or glued human amniotic membrane	• Medical therapy • Bandage contact lens	• Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • Who have undergone Mohs micrographic surgery for skin cancer on the face, head, neck, or dorsal hand	Interventions of interest are: • Human amniotic membrane	Comparators of interest are: • Autologous tissue-based surgical repair (full-thickness skin grafts and flaps) • Non-surgical treatment (e.g., secondary intention healing)	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.

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 HAM products, resulting in a readily available tissue with regenerative potential. In support, 1 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.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) 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. In 2017, the FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps).[4,]

HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

1. "The HCT/P is minimally manipulated;
2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;

3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4. Either:
    i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
        a. Is for autologous use;
        b. Is for allogeneic use in a first-degree or second-degree blood relative; or
        c. Is for reproductive use."

The guidance provides the following specific examples of homologous and non-homologous use for amniotic membrane:

a. "Amniotic membrane is used for bone tissue replacement to support bone regeneration following surgery to repair or replace bone defects. This is not a homologous use because bone regeneration is not a basic function of amniotic membrane.
b. An amniotic membrane product is used for wound healing and/or to reduce scarring and inflammation. This is not homologous use because wound healing and reduction of scarring and inflammation are not basic functions of amniotic membrane.
c. An amniotic membrane product is applied to the surface of the eye to cover or offer protection from the surrounding environment in ocular repair and reconstruction procedures. This is homologous use because serving as a covering and offering protection from the surrounding environment are basic functions of amniotic membrane."

The FDA noted the intention to exercise enforcement discretion for the next 36 months after publication of the guidance.

In 2003, Prokera was cleared for marketing by the FDA through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). The 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."[5,] The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

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

POLICY

A. Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered **medically necessary**.
   1. Affinity® (Q4159)
   2. AmnioBand® Membrane (Q4151)
   3. Biovance® (Q4154)
   4. EpiCord® (Q4187)
   5. EpiFix® (Q4186)
   6. Grafix™ (Q4132, Q4133)

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

   1. Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy;
   2. Corneal ulcers and melts that do not respond to initial conservative therapy;
   3. Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment;
   4. Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty);
   5. Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient;
   6. Moderate or severe Stevens-Johnson syndrome;
   7. Persistent epithelial defects that do not respond as stated in policy guidelines.
   8. Severe dry eye (DEWS 3 or 4) with ocular surface damage and inflammation that remains symptomatic after Steps 1, 2, and 3 of the dry eye disease management algorithm (see Policy Guidelines);
   9. Moderate or severe acute ocular chemical burn;
   10. Corneal perforation when corneal tissue is not immediately available; or
   11. Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft

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

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 human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) not listed above are considered **experimental / investigational** (see policy guidelines).

G. All other indications not listed above are considered **experimental / investigational**, including, but not limited to, treatment of lower-extremity ulcers due to venous insufficiency and repair following Mohs micrographic surgery.

POLICY GUIDELINES

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

B. 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.

C. 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.

Tables PG1 and PG2 list the medically necessary and investigational amniotic products that have an HCPCS code.

Table PG1 Amniotic Products Listed in the Policy Statements

Trade Name	Supplier	HCPCS Code
Affinity®	Organogenesis (previously NuTech Medical)	Q4159
AmnioBand® Membrane	MTF Wound Care	Q4151
Biovance®	Celularity	Q4154
Epifix®	MiMedx	Q4186
Epicord®	MiMedx	Q4187
Grafix®	Osiris	Q4132, Q4133

Table PG2 Other Amniotic Products with HCPCS Codes

Trade Name	Supplier	HCPCS Code
Allogen	Vivex Biomedical	Q4212
AlloWrap™	AlloSource	Q4150
AmnioAMP-MP	Stratus BioSystems	Q4250
Amnioarmor™	Tissue Transplant Technology	Q4188
AmnioBand® Particulate	MTF Wound Care	Q4168
AmnioExcel®	Derma Sciences	Q4137

Trade Name	Supplier	HCPCS Code
Amnio-maxx or Manio-maxx lite	Royal Biologics	Q4239
Amniotext	Regenerative Labs	Q4245
Amniowound	Alpha Tissue	Q4181
Amnion bio or Axomembrane	Axolotl Biologix	Q4211
Amniocore™	Stability Biologics	Q4227
Amniocyte	Predictive Biotech	Q4242
AmnioMatrix®	Integra Life Sciences	Q4139
Amniply	International Tissue	Q4249
Amniorepair or AltiPly	Zimmer Biomet	Q4235
Amniotext patch	Regenerative Labs	Q4247
AmnioWrap2™	Direct Biologics	Q4221
Articent ac (flowable)	Tides Medical	Q4189
Artacent ac (patch)	Tides Medical	Q4190
Artacent® Wound	Tides Medical	Q4169
Artacent® Cord	Tides Medical	Q4126
Ascent	StimLabs	Q4213
Axolotl ambien or Axolotl Cryo	Axolotl Biology	Q4215
BioDDryFlex®	BioD	Q4138
BioDfence™	Integra Life Science	Q4140
BioNextPATCH	BioNext Solutions	Q4228
BioWound, BioWound Plus™, BioWound XPlus™	HRT[a]	Q4217
carePATCH	Extremity Care	Q4236
Cellesta/Cellesta duo	Ventris Medical	Q4184
Cellesta Cord	Ventris Medical	Q4214
Cellesta flowable	Ventris Medical	Q4185
Clarix®	Amniox Medical	Q4156
Clarix® Flo	Amniox Medical	Q4155
Cogenex flowable amnion	Ventris Medical	Q4230
Cogenex amniotic membrane	Ventris Medical	Q4229
Corecyte	Predictive Biotech	Q4240
Corplex	StimLabs	Q4232
Corplex P	StimLabs	Q4231
Coretext or Protext	Regenerative Labs	Q4246

Trade Name	Supplier	HCPCS Code
Cryo-cord	Royal Biologics	Q4237
Cygnus	Vivex Biomedical	Q4170
Dermacyte	Merakris Therapeutics	Q4248
Dermavest™ or Plurivest	AediCell[a]	Q4153
Derm-maxx	Royal Biologics	Q4238
Epifix Injectable	MiMedx	Q4145
Floweramnioflo	Flower Orthopedics	Q4177
Floweramniopatch	Flower Orthopedics	Q4178
Fluid flow or Fluid GF	BioLab Sciences	Q4206
Genesis	Genesis Biologics	Q4198
Guardian/AmnioBand®	MTF Wound Care	Q4151
Interfyl®	Celularity	Q4171
Matrion	LifeNet Health	Q4201
Neopatch or Therion	CryoLife	Q4176
Neox® Cord	Amniox Medical	Q4148
Neox® Flo	Amniox Medical	Q4155
Neox® Wound	Amniox Medical	Q4156
Novachor	Organogenisis	Q4191
Novafix®	Triad Life Sciences	Q4208
Novafix DL	Triad Life Sciences	Q4254
NuShield	Organogenesis	Q4160
PalinGen® Membrane	Amnio ReGen Solutions	Q4173
PalinGen® SportFlow	Amnio ReGen Solutions	Q4174
Plurivest™	AediCell	Q4153
Polycyte	Predictive Biotech	Q4241
Procenta	Lucina BioSciences	Q4244
Reguard	New Life Medical	Q4255
Restorigin	UMTB Biomedical	Q4191
Restorigin Injectable	UMTB Biomedical	Q4192
Revita	StimLabs	Q4180
Revitalon™	Medline Industries	Q4157
Surgenex, Surfactor, and Nudyn	Surgenex	Q4233
Surgicord	Synergy Biologics	Q4218

Trade Name	Supplier	HCPCS Code
SurgiGRAFT™	Synergy Biologics	Q4183
WoundEx®	Skye Biologics[a]	Q4163
WoundEx® Flow	Skye Biologics[a]	Q4162
Woundfix, Woundfix Plus, Wounfix XPlus (see BioWound above)	HRT	Q4217
Xcellerate	Precise Bioscience	Q4234
Xwrap	Applied Biologics	Q4204

HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation
[a] Processed by HRT and marketed under different tradename

Tear Film and Ocular Surface Society staged management for dry eye disease (Jones et al, 2017)
Step 1:

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

Step 2:
If above options are inadequate consider:

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

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

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

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

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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through January 20, 2023.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable

intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

DIABETIC LOWER-EXTREMITY ULCERS

PATCH OR FLOWABLE AMNIOTIC MEMBRANE OR PLACENTAL MEMBRANE

Clinical Context and Therapy Purpose

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

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

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is an amniotic membrane or placental membrane applied every 1 to 2 weeks. It is applied in addition to the SOC.

