

## Medical Policy



### Title: Amniotic Membrane and Amniotic Fluid

<i>Related Policies:</i>	▪ <i>Bio-Engineered Skin and Soft Tissue Substitutes</i>
	▪ <i>Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)</i>

#### **Professional**

Original Effective Date: March 20, 2017  
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 2021  
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#### **Institutional**

Original Effective Date: March 20, 2017  
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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:	Interventions of interest are:	Comparators of interest are: • Compression therapy	Relevant outcomes include: • Symptoms • Morbid events

<b>Populations</b>	<b>Interventions</b>	<b>Comparators</b>	<b>Outcomes</b>
<ul style="list-style-type: none"> <li>With lower-extremity ulcers due to venous insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>Patch or flowable formulation of human amniotic membrane</li> </ul>	<ul style="list-style-type: none"> <li>Advanced wound therapies</li> </ul>	<ul style="list-style-type: none"> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
<p>Individuals:</p> <ul style="list-style-type: none"> <li>With knee osteoarthritis</li> </ul>	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> <li>Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid</li> </ul>	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> <li>Conservative therapy</li> <li>Corticosteroid injections</li> </ul>	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> <li>Symptoms</li> <li>Functional outcomes</li> <li>Quality of life</li> <li>Treatment-related morbidity</li> </ul>
<p>Individuals:</p> <ul style="list-style-type: none"> <li>With plantar fasciitis</li> </ul>	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> <li>Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid</li> </ul>	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> <li>Conservative therapy</li> <li>Corticosteroid injections</li> </ul>	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> <li>Symptoms</li> <li>Functional outcomes</li> <li>Quality of life</li> <li>Treatment-related morbidity</li> </ul>
<p>Individuals:</p> <ul style="list-style-type: none"> <li>With neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative treatment</li> </ul>	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> <li>Sutured or self-retained human amniotic membrane</li> </ul>	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> <li>Medical therapy</li> <li>Bandage contact lens</li> </ul>	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
<p>Individuals:</p> <ul style="list-style-type: none"> <li>With corneal ulcers or melts that do not respond to initial medical therapy</li> </ul>	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> <li>Sutured or self-retained human amniotic membrane</li> </ul>	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> <li>Medical therapy</li> <li>Bandage contact lens</li> </ul>	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
<p>Individuals:</p> <ul style="list-style-type: none"> <li>With corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment</li> </ul>	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> <li>Sutured or self-retained human amniotic membrane</li> </ul>	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> <li>Medical therapy</li> <li>Bandage contact lens</li> </ul>	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
<p>Individuals:</p> <ul style="list-style-type: none"> <li>With bullous keratopathy as a palliative measure in patients who are not candidates for a curative treatment (e.g., endothelial or penetrating keratoplasty)</li> </ul>	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> <li>Sutured or self-retained human amniotic membrane</li> </ul>	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> <li>Medical therapy</li> <li>Bandage contact lens</li> </ul>	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
<p>Individuals:</p> <ul style="list-style-type: none"> <li>With partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient</li> </ul>	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> <li>Sutured or self-retained human amniotic membrane</li> </ul>	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> <li>Medical therapy</li> <li>Bandage contact lens</li> </ul>	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
<p>Individuals:</p> <ul style="list-style-type: none"> <li>With moderate or severe Stevens-Johnson syndrome</li> </ul>	<p>Interventions of interest are:</p> <ul style="list-style-type: none"> <li>Sutured or self-retained human amniotic membrane</li> </ul>	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> <li>Medical therapy</li> <li>Bandage contact lens</li> </ul>	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
<p>Individuals:</p>	<p>Interventions of interest are:</p>	<p>Comparators of interest are:</p> <ul style="list-style-type: none"> <li>Medical therapy</li> </ul>	<p>Relevant outcomes include:</p> <ul style="list-style-type: none"> <li>Symptoms</li> </ul>