Comparators

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

Outcomes

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

- Incidence of complete wound closure.

- Time to complete wound closure (reflecting accelerated wound closure).
- Incidence of complete wound closure following surgical wound closure.
- Pain control.
- Complete ulcer healing with advanced wound therapies may be measured at 6 to 12 weeks.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

At least 7 RCTs have evaluated rates of healing with amniotic membrane grafts or placental membrane graft compared to SOC or an advanced wound therapy in patients with chronic diabetic foot ulcers (see Table 1). The number of patients in these studies ranged from 25 to 155. Human amniotic membrane (HAM) or placental membrane grafts improved healing compared to SOC by 22% (EpiCord vs. Alginate dressing) to 60% (EpiFix) in the intention-to-treat (ITT) analysis (see Table 2). In a 2018 trial, the cryopreserved placental membrane Grafix was found to be non-inferior to an advanced fibroblast-derived wound therapy (Dermagraft).

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator
Serena et al (2020)[6,]	U.S.	14		76 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers unresponsive to SOC and extending into dermis, subcutaneous tissue, muscle, or tendon	n=38, Affinity	n=38, SOC
Ananian et al (2018)[7,]	U.S.	7	2016-2017	75 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers between 1 cm2 and 15 cm2	n=38, Grafix weekly for up to 8 weeks	n=37, Dermagraft (fibroblast-derived) weekly for up to 8 weeks
Tettelbach et al (2018)[8,]	U.S.	11	2016-2018	155 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers	n=101 EpiCord plus SOC	n=54 SOC with alginate dressing

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator
DiDomenico et al (2018)[9,]				80 patients with non-healing (4 weeks) diabetic foot ulcers	AmnioBand Membrane plus SOC	SOC
Snyder et al (2016)[10,]				29 patients with non-healing diabetic foot ulcers	AmnioExcel plus SOC	SOC
Zelen et al (2015, 2016)[11,12,]		4		60 patients with less than 20% wound healing in a 2 week run-in period	EpiFix	Apligraf or SOC with collagen-alginate dressing
Tettelbach et al (2019)[13,]	U.S.	14		110 patients with non-healing (4 weeks) lower extremity ulcers	EpiFix	SOC with alginate dressing
Lavery et al (2014)[14,]				97 patients with chronic diabetic foot ulcers	Grafix Weekly	SOC

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

Table 2. Summary of Key RCT Results

Study	Wounds Healed	Wounds Healed	Time to Complete Healing	Adverse Events and Number of Treatments
Serena et al (2020)[6,]	12 Weeks (ITT) (%)	16 Weeks (ITT) (%)	Median	
N	76	76	76	
Affinity	55%	58%	11 weeks	
SOC	29%	29%	not attained by 16 weeks	
p-value	.02	.01		
HR (95% CI)		1.75 (1.16 to 2.70)		
Ananian et al (2018)[7,]	8 Weeks (PP) n (%)			Patients with Index Ulcer Related Adverse Events n (%)
N	62			75
Grafix	15 (48.4%)			1 (5.9%)
Dermagraft	12 (38.7%)			4 (16.7%)
Diff (95% CI)	9.68% (−10.7 to 28.9)			
Lower bound for non-inferiority	-15%			

Study	Wounds Healed	Wounds Healed	Time to Complete Healing	Adverse Events and Number of Treatments
Tettlebach et al (2018)[8,]	12 Weeks (PP) n (%)	12 Weeks (ITT) n (%)		Patients with Adverse Events (% of total)
N	134	155		155
EpiCord	81 (81%)	71 (70%)		42 (42%)
SOC	29 (54%)	26 (48%)		33 (61%)
p-value	.001	.009		
DiDomenico et al (2018)[9,]	6 Weeks (ITT) n (%)	12 weeks ITT n (%)	Mean Days (95% CI)	
N	80	80	80	
AmnioBand	27 (68)	34 (85)	37.0 (29.5 to 44.4)	
SOC	8 (20)	13 (33)	67.3 (59.0 to 79.6)	
HR (95% CI)		4.25 (0.44 to 0.79)		
p-value	<.001	<.001	<.001	
Snyder et al. (2016)[10,]	6 Weeks (PP) Mean (95% CI)			
N	21			
AmnioExcel	45.5% (32.9% to 58.0%)			
SOC	0%			
p-value	.014			
Zelen et al (2015, 2016)[11,12,]	6 Weeks ITT n (%)	Wounds Healed at 12 Weeks		Weekly Treatments
N	60	100		
EpiFix	19 (95%)	NR		3.4
Apligraf	9 (45%)	NR		5.9
SOC	7 (35%)	NR		
HR (95% CI)		5.66; (3.03 to 10.57)		
p-value	.003	<.001 vs. SOC		.003

Study	Wounds Healed	Wounds Healed	Time to Complete Healing	Adverse Events and Number of Treatments
Tettelbach et al (2019)[13,]		Wounds Healed at 12 Weeks (ITT) n(%)		
N		110		110
EpiFix		38 (81)		
SOC		28 (55)		
p-value				
Lavery et al (2014)[14,]		Wounds Healed at 12 Weeks		Patients With Adverse Events
N		97a	97	97
Grafix		62.0%	42.0	44.0%
SOC		21.3%	69.5	66.0%
p-value		<.001	.019	.031
Difference in wounds healed between amniotic or placental membrane and SOC	Affinity 26% AmnioBand 55% AmnioExcel 33% EpiFix 60%	Affinity 28% EpiCord 22% Grafix 41%		

CI: confidence interval; DIFF: difference; HR: hazard ratio; ITT: intention-to-treat; NR: not reported; PP: per-protocol; RCT: randomized controlled trial; SOC: standard of care.
a. Power analysis indicated that 94 patients per arm would be needed. However, after a prespecified interim analysis at 50% enrollment, the blinded review committee recommended the trial is stopped due to the efficacy of the treatment.

Limitations in study design and conduct are shown in Table 3. Studies without notable limitations reported power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and ITT analysis. Limitations from the RCT with AmnioExcel (Snyder et al, 2016) [10,] preclude conclusions for this product.

Table 3. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Serena et al (2020)[6,]	3. The randomization process and allocation concealment were not described	1, 2. No blinding of patients or investigators. Assessors were blinded		1. Although ITT analysis, there was substantial missing data for depth and volume with the digital analysis system.		
Ananian et al (2018)[7,]		2, 3. No blinding for				

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
		outcomes assessment				
Tettelbach et al (2018)[8,]		1, 2, 3. No blinding				
DiDomenico et al (2018)[9,]						
Snyder et al (2016)[10,]				1. There was high loss to follow-up with discontinuation of 8 of 29 participants	1. Power analysis was not reported	
Zelen et al (2015, 2016)[11,12,]				1. Thirteen of 35 patients in the SOC group exited the study at 6 weeks due to less than 50% healing, which may have affected the 12-week results.		
Tettelbach et al (2019)[13,]		1, 2. No blinding of patients or investigators. Assessors were blinded				
Lavery et al (2014)[14,]						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
ITT: intention to treat; SOC: standard of care.
a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Prospective Single-arm or Registry Studies

Prospective single-arm or registry studies are described in Tables 4 and 5.

Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about a third (n=47) were diabetic foot wounds.[15,] Of those treated, 28 ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of 8 weeks and a mean of 2.4 amniotic membrane applications.

In 2016, Frykberg et al reported treatment of complex chronic wounds (exposed tendon or bone) with Grafix. With the cryopreserved placental membrane applied weekly for up to 16 weeks, 59% of wounds closed with a mean time to closure of 9 weeks.[16,]

Table 4. Summary of Prospective Single-arm Studies or Registry Characteristics

Study	Study Design	Participants	Treatment Delivery
Smiell et al (2015)[15,]	Multicenter Registry	Various chronic wounds: 47 diabetic foot wounds, 20 pressure ulcers, and 89 venous ulcers; 28 had failed prior treatment with advanced biologic therapies (Apligraf, Dermagraft, or Regranex)	Biovance
Frykberg et al (2016)[16,]	Prospective multi-center single-arm study	31 patients with chronic complex diabetic foot wounds with exposed tendon or bone	Grafix weekly until closure or 16 weeks

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

Study	Treatment	Wounds Closed	Mean Time to Closure	Number of Applications
Smiell et al (2015)[15,]	Biovance	41.6%	8 weeks	2.4
Frykberg et al (2016)[16,]	Grafix	59.3%	9 weeks	9

Section Summary: Diabetic Lower-Extremity Ulcers

For individuals who have non-healing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM or placental membrane (i.e., Affinity, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix), the evidence includes RCTs. The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing (<20% healing with ≥2 weeks of standard care) diabetic lower-extremity ulcers have compared HAM with standard care or with an established advanced wound care product. These trials used wound closure as the primary outcome measure, and some included power analysis, blinded assessment of wound healing, and ITT analysis. For the HAM products that have been sufficiently evaluated (i.e., Affinity, AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix), results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries. No studies were identified that compared different amniotic or placental products, and indirect comparison between products is limited by variations in the patient populations.

LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

AMNIOTIC MEMBRANE

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does amniotic membrane or placental membrane improve the net health outcome in patients with venous ulcers?

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is amniotic membrane or placental membrane applied every 1 to 2 weeks. It is applied in addition to the SOC.

Comparators

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

Outcomes

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

- Incidence of complete wound closure.
- Time to complete wound closure (reflecting accelerated wound closure).
- Incidence of complete wound closure following surgical wound closure.
- Pain control.
- Complete ulcer healing with advanced wound therapies may be measured at 6 to 12 weeks.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Two RCTs, both with EpiFix, were identified on HAM for venous leg ulcers. Serena et al (2014) reported on an industry-sponsored multicenter open-label RCT that compared EpiFix d-HAM plus compression therapy with compression therapy alone for venous leg ulcers (see Tables 6 and 7).[17,] The primary outcome in this trial was the proportion of patients with 40% wound closure at 4 weeks, which was achieved by about twice as many patients in the combined EpiFix group compared with the control group (see Table 8). However, a similar percentage of patients in the combined EpiFix group and the control group achieved complete wound closure during the 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 trial included adequate power and ITT analysis with last observation carried forward. Limitations included the lack of blinding for wound evaluation and use of 40% closure rather than complete closure. A 2015 retrospective study of 44 patients from this RCT (31 treated with amniotic membrane) found that wounds with at least 40% closure at 4 weeks (n=20) had a closure rate of 80% by 24 weeks; however, this analysis did not take into account additional treatments after the 4-week randomized trial period.

A second industry-sponsored, multicenter, open-label RCT (Bianchi et al [2018; 2019]) evaluated the time to complete ulcer healing following weekly treatment with EpiFix d-HAM plus compression therapy or compression wound therapy alone (see Tables 6 and 7).[18,19,] 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=.01), and improved time to complete healing, as assessed by Kaplan-Meier analysis. In per-protocol analysis, healing within 12 weeks was reported for 60% of patients in the EpiFix group and 35% of patients in the control group (p<.013) (see Table 8). Intent-to-treat analysis found complete healing in 50% of patients in the EpiFix group compared to 31% of patients in the control group (p=.0473). There were several limitations of this trial (see Tables 8 and 9). In the per-protocol analysis, 19 (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). 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. The ITT analysis used last-observation-carried-forward for these patients and sensitivity analysis was not performed to determine how alternative methods of handling the missing data would affect results. Kaplan-Meier analysis suggested a modest improvement in the time to heal when measured by ITT analysis, but may be subject to the same methodological limitations.

Two additional studies, one with Amnioband and a second with Artacent, are listed on clinicaltrials.gov as completed in 2018, but results have not been published (see Table 14)

Table 6. Summary of Key RCT Characteristics

					Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Serena et al (2014)[17,]	U.S.	8	2012-2014	84 patients with a full-thickness chronic VLU between 2 and 20 cm2 treated for at least 14 d	1 (n=26) or 2 (n=27) applications of EpiFix plus standard wound therapy (n=53)	Standard wound therapy (debridement with alginate dressing and compression) (n=31)
Bianchi et al (2018, 2019)[18,19,]	U.S.	15	2015-2017	128 patients with a full-thickness VLU of at least 30-d duration	Weekly EpiFix plus moist wound therapy plus compression (n=64 ITT; 52 PP)	Moist wound therapy plus compression (n=64 ITT; 57 PP)

ITT: Intent-to-treat; PP: per-protocol; RCT: randomized controlled trial; VLU: venous leg ulcer.

Table 7. Summary of Key RCT Results

Study	**Percent With 40% Wound Closure at 4 Weeks**	**Percent With Complete Wound Closure at 4 Weeks**	**Complete Wound Closure at 12 Weeks n (%)**		**Complete Wound Closure at 16 Weeks n (%)**	
			PP	**ITT**	**PP**	**ITT**
Serena et al (2014)[17,]						
EpiFix	62	11.3				
Control	32	12.9				
p-Value	.005					
Bianchi et al (2018, 2019)[18,19,]						
EpiFix			31 (60)	32 (50)	37 (71)	38 (59)
Control			20 (35)	20 (31)	25 (44)	25 (39)
p-Value			.013	.047	.007	.034

ITT: Intent-to-treat; PP: per protocol; RCT: randomized controlled trial.

Table 8. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Serena et al (2014)[17,]					
Bianchi et al (2018, 2019)[18,19,]					1. Advanced wound therapy was allowed in the control group before the primary endpoint was reached.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 9. Study Design and Conduct Limitations

Study	**Allocation[a]**	**Blinding[b]**	**Selective Reporting[c]**	**Data Completeness[d]**	**Power[e]**	**Statistical[f]**
Serena et al (2014)[17,]						
Bianchi et al (2018, 2019)[18,19,]		1. Open-label with blinded assessors		1. Unequal exclusion of patients in the 2 groups in the per-protocol analysis.3. Advanced wound therapy was allowed in the control group before the primary endpoint was reached		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by

treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

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.[15,] 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

The evidence on HAM for the treatment of venous leg ulcers includes 2 multicenter RCTs with EpiFix. One RCT 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 the SOC. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression. Although a significant difference in complete healing was reported, interpretation is limited by the differential loss to follow-up and exclusions between groups. Although a subsequent publication reported ITT analysis, the handling of missing data differed between the groups and sensitivity analysis was not performed. The methodological flaws in the design, execution, and reporting of both of these RCTs limit inference that can be drawn from the results. Two additional studies with other HAM products have been completed but not published, raising further questions about the efficacy of HAM for lower-extremity ulcers due to venous insufficiency. Therefore, corroboration with well-designed and well-conducted RCTs evaluating wound healing in patients with venous leg ulcers is needed to demonstrate efficacy. The corroborating RCTs should report ITT and sensitivity analysis, with analysis of all patients, including those who were off treatment or had protocol deviations and exclusions.