Populations	Interventions	Comparators	Outcomes
<ul style="list-style-type: none"> <li>With persistent epithelial defects that do not respond to conservative therapy</li> </ul>	<ul style="list-style-type: none"> <li>Sutured or self-retained human amniotic membrane</li> </ul>	<ul style="list-style-type: none"> <li>Bandage contact lens</li> </ul>	<ul style="list-style-type: none"> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Sutured or self-retained human amniotic membrane</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Medical therapy</li> <li>Bandage contact lens</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With moderate or severe acute ocular chemical burn</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Sutured or self-retained human amniotic membrane</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Medical therapy</li> <li>Bandage contact lens</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With corneal perforation when corneal tissue is not immediately available</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Sutured human amniotic membrane</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Medical therapy</li> <li>Bandage contact lens</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Sutured or glued human amniotic membrane</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Medical therapy</li> <li>Bandage contact lens</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Symptoms</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Quality of life</li> </ul>

## **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.<sup>1</sup> There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause a substantial immune response. It is believed that these properties are retained in cryopreserved HAM and dehydrated HAM products, resulting in a readily available tissue with regenerative potential. In support, 1 dehydrated HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.<sup>2</sup>

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.<sup>1</sup> 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.<sup>1</sup> 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.<sup>3</sup> 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.<sup>1</sup> Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type. The use of stem cells in orthopedic applications is addressed in the BCBSKS medical policy *Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow)* evidence review.

### **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).<sup>4</sup>

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."<sup>5</sup> 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 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
  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.

### Policy Guidelines

1. 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).
2. A persistent epithelial defect is one that failed to close completely after 5 days of conservative treatment or has failed to demonstrate a decrease in size after 2 days of conservative treatment.
3. Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. Failure of multiple modalities should not be required prior to moving to human amniotic membrane grafts. An amniotic membrane graft requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in regard to treatments requiring multiple drops per day.

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
Amnio-maxx or Manio-maxx lite	Royal Biologics	Q4239
Amniotext	Regenerative Labs	Q4245

<b>Trade Name</b>	<b>Supplier</b>	<b>HCPCS Code</b>
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
Artacent 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 <sup>a</sup>	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 Prottext	Regenerative Labs	Q4246
Cryo-cord	Royal Biologics	Q4237
Cygnus	Vivex Biomedical	Q4170



<b>Trade Name</b>	<b>Supplier</b>	<b>HCPCS Code</b>
Dermacyte	Merakris Therapeutics	Q4248
Dermavest™ or Plurivest	AediCell <sup>a</sup>	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	Amnio Medical	Q4148
Neox® Flo	Amnio Medical	Q4155
Neox® Wound	Amnio Medical	Q4156
Novachor	Organogenesis	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
SurgiGRAFT™	Synergy Biologics	Q4183
WoundEx®	Skye Biologics <sup>a</sup>	Q4163

Trade Name	Supplier	HCPCS Code
WoundEx® Flow	Skye Biologics <sup>a</sup>	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

<sup>a</sup> 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

**RATIONALE**

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through December 28, 2020.

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

## **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.

#### **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) <sup>6</sup> ,	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) <sup>7</sup> ,	U.S.	7	2016-2017	75 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers between 1 cm <sup>2</sup> and 15 cm <sup>2</sup>	n=38, Grafix weekly for up to 8 weeks	n=37, Dermagraft (fibroblast-derived) weekly for up to 8 weeks
Tettelbach et al. (2018) <sup>8</sup> ,	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
DiDomenico et al. (2018) <sup>9</sup> ,				80 patients with non-healing (4 weeks) diabetic foot ulcers	AmnioBand Membrane plus SOC	SOC
Snyder et al. (2016) <sup>10</sup> ,				29 patients with non-healing diabetic foot ulcers	AmnioExcel plus SOC	SOC
Zelen et al. (2015, 2016) <sup>11,12</sup> ,		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) <sup>13</sup> ,	U.S.	14		110 patients with non-healing (4 weeks) lower extremity ulcers	EpiFix	SOC with alginate dressing
Lavery et al. (2014) <sup>14</sup> ,				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) <sup>6</sup> ,	12 Weeks (ITT) (%)	16 Weeks (ITT) (%)	Median	
N	76	76	76	