OSTEOARTHRITIS

ReNu™ Knee Injection in Patients with Osteoarthritis

In 2016, a feasibility study (N=6) was reported of cryopreserved human amniotic membrane (c-HAM) suspension with amniotic fluid-derived cells for the treatment of knee osteoarthritis.[20,] A single intra-articular injection of the suspension was used, with follow-up at 1 and 2 weeks and at 3, 6, and 12 months posttreatment. Outcomes included the Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee scale, and a numeric pain scale. Statistical analyses were not performed for this small sample. No adverse events, aside from a transient increase in pain, were noted. RCTs are in progress.

A trial with 200 participants was completed in February 2019 (see Table 14). No publications from this trial have been identified.

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

PLANTAR FASCIITIS

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

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

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with plantar fasciitis that has failed to heal with SOC therapy.

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

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

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

Acute effects of HAM injection may be measured at 2 to 4 weeks. The durability of treatment would be assessed at 6 to 12 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
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.[21,] In addition to c-HAM and micronized d-HAM/chorionic membrane, treatments included corticosteroids, botulinum toxin type A, autologous whole blood, platelet-rich plasma, nonsteroidal anti-inflammatory drugs, dry needling, dextrose prolotherapy, and polydeoxyribonucleotide. Placebo arms included normal saline, local anesthetic, sham dry needling, and tibial nerve block. Analysis indicated d-HAM had the highest probability for improvement in pain and composite outcomes in the short-term, however, this finding was based only on a single RCT. Outcomes at 2 to 6 months (7 RCTs) favored botulinum toxin for pain and patient recovery plan for composite outcomes.

Randomized Controlled Trials
Zelen et al (2013) reported a preliminary study with 15 patients per group (placebo, 0.5 cc, and 1.25 cc) and 8-week follow-up.[22,] A subsequent RCT by Cazell et al (2018) enrolled 145 patients and reported 3-month follow-up (see Table 10).[23,] In Cazell et al (2018) amniotic membrane injection led to greater improvements in the VAS for pain and the Foot Functional Index between baseline and 3 months (see Table 11) compared to controls. VAS at 3 months had decreased to 17.1 in the AmnioFix group compared to 38.8 in the placebo control group, which would be considered a clinically significant difference.

Table 10. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator Intervention
Cazzell et al (2018)[23,];AIPF004 (NCT02427191)	U.S.	14	2015-2018	Adult patients with plantar fasciitis with VAS for pain > 45	n=73; Single injection of AmnioFix 40 mg/ml	n = 72; Single injection of saline

NCT02427191: Micronized dHACM Injection as Compared to the Saline Placebo Injection in the Treatment of Plantar Fasciitis; RCT: randomized controlled trial; VAS: visual analog score.

Table 11. Summary of Key RCT Results

Study	Change in VAS-Pain Between Baseline and 3 mo (95% CI)	Change in FFI-R Between Baseline and 3mo (95% CI)	Patients with Adverse Events up to 3 mo n(%)	Patients with Serious Adverse Events up to 3 mo n(%)
Cazzell et al (2018)[23,]; AIPF004	N=145	N=145	N=145	N=145
AmnioFix	54.1 (48.3 to 59.9)	35.7 (30.5 to 41.0)	30 (41.1%)	1 (0.6%)
Placebo	31.9 (24.8 to 39.1)	22.2 (17.1 to 27.4)	39 (54.2%)	3 (1.8%)

Study	Change in VAS-Pain Between Baseline and 3 mo (95% CI)	Change in FFI-R Between Baseline and 3mo (95% CI)	Patients with Adverse Events up to 3 mo n(%)	Patients with Serious Adverse Events up to 3 mo n(%)
Diff (95% CI)	22.2 (13.1 to 31.3)	13.5 (6.2 to 20.8)		
p-Value	<.001	<.001		

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

Limitations in relevance and design and conduct of this publication are described in Tables 12 and 13. The major limitation of the study is the short-term follow-up, which the authors note is continuing to 12 months. The extended follow-up will be reported in a separate publication.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Cazzell et al (2018)[23]; AIPF004			3. Placebo injections were used. A control delivered at a similar intensity as the investigational treatment would be corticosteroid injections.		1, 2. Follow-up to 12 mo will be reported in a subsequent publication.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 13. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Cazzell et al (2018)[23]; AIPF004		1. Single blinded trial, although outcomes were self-reported by blinded patients		1. Only the first 3 months of 12-month follow-up were reported.		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Plantar Fasciitis

The evidence on injection of amniotic membrane for the treatment of plantar fasciitis includes preliminary studies and a larger (N =145) patient-blinded comparison of micronized injectable-HAM and placebo control. Injection of micronized amniotic membrane resulted in greater improvements in VAS for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is this is an interim report of 3 months' results. The authors noted that 12-month follow-up will be reported in a subsequent publication. No additional publications have been identified as of the latest update.

Human Amniotic Membrane for Ophthalmologic Conditions

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

NEUROTROPHIC KERATITIS WITH OCULAR SURFACE DAMAGE OR INFLAMMATION THAT DOES NOT RESPOND TO CONSERVATIVE TREATMENT

Clinical Context and Therapy Purpose

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

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

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

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

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

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

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

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

Suri et al (2013) reported on 11 eyes of 11 patients with neurotrophic keratopathy that had not responded to conventional treatment.[24,] The mean duration of treatment prior to ProKera insertion was 51 days. Five of the 11 patients (45.5%) were considered to have had a successful outcome.

Section Summary: Neurotrophic Keratitis with Ocular Surface Damage and Inflammation that Does Not Respond to Conservative Therapy
An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens.

CORNEAL ULCERS AND MELTS THAT D O NOT RESPOND TO INITIAL MEDICAL THERAPY

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

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net heath outcome in patients who have corneal ulcers and melts?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients who have corneal ulcers and melts that do not respond to initial medical therapy.

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

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

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

Changes in symptoms may be measured in days, while changes in ocular surface would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Liu et al (2019) conducted a systematic review of 17 studies (390 eyes) of amniotic membrane for corneal ulcers.[25,] All but 1 of the studies was conducted outside of the U.S. There was 1 RCT with 30 patients, the remainder of the studies were prospective or retrospective case series. Corneal healing was obtained in 97% (95% CI: 0.94 to 0.99, p=.089) of patients evaluated. In the 12 studies (222 eyes) that reported on vision, the vision improvement rate was improved in 113 eyes (53%, 95% CI: 0.42 to 0.65, p<.001).

Yin et al (2020) compared epithelialization and visual outcomes of 24 patients with corneal infectious ulcers and visual acuity of less than 20/200 who were treated with (n=11) or without (n=13) self-retained amniotic membrane.[26,] Utilization of amniotic membrane was initiated in their institution in 2018, allowing a retrospective comparison of the 2 treatment groups. Complete epithelialization occurred more rapidly (3.56± 1.78 weeks vs. 5.87 ± 2.20 weeks, p=.01) and was reached in significantly more patients (72.7% vs. 23.1%, p=.04). The group treated with amniotic membrane plus the standard therapy had more patients with clinically significant (> 3 lines) improvement in visual acuity (81.8% vs 38.4%, p=.047) and greater total improvement in visual acuity (log MAR 0.7 ± 0.6 vs 1.6 ± 0.9, p=.016).

Suri et al (2013) reported on a series of 35 eyes of 33 patients who were treated with the self-retained ProKera HAM for a variety of ocular surface disorders.[24,] Nine of the eyes had non-healing corneal ulcers. Complete or partial success was seen in 2 of 9 (22%) patients with this indication.

Section Summary: Corneal Ulcers and Melts That Do Not Respond to Initial Medical Therapy

Corneal ulcers and melts are uncommon and variable and additional RCTs are not expected. A systematic review of 1 RCT and case series showed healing in 97% of patients with an improvement of vision in 53% of eyes. One retrospective comparative study with 22 patients found more rapid and complete epithelialization and more patients with a clinically significant improvement in visual acuity following early treatment with self-retained amniotic membrane when compared to historical controls. These results support the use of non-sutured amniotic membrane for corneal ulcers and melts that do not respond to initial medical therapy.

CORNEAL PERFORATION WHEN THERE IS ACTIVE INFLAMMATION AFTER CORNEAL TRANSPLANT REQUIRING ADJUNCTIVE TREATMENT

Clinical Context and Therapy Purpose

The purpose of HAM in patients who have active inflammation after a corneal transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have corneal perforation when there is active inflammation after corneal transplant?

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

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

Comparators

The following therapies are currently being used: medical therapy.

Outcomes

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

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
No evidence was identified for this indication.

Section Summary: Corneal Perforation When There is Active Inflammation After Corneal Transplant Requiring Adjunctive Treatment
No evidence was identified for this indication.

BULLOUS KERATOPATHY IN PATIENTS WHO ARE NOT CANDIDATES FOR A CURATIVE TREATMENT (EG, ENDOTHELIAL OR PENETRATING KERATOPLASTY)

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

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have bullous keratopathy and are not candidates for a curative treatment?

The following PICO was used to select literature to inform this review.

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

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

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

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

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Dos Santos Paris et al (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy.[27,] 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.

Section Summary: Bullous Keratopathy in Patients Who are Not Candidates for a Curative Treatment and Who are Unable to Remain Still for Stromal Puncture
An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy.

PARTIAL LIMBAL STEM CELL DEFICIENCY WITH EXTENSIVE DISEASED TISSUE WHERE SELECTIVE REMOVAL ALONE IS NOT SUFFICIENT

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

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have partial limbal stem cell deficiency?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients who have limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient.

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

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

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

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
No RCTs were identified on HAM for limbal stem cell deficiency.
Keirkhah et al (2008) reported on the use of HAM in 11 eyes of 9 patients who had limbal stem cell deficiency.[28,] Patients underwent superficial keratectomy to remove the conjunctivalized pannus followed by HAM transplantation using fibrin glue. An additional ProKera patch was used in 7 patients. An improvement in visual acuity was observed in all but 2 patients. Pachigolla et al (2009) reported a series of 20 patients who received a ProKera implant for ocular surface disorders; 6 of the patients had limbal stem cell deficiency with a history of chemical burn.[29,] Following treatment with ProKera, 3 of the 6 patients had a smooth corneal surface and improved vision to 20/40.[29,] The other 3 patients had final visual acuity of 20/400, counting fingers, or light perception.

Section Summary: Partial Limbal Stem Cell Deficiency with Extensive Diseased Tissue Where Selective Removal Alone is Not Sufficient
No RCTs were identified on HAM for partial limbal stem cell deficiency. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus.

MODERATE OR SEVERE STEVENS-JOHNSON SYNDROME

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

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

The following PICO was used to select literature to inform this review.

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

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

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

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

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
One RCT from India by Sharma et al (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or medical therapy alone.[30,] The c-HAM was prepared locally and applied with fibrin glue rather than sutures. Application of c-HAM in the early stages of SJS resulted in improved visual acuity (p=.042), better tear breakup time (p=.015), improved Schirmer test results (p<.001), and less conjunctival congestion (p=.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=.001), 6 (24%) cases of corneal vascularization and conjunctivalization (p=.03), and 6 (24%) cases of trichiasis and metaplastic lashes.

Section Summary: Moderate or Severe Stevens-Johnson Syndrome
The evidence on HAM for the treatment of SJ Syndrome includes 1 RCT with 25 patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone.

PERSISTENT EPITHELIAL DEFECTS AND ULCERATIONS THAT DO NOT RESPOND TO CONSERVATIVE THERAPY

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

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

The following PICO was used to select literature to inform this review.

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

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

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

Outcomes
The general outcomes of interest are epithelial closure.

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease.[31,] 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.

Section Summary: Persistent Epithelial Defects and Ulceration that Do Not Respond to Conservative Therapy
No RCTs were identified on persistent epithelial defects and ulceration.

SEVERE DRY EYE DISEASE WITH OCULAR SURFACE DAMAGE AND INFLAMMATION THAT DOES NOT RESPOND TO CONSERVATIVE THERAPY

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

The following PICO was used to select literature to inform this review.

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

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

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

Outcomes
The general outcomes of interest are the pain, corneal surface regularity, and vision, which may be measured by the Report of the International Dry Eye WorkShop score (DEWS). The DEWS assess 9 domains with a score of 1 to 4 including discomfort, visual symptoms, tear breakup time, corneal signs and corneal staining. Corneal staining with fluorescein or Rose Bengal indicates damaged cell membranes or gaps in the epithelial cell surface. A DEWS of 2 to 4 indicates moderate-to-severe dry eye disease.

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
John et al (2017) reported on an RCT with 20 patients with moderate-to-severe dry eye disease who were treated with Prokera c-HAM or maximal conventional treatment.[32,] 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 treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study (McDonald et al [2018]) was a retrospective series of 84 patients (97 eyes) with severe dry eye despite maximal medical therapy who were treated with Prokera self-retained c-HAM.[33,] A majority of patients (86%) had superficial punctate keratitis. Other patients had filamentary keratitis (13%), exposure keratitis (19%), neurotrophic keratitis (2%), and corneal epithelial defect (7%). Treatment with Prokera for a mean of 5.4 days (range, 2 to 11) resulted in an improved ocular surface and reduction in the DEWS score from 3.25 at baseline to 1.44 at 1 week, 1.45 at 1 month and 1.47 at 3 months (p=.001). Ten percent of eyes required repeated treatment. There was no significant difference in the number of topical medications following c-HAM treatment.

Section Summary: Severe Dry Eye with Ocular Surface Damage and Inflammation that Does Not Respond to Conservative Therapy
The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months.

MODERATE OR SEVERE ACUTE OCULAR CHEMICAL BURNS

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

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have moderate or severe acute ocular chemical burns?

The following PICO was used to select literature to inform this review.

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

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

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

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

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
An RCT of 100 patients with chemical or thermal ocular burns was published by Tandon et al (2011).[34,] Half of the patients (n=50) had moderate ocular burns and the remainder (n=50) had severe ocular burns. All but 8 of the patients had alkali or acid burns. Patients were randomized to HAM transplantation plus medical therapy or medical therapy alone. Epithelial healing, which was the primary outcome, was improved in the group treated with HAM, but there was no significant difference between the 2 groups for final visual outcome, symblepharon formation, corneal clarity or vascularization.

A second RCT that compared amniotic membrane plus medical therapy (30 eyes) to medical therapy alone (30 eyes) for grade IV ocular burn was reported by Eslani et al (2018).[35,] Medical therapy at this tertiary referral hospital included topical preservative-free lubricating gel and drops, chloramphenicol, betamethasone, homatropine, oral vitamin C, and doxycycline. There

was no significant difference in the time to epithelial healing (amniotic membrane: 75.8 vs. 72.6 days) or in visual acuity between the 2 groups (2.06 logMAR for both groups). There was a trend for a decrease in corneal neovascularization (p=.108); the study was not powered for this outcome.