Study	Wounds Healed	Wounds Healed	Time to Complete Healing	Adverse Events and Number of Treatments
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) <sup>7</sup> ,	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%			
Tettlebach et al (2018) <sup>8</sup> ,	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	0.001	0.009		
DiDomenico et al. (2018) <sup>9</sup> ,	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	< 0.001	<0.001	<0.001	
Snyder et al. (2016) <sup>10</sup> ,	<b>6 Weeks (PP) Mean (95% CI)</b>			
N	21			

Study	Wounds Healed	Wounds Healed	Time to Complete Healing	Adverse Events and Number of Treatments
AmnioExcel	45.5% (32.9% to 58.0%)			
SOC	0%			
p-value	0.014			
Zelen et al. (2015, 2016) <sup>11,12,</sup>	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	0.003	<0.001 vs. SOC		0.003
Tettelbach (2019) <sup>13,</sup>		Wounds Healed at 12 Weeks (ITT) n(%)		
N		110		110
EpiFix		38 (81)		
SOC		28 (55)		
p-value				
Lavery et al (2014) <sup>14,</sup>		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		<0.001	0.019	0.031
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) <sup>10</sup>, preclude conclusions for this product.

**Table 3. Study Design and Conduct Limitations**

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Serena et al (2020) <sup>6</sup> ,	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) <sup>7</sup> ,		2, 3. No blinding for outcomes assessment				
Tettelbach et al (2018) <sup>8</sup> ,		1, 2, 3. No blinding				
DiDomenico et al (2018) <sup>9</sup> ,						
Snyder et al (2016) <sup>10</sup> ,				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) <sup>11,12</sup> ,				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) <sup>13</sup> ,		1, 2. No blinding of patients or investigators. Assessors were blinded				
Lavery et al (2014) <sup>14</sup> ,						

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.<sup>15</sup> 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.

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

Study	Study Design	Participants	Treatment Delivery
Smiell et al. (2015) <sup>15</sup> ,	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) <sup>16</sup> ,	Prospective multicenter 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) <sup>15</sup> ,	Biovance	41.6%	8 weeks	2.4
Frykberg et al. (2016) <sup>16</sup> ,	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  $\geq 2$  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**

### **DEHYDRATED AMNIOTIC MEMBRANE**

#### **Clinical Context and Therapy Purpose**

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

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

The following 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.

## 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).<sup>17</sup> 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).<sup>18,19</sup> Patients treated with EpiFix had a higher probability of complete healing by 12 weeks, as adjudicated by blinded outcome assessors (hazard ratio, 2.26; 95% CI, 1.25 to 4.10; p=0.01), and improved time to complete healing, as assessed by Kaplan-Meier analysis. 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 < 0.013) (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=0.0473). 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**

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Serena et al. (2014) <sup>17</sup>	U.S.	8	2012-2014	84 patients with a full-thickness chronic VLU between 2 and 20 cm <sup>2</sup> treated for at least 14 d	1 (n=26) or 2 (n=27) applications of EpiFix plus	Standard wound therapy (debridement with alginate dressing)

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
					standard wound therapy (n=53)	and compression) (n=31)
Bianchi et al. (2018, 2019) <sup>18,19</sup>	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) <sup>17</sup>						
EpiFix	62	11.3				
Control	32	12.9				
p-Value	0.005					
Bianchi et al. (2018, 2019) <sup>18,19</sup>						
EpiFix			31 (60)	32 (50)	37 (71)	38 (59)
Control			20 (35)	20 (31)	25 (44)	25 (39)
p-Value			0.013	0.047	0.007	0.034

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

**Table 8. Study Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Serena et al. (2014) <sup>17</sup>					
Bianchi et al. (2018, 2019) <sup>18,19</sup>					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.

<sup>a</sup> 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.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> 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.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 9. Study Design and Conduct Limitations**

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Serena et al. (2014) <sup>17</sup> ,						
Bianchi et al. (2018, 2019) <sup>18,19</sup> ,		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.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> 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).

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

<sup>f</sup> 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.<sup>15</sup> 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.<sup>20</sup> 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.

**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.<sup>21</sup> 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.<sup>22</sup> A subsequent RCT by Cazzell et al. (2018) enrolled 145 patients and reported 3-month follow-up (see Table 10).<sup>23</sup> In Cazzell 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) <sup>23</sup> ; 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) <sup>23</sup> ; 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%)
Diff (95% CI)	22.2 (13.1 to 31.3)	13.5 (6.2 to 20.8)		
p-Value	<0.001	<0.001		

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 <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Cazzell et al. (2018) <sup>23</sup> ; 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 <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Cazzell et al. (2018) <sup>23</sup> ; 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.