A third RCT by Tamhane et al (2005) found no difference between amniotic membrane and medical therapy groups in an RCT of 37 patients with severe ocular burns.[36,]

Section Summary: Moderate or Severe Acute Ocular Chemical Burns
Evidence includes 3 RCTs with a total of 197 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Patients in the HAM group had a faster rate of epithelial healing in 1 of the 3 trials, without a significant benefit for other outcomes. The other 2 trials did not find an increase in the rate of epithelial healing in patients with severe burns.

CORNEAL PERFORATION WHEN CORNEAL TISSUE IS NOT IMMEDIATELY AVAILABLE

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

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

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients who have corneal perforation when corneal tissue is not immediately available.

Interventions
The therapy being considered is sutured HAM.

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

Outcomes
The general outcomes of interest are eye pain.

Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
No RCTs were identified on corneal perforation.

Section Summary: Corneal Perforation When Corneal Tissue is Not Immediately Available
The standard treatment for corneal perforation is corneal transplantation, however, sutured HAM may be used as a temporary covering for this severe defect when corneal tissue is not immediately available.

FOLLOWING PTERYGIUM REPAIR WHEN THERE IS INSUFFICIENT HEALTHY TISSUE TO CREATE A CONJUNCTIVAL AUTOGRAFT

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

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

The following PICO was used to select literature to inform this review.

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

Interventions
The therapy being considered is sutured or glued HAM.

Comparators
The following therapies are currently being used: conjunctival autograft.

Outcomes
The general outcomes of interest are a recurrence of pterygium.

Pterygium recurrence would be measured at 1 to 3 months.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
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.[37,] 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.[38,]

Section Summary: Following Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft
Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence.

REPAIR FOLLOWING MOHS MICROSCOPIC SURGERY

Clinical Context and Therapy Purpose
The purpose of repair with human amniotic membrane in patients who have undergone Mohs microsurgery for skin cancer is to provide a treatment option that is an alternative to or an improvement on existing procedures.

The question addressed in this evidence review is: Does amniotic membrane improve the net health outcome in patients requiring repair following Mohs microsurgery?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients who require reconstruction following Mohs microsurgery for skin cancer on the head, neck, face, or dorsal hand.

Interventions
The therapy being considered is repair following Mohs microsurgery with human amniotic membrane. It is proposed as a nonsurgical alternative to cutaneous repair in cosmetically sensitive areas such as the head, neck, face, or dorsal hand.

Comparators
Comparators of interest include surgical repair using autologous tissue (e.g., local flaps and full-thickness skin grafts) and healing without surgery. Second intention healing (i.e., the wound is

left open to heal by granulation, contraction, and epithelialization) is a nonsurgical option for certain defects.

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

- Incidence of complete wound closure.
- Time to complete wound closure (reflecting accelerated wound closure).
- Incidence of complete wound closure following surgical wound closure.
- Pain control.
- Complete ulcer healing with advanced wound therapies may be measured at 6 to 12 weeks.

In trials comparing human amniotic membrane to surgical repair in patients post-Mohs microscopic surgery, other important outcomes are postprocedure morbidity and mortality, surgical complications, development of a non-healing wound, and quality of life.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence
No RCTs were identified for this indication.

Nonrandomized Studies
Toman et al (2022) conducted an observational study that compared repair using a dehydrated human amnion/chorion membrane product (Epifix) with surgical repair using autologous tissue in patients who underwent same-day repair following Mohs microsurgery for removal of skin cancer on the face, head, or neck (Table 14).[39,] Propensity-score matching using retrospective data from medical records was used to identify 143 matched pairs. The primary endpoint was the incidence of postoperative morbidity, including the rate of infection, bleeding/hematoma, dehiscence, surgical reintervention, or development of a nonhealing wound. Postoperative cosmetic outcomes were assessed at 9 months or later and included documentation of suboptimal scarring, scar revision treatment, and patient satisfaction.

Results are summarized in Table 15, and study limitations in Tables 16 and 17. A greater proportion of patients who received dHACM repair experienced zero complications (97.9% vs. 71.3%; p<.0001; relative risk 13.67; 95% CI 4.33 to 43.12). Placental allograft reconstructions developed less infection (p=.004) and were less likely to experience poor scar cosmesis (P

<.0001). Confidence in these findings is limited, however, by the study's retrospective design and potential for bias due to missing data. Additionally, the study's relevance is limited due to a lack of diversity in the study population and no comparison to non-surgical treatment options.

Table 14. Nonrandomized Study of Dehydrated Human Amnion/Chorion Membrane for Repair Following Mohs Microsurgery - Characteristics

Study	Study Type	Country	Dates	Participants	Repair using dHACM	Repair using autologous tissue	Follow-Up
Toman et al (2022)[39,]	Retrospective, observational Propensity-score matching used to identify matched pairs	US	2014-2018	Patients who underwent Mohs microsurgery for removal of a basal or squamous cell carcinoma and required same day repair for moderate- to high-risk defects on the face, head, and neck. Mean age 78.0 years; 76.9% male 100% white	n = 143	n = 143	Unclear; 9 months or later for postoperative cosmetic outcomes.

dHACM: dehydrated human amnionic/chorionic membrane.

Table 15. Nonrandomized Study of Dehydrated Human Amnion/Chorion Membrane for Repair Following Mohs Microsurgery- Results

Study	dHACM repair n = 143	Autogolous tissue Repair n = 143	P
Toman et al (2022)[39,]			
Experienced no complications, n (%)	140 (97.9)	102 (71.3)	<.0001
Infection, n (%)	3 (2.0)	15 (10.0)	.004
Bleeding or hematoma, n (%)	0 (0.0)	7 (5.0)	.015
Wound dehiscence, n (%)	0 (0.0)	4 (3.0)	.122
Surgical reintervention, n (%)	0 (0.0)	11 (8.0)	.0007
Nonhealing wound, n (%)	0 (0.0)	5 (3.5)	.060
Poor scar cosmesis, n (%)	0 (0.0)	21 (15.0)	<.0001

Study	dHACM repair n = 143	Autogolous tissue Repair n = 143	P
Scar revision, n (%)	0 (0.0)	14 (9.8)	<.0001
Follow-up visits, mean (SD)	3.4 (1.6)	2.5 (1.1)	<.0001
Days to discharge, mean (SD)	30.7 (16.9)	30.3 (22.9)	.840

SD: standard deviation; dHACM: dehydrated human amnionic/chorionic membrane.

Table 16. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Toman et al (2022)[39,]	4. Study participants were 100% white, over two-thirds male		2. No comparison to non-surgical options (e.g., second intention healing)	1. Not all outcomes mentioned in methods had results reported (e.g., patient satisfaction with scar appearance)	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 17. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Toman et al (2022)[39,]	1. Not randomized	1, 2. Not blinded		7. Data extracted from medical records could be incomplete/ inaccurate; 10 of 153 patients excluded because no match identified		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear;

4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Repair Following Mohs Microscopic Surgery

A retrospective observational study found a higher complication-free rate in 143 propensity score-matched pairs of patients who had received autologous tissue or dHACM repair following Mohs microsurgery for skin cancer on the face, head, or neck. This study was limited by its retrospective design. Additional evidence from well-designed and conducted prospective studies is needed.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.

2019 Input

Clinical input was sought to help determine whether the use of human amniotic membrane graft either without or with suture fixation for several ophthalmic conditions would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 1 specialty society-level response and 1 physician-level response identified through specialty societies including physicians with academic medical center affiliations. Clinical input supported the use of amniotic membrane in individuals with the following indications:

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.
- Corneal ulcers and melts that do not respond to initial medical therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment.
- Bullous keratopathy and who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty) as an alternative to stromal puncture.

- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient.
- Persistent epithelial defects and ulcerations that do not respond to conservative therapy.
- Severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy.
- Moderate or severe acute ocular chemical burn.
- Corneal perforation when corneal tissue is not immediately available.
- Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Society for Vascular Surgery et al.
In 2016, the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine made the following recommendation: "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amnionic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."[40,]

Tear Film and Ocular Surface Society
In 2017, the Tear Film and Ocular Surface Society published the Dry Eye Workshop II (DEWS) management and therapy report.[23,] The report evaluated the evidence on treatments for dry eye and provided the following treatment algorithm for dry eye disease management:

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

Step 2:
If above options are inadequate consider:

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

Step 3:
If above options are inadequate consider:

- Oral secretagogues
- Autologous/allogeneic serum eye drops
- Therapeutic contact lens options
- Soft bandage lenses
- Rigid scleral lenses

Step 4:
If above options are inadequate consider:

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

Wound Healing Society
In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.[41,] The Society concluded that there was level 1 evidence that cellular and acellular skin equivalents improve diabetic foot ulcer healing, noting that, "healthy living skin cells assist in healing DFUs [diabetic foot ulcers] by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed." References from 2 randomized controlled trials on amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

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 18.

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04457752[a]	A Randomized Controlled Multicentre Clinical Trial, Evaluating the Efficacy of Dual Layer Amniotic Membrane (Artacent®) and Standard of Care Versus Standard of Care Alone in the Healing of Chronic Diabetic Foot Ulcers	124	Mar 2023
NCT03390920[a]	Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions	200	Jan 2030
NCT04612023	A Prospective, Double-Blinded, Randomized Controlled Trial of an Amniotic Membrane Allograft Injection Comparing Two Doses (1 mL and 2 mL Injection) and a Placebo (Sterile Saline) in the Treatment of Osteoarthritis of the Knee	90	Jul 2022
NCT04553432[a]	Dry Eye OmniLenz Application of Omnigen Research Study	130	Jul 2024
NCT04599673	Prospective Analysis of Intraoperative AMNIOGEN® Injection in Patients With Rotator Cuff Tear	100	Sep 2022
NCT04636229[a]	A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients With Osteoarthritis of the Knee	474	Dec 2023
Unpublished			
NCT03855514[a]	A Prospective, Multicenter, Randomized, Controlled Clinical Study Of NuShield® and Standard of Care (SOC) Compared to SOC Alone For The Management Of Diabetic Foot Ulcers	200	Dec 2021 (Recruiting)

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. This may not be a comprehensive list of procedure codes applicable to this policy.

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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

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
A2001	Innovamatrix ac, per square centimeter
Q4132	Grafix Core and GrafixPL Core, per sq cm
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq cm
Q4137	AmnioExcel, AmnioExcel Plus or BioDExcel, per sq cm
Q4138	BioDFence DryFlex, 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
Q4176	NeoPatch or Therion per sq. cm
Q4177	FlowerAmnioFlo, 0.1 cc
Q4178	FlowerAmnioPatch, per sq cm
Q4180	Revita, per square centimeter
Q4181	Amnio Wound, per sq cm

CPT/HCPCS	
Q4183	Surgigraft, per sq cm
Q4184	Cellesta, per sq cm
Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4186	Epifix, per sq cm
Q4187	Epicord, per sq cm
Q4188	AmnioArmor, per sq cm
Q4189	Artacent AC, 1 mg
Q4190	Artacent AC, per sq cm
Q4191	Restorigin, per sq cm
Q4192	Restorigin, 1 cc
Q4194	Novachor, per sq cm
Q4198	Genesis Amniotic Membrane, per sq cm
Q4199	Cygnus matrix, per square centimeter
Q4201	Matrion, per sq cm
Q4204	XWRAP, per sq cm
Q4205	Membrane graft or membrane wrap, per square centimeter
Q4206	Fluid flow or fluid GF, 1 cc
Q4208	Novafix, per square centimeter
Q4209	Surgraft, per square centimeter
Q4210	Axolotl graft or axolotl dualgraft, per square centimeter
Q4211	Amnion bio or Axobiomembrane, per square centimeter
Q4212	Allogen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta cord, per square centimeter
Q4215	Axolotl ambient or axolotl cryo, 0.1 mg
Q4216	Artacent cord, per square centimeter
Q4217	Woundfix, BioWound, Woundfix Plus, BioWound Plus, Woundfix Xplus or BioWound Xplus, per square centimeter
Q4218	Surgicord, per square centimeter
Q4219	Surgigraft-dual, per square centimeter
Q4220	BellaCell HD or Surederm, per square centimeter
Q4221	Amniowrap2, per square centimeter
Q4224	Human health factor 10 amniotic patch (hhf10-p), per square centimeter
Q4225	Amniobind, per square centimeter
Q4227	Corplex, per square centimeter
Q4229	Cogenex Amniotic Membrane
Q4230	Cogenex Flowable Amnion, per 0.5 cc
Q4231	Corplex P, per cubic centimeter
Q4232	Corplex, per square centimeter
Q4233	SurFactor or NuDyn, per 0.5 cc
Q4234	XCellerate, per square centimeter
Q4235	Amniorepair, altiply, per square centimeter
Q4236	Carepatch, per square centimeter (reactivated 01-01-2023)
Q4237	Cryo-Cord, per square centimeter
Q4238	Derm-maxx, per square centimeter

CPT/HCPCS	
Q4239	Amnio-Maxx, Amnio-Maxx Lite, per square centimeter
Q4240	Amniotext patch, per square centimeter
Q4241	PolyCyte, per 0.5 mL
Q4242	AmnioCyte Plus, per 0.5 mL
Q4244	Procenta 200 mg, 1-6 square centimeter
Q4245	AmnioText, per square centimeter
Q4246	CoreText, ProText, per cc
Q4247	Amniotext patch, per square centimeter
Q4248	Dermacyte Matrix, per sq cm
Q4249	Amniply, for topical use only, per square centimeter
Q4250	Amnioamp-mp, per square centimeter
Q4251	Vim, per square centimeter
Q4252	Vendaje, per square centimeter
Q4253	Zenith amniotic membrane, per square centimeter.
Q4254	Novafix dl, per square centimeter
Q4255	Reguard, for topical use only, per square centimeter
Q4256	Mlg-complete, per square centimeter
Q4257	Relese, per square centimeter
Q4258	Enverse, per square centimeter
Q4259	Celera dual layer or celera dual membrane, per square centimeter
Q4260	Signature apatch, per square centimeter
Q4261	Tag, per square centimeter
Q4262	Dual layer impax membrane, per square centimeter
Q4263	Surgraft tl, per square centimeter
Q4264	Cocoon membrane, per square centimeter
Q4265	Neostim tl, per square centimeter (eff. 04-01-2023)
Q4266	Neostim membrane, per square centimeter (eff. 04-01-2023)
Q4267	Neostim dl, per square centimeter (eff. 04-01-2023)
Q4268	Surgraft ft, per square centimeter (eff. 04-01-2023)
Q4269	Surgraft xt, per square centimeter (eff. 04-01-2023)
Q4270	Complete sl, per square centimeter (eff. 04-01-2023)
Q4271	Complete ft, per square centimeter (eff. 04-01-2023)
Q4272	Esano a, per square centimeter
Q4273	Esano aaa, per square centimeter
Q4274	Esano ac, per square centimeter
Q4275	Esano aca, per square centimeter
Q4276	Orion, per square centimeter
Q4277	Woundplus membrane or e-graft, per square centimeter
Q4278	Epieffect, per square centimeter
Q4280	Xcell amnio matrix, per square centimeter
Q4281	Barrera sl or barrera dl, per square centimeter
Q4282	Cygnus dual, per square centimeter
Q4283	Biovance tri-layer or biovance 3l, per square centimeter
Q4284	Dermabind sl, per square centimeter