### **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.<sup>24</sup> 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 DO 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 health 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.

## **Review of Evidence**

Liu et al. (2019) conducted a systematic review of 17 studies (390 eyes) of amniotic membrane for corneal ulcers.<sup>25</sup> 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,  $p=0.089$ ) 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,  $p<0.001$ ).

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.<sup>26</sup> 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 ( $3.56 \pm 1.78$  weeks vs  $5.87 \pm 2.20$  weeks,  $p = 0.01$ ) and was reached in significantly more patients (72.7% vs 23.1%,  $p = 0.04$ ). 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%,  $p = 0.047$ ) and greater total improvement in visual acuity (log MAR  $0.7 \pm 0.6$  vs  $1.6 \pm 0.9$ ,  $p = 0.016$ ).

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.<sup>24</sup> 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.

#### **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.

**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.<sup>27</sup> 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.

**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.<sup>28</sup> 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.<sup>29</sup> Following treatment with ProKera, 3 of the 6 patients had a smooth corneal surface and improved vision to 20/40.<sup>29</sup> 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.

### **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.<sup>30</sup> 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 ( $p=0.042$ ), better tear breakup time ( $p=0.015$ ), improved Schirmer test results ( $p<0.001$ ), and less conjunctival congestion ( $p=0.03$ ). In the c-HAM group at 180 days, there were no cases of corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. These outcomes are dramatically better than those in the medical therapy alone group, which had 11 (44%) cases with corneal haze ( $p=0.001$ ), 6 (24%) cases of corneal vascularization and conjunctivalization ( $p=0.03$ ), and 6 (24%) cases of trichiasis and metaplastic lashes.

### **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 DOES NOT RESPOND TO CONSERVATIVE THERAPY**

### **Clinical Context and Therapy Purpose**

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

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

The following 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.

### **Review of Evidence**

Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease.<sup>31</sup> 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 Does 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 question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have severe dry eye with ocular surface damage and inflammation?

The following 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.

### **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.<sup>32</sup> 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.<sup>33</sup> A majority of patients (86%) had superficial punctate keratitis. Other patients had filamentary keratitis (13%), exposure keratitis (19%), neurotrophic keratitis (2%), and corneal epithelial defect (7%). Treatment with Prokera for a mean of 5.4 days (range, 2 to 11) resulted in an improved ocular surface and reduction in the DEWS score from 3.25 at baseline to 1.44 at 1 week, 1.45 at 1 month and 1.47 at 3 months ( $p=0.001$ ). Ten percent of eyes required repeated treatment. There was no significant difference in the number of topical medications following c-HAM treatment.

### **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.

**Review of Evidence**

An RCT of 100 patients with chemical or thermal ocular burns was published by Tandon et al (2011).<sup>34</sup> 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).<sup>35</sup> 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 ( $p=0.108$ ); 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.<sup>36</sup>

**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.

**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.

**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.<sup>37</sup> 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.<sup>38,</sup>

### **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.

## **SUMMARY OF EVIDENCE**

### **Diabetic Lower-Extremity Ulcers**

For individuals who have non-healing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM or placental membrane (i.e., Affinity, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix), the evidence includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing (<20% healing with  $\geq 2$  weeks of standard care) diabetic lower-extremity ulcers have compared HAM with standard care or with an established advanced wound care product. These trials used wound closure as the primary outcome measure, and some used power analysis, blinded assessment of wound healing, and intention-to-treat analysis. For the HAM products that have been sufficiently evaluated (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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

### **Lower-Extremity Ulcers due to Venous Insufficiency**

For individuals who have lower-extremity ulcers due to venous insufficiency who receive a patch or flowable formulation of HAM, the evidence includes 2 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The published 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 standard of care. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression, but interpretation is limited by methodologic concerns. Two additional studies with other HAM products have been completed but not published, raising further questions about the efficacy of HAM for venous insufficiency ulcers. Therefore, corroboration with well-designed and well-conducted RCTs evaluating wound healing is needed to demonstrate efficacy for this indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **Osteoarthritis**

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

**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 the visual analog score for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is that this is an interim report with 12-month results pending. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Ophthalmic Conditions**

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.

**Neurotrophic Keratitis with Ocular Surface Damage and Inflammation That Does Not Respond to Conservative Therapy**

For individuals who have neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy who receive HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Corneal Ulcers and Melts That Does Not Respond to Initial Medical Therapy**

For individuals who have corneal ulcers and melts, that does not respond to initial medical therapy who receive HAM, the evidence includes a systematic review of primarily case series and a non-randomized comparative study. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Corneal ulcers and melts are uncommon and variable and additional RCTs are not expected. The systematic review 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. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment who receive HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative evidence was identified for this indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Bullous Keratopathy as a Palliative Measure in Patients Who are Not Candidates for a Curative Treatment (e.g., Endothelial or Penetrating Keratoplasty)**

For individuals who have bullous keratopathy and who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty) who receive HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient who receive HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative trials were identified on HAM for 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Moderate or Severe Stevens-Johnson Syndrome**

For individuals who have moderate or severe Stevens-Johnson syndrome who receive HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of Stevens-Johnson syndrome (includes 1 RCT with 25 patients (50 eyes) found improved symptoms and function with HAM compared to medical therapy alone. Large RCTs are unlikely due to the severity and rarity of the disease.. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

**Persistent Epithelial Defects and Ulceration That Do Not Respond to Conservative Therapy**

For individuals who have persistent epithelial defects that do not respond to conservative therapy who receive HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative trials were identified on persistent epithelial defects and ulceration. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Severe Dry Eye with Ocular Surface Damage and Inflammation That Does Not Respond to Conservative Therapy**

For individuals who have severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy, who receive HAM, the evidence includes an RCT and a large case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

**Moderate or Severe Acute Ocular Chemical Burns**

For individuals who have moderate or severe acute ocular chemical burn who receive HAM, the evidence includes 3 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Evidence includes a total of 197 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Two of the 3 RCTs did not show a faster rate of epithelial healing, and there was no significant benefit for other outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Corneal Perforation When Corneal Tissue is Not Immediately Available**

For individuals who have corneal perforation when corneal tissue is not immediately available who receive sutured HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The standard treatment for corneal perforation is corneal transplantation, however, HAM may provide temporary coverage of the severe defect when corneal tissue is not immediately available. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft who receive HAM, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**SUPPLEMENTAL INFORMATION****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.

Further details from clinical input are included in the Appendix.

## **PRACTICE GUIDELINES AND POSITION STATEMENTS**

### **Wound Healing Society**

In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.<sup>39</sup> 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 dehydrated amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

### **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.<sup>23</sup> The report evaluated the evidence on treatments for dry eye and provided the following treatment algorithm for dry eye disease management:

Step 1:

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

Step 2:

If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity

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

### Step 3:

If above options are inadequate consider:

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

### Step 4:

If above options are inadequate consider:

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

### **Society for Vascular Surgery et al.**

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, amniotic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."<sup>40</sup>

### **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 14.

**Table 14. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT03414268 <sup>a</sup>	A Phase 3, Prospective, Double-Blinded, Randomized Controlled Trial of the Micronized dHACM Injection As Compared To Saline Placebo Injection In The Treatment Of Plantar Fasciitis	276	Apr 2021
NCT02982226 <sup>a</sup>	A Comparative Study of Injectable Human Amniotic Allograft (ReNu™) Versus Corticosteroids for Plantar Fasciitis: A Prospective, Randomized, Blinded Study	150	Apr 2021
NCT03414255 <sup>a</sup>	A Phase 3, Prospective, Double-Blinded, Randomized Controlled Trial Of The Micronized dHACM Injection As Compared To Saline Placebo Injection In The Treatment Of Achilles Tendonitis	158	May 2021
NCT03485157 <sup>a</sup>	A Phase 2B, Prospective, Double-blinded, Randomized Controlled Trial of the Micronized Dehydrated Human Amnion Chorion