REVISIONS	
03-20-2017	Policy added to the bcbsks.com web site.
01-01-2019	Updated Description section.
	In Policy section: ▪ In Item A 1, added "Q4168". ▪ In Item A 3, removed "Q4131" and added "Q4145, Q4186". ▪ Added new Item 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. ▪ Added new Item 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, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy." ▪ 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. ▪ Added ICD-10 codes: H11.001, H11.002, H11.003, H11.011, H11.012, H11.013, H11.021, H11.022, H11.023, H11.031, H11.032, H11.033, H11.041, H11.042, H11.043, H11.051, H11.052, H11.053, H11.061, H11.062, H11.063, H16.011, H16.012, H16.013, H16.021, H16.022, H16.023, H16.031, H16.032, H16.033, H16.041, H16.042, H16.043, H16.051, H16.052, H16.053, H16.061, H16.062, H16.063, H16.121, H16.122, H16.123, H16.231, H16.232, H16.233, H18.831, H18.832, H18.833, T26.11XA, T26.11XD, T26.11XS, T26.12XA, T26.12XD, T26.12XS, T26.31XA, T26.31XD, T26.31XS, T26.32XA, T26.32XD, T26.32XS, T26.51XA, T26.51XD, T26.51XS, T26.52XA, T26.52XD, T26.52XS, T26.61XA, T26.61XD, T26.61XS, T26.62XA, T26.62XD, T26.62XS, T26.81XA, T26.81XD, T26.81XS, T26.82XA, T26.82XD, T26.82XS.
	Updated References section.
02-18-2019	In Policy section: ▪ In Item A 3, removed "Q4145".
03-27-2019	Updated Description section.
	In Policy section: ▪ In Item A, added new Item A 3, "Epicord (Q4187)".
	Updated Rationale section.

REVISIONS	
	In Coding section: ▪ Removed ICD-10 codes: T26.51XA, T26.51XD, T26.51XS, T26.52XA, T26,52XD, T26.52XS.
	Updated References section.
05-21-2019	In Policy section: ▪ In Item A 1, removed HCPCS code Q4168.
09-27-2019	Policy published to the bcbsks.com website on 08-28-2019 with an effective date of 09-27-2019.
	In Coding section: ▪ Added ICD-10 codes: H18.891, H18.892, H18.893.
	Updated References section.
10-01-2019	In Coding section: ▪ Added HCPCS Codes: Q4205, Q4206, Q4208, Q4209, Q4210, Q4211, Q4212, Q4213, Q4214, Q4215, Q4216, Q4217, Q4218, Q4219, Q4221
07-01-2020	In Coding section: ▪ Added HCPCS Codes: Q4176, Q4177, Q4178, Q4181, Q4227, Q4228, Q4229, Q4230, Q4231, Q4232, Q4233, Q4234, Q4235, Q4236, Q4237, Q4239, Q4240, Q4241, Q4242, Q4244, Q4245, Q4246, Q4247, Q4248
07-16-2021	Updated Description section
	In Policy section Added item A.1 In Item B • Removed: "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" • Added: "Human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) or glue may be considered medically necessary for the treatment of the following ophthalmic indications: 1. Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy; 2. Corneal ulcers and melts that do not respond to initial conservative therapy; 3. Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment; 4. Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty); 5. Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient; 6. Moderate or severe Stevens-Johnson syndrome; 7. Persistent epithelial defects that do not respond as stated in policy guideline #2; 8. Severe dry eye (DEWS 3 or 4) with ocular surface damage and inflammation that remains symptomatic after Steps 1, 2, and 3 of the dry eye disease management algorithm (see Policy Guidelines); or 9. Moderate or severe acute ocular chemical burn." 10. Corneal perforation when corneal tissue is not immediately available; or

REVISIONS	
	11. Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft In Item C • Removed: "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, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy." • Added: "Human amniotic membrane grafts with or without suture are considered **experimental / investigational** for all ophthalmic indications not outlined above." Added • Item F • Policy Guidelines
	Updated Rationale section
	In Coding section: • Added HCPCS Codes: Q4180, Q4220, Q4238, Q4249, Q4250, Q4254, Q4255 • Added ICD 10 Diagnosis codes: H18.11, H18.12, H18.13, H18.30, H18.52, I87.2, L51.1, T26.50XA, T26.50XD, T26.50XS, T26.51XA, T26.51XD, T26.51XS, T26.52XA, T26.52XD, T26.52XS • Removed ICD 10 Diagnosis codes: H16.121, H16.122, H16.123, L97.212, L97.213, L97.214, L97.222, L97.223, L97.224, L97.312, L97.313, L97.314, L97.322, L97.323, L97.324, L97.412, L97.413, L97.414, L97.422, L97.423, L97.424, L97.512, L97.513, L97.514, L97.522, L97.523, L97.524, L97.812, L97.813, L97.814, L97.822, L97.823, L97.824, T26.31XA, T26.31XD, T26.31XS, T26.32XA, T26.32XD, T26.32XS, T26.61XA, T26.61XD, T26.61XS, T26.62XA, T26.62XD, T26.62XS, T26.81XA, T26.81XD, T26.81XS, T26.82XA, T26.82XD, T26.82XS
	Updated Reference section
	Added Appendix
10-08-2021	In Coding section: Effective 10-01-2021 Added HCPCS codes: Q4251, Q4252, Q4253 Deleted HCPCS codes: Q4228, Q4236 (no longer being manufactured)
01-03-2022	In Coding Section Added HCPCS code A2001, Q4199 (effective 01-01-2022)
04-01-2022	In Coding Section Added: Q4224, Q4225, Q4256, Q4257, Q4258 (new codes 04-01-2022)
04-08-2022	Updated Description Section
	Updated Policy Section ▪ Section G "All other indications not listed above are considered experimental / investigational, including, but not limited to, treatment of lower-extremity ulcers due to venous insufficiency." added "and repair following Mohs micrographic surgery" to the end of the statement.
	Updated Rationale Section
	Updated Coding Section ▪ Removed coding bullets • There are specific HCPCS codes for some of these products. If no specific HCPCS code exists for the product, an unlisted code such as Q4100 would be used. • There are no specific codes for AmnioFix or OrthoFlo. It might be reported using the code for another MiMedx product such as Q4145 or the not otherwise specified code Q4100.

REVISIONS	
	• There is no specific code for this type of injection. It might be reported with one of the musculoskeletal system injection codes (e.g., 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, 65779 ▪ Removed Code: Q4100 ▪ Added ICD-10 Codes: H04.121-H04.129, M17.10-M17.9 and M72.2 ▪ Converted ICD-10 codes to ranges
	Updated References Section
01-03-2023	Updated Coding Section ▪ Added codes Q4259, Q4260, Q4261 (eff. 07-01-2022) and Q4262, Q4263, Q4264 (eff. 01-01-2023)
03-28-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Added Q4236 (reactivated 01-01-2023), Q4265, Q4266, Q4267, Q4268, Q4269, Q4270, Q4271 (eff. 04-01-2023) ▪ Removed ICD-10 Codes
	Updated References Section
	Removed Appendix Section
07-03-2023	Updated Coding Section ▪ Added: Q4272, Q4273, Q4274, Q4275, Q4276, Q4277, Q4278, Q4280, Q4281, Q4282, Q4283 and Q4284 (eff. 7-1-2023)

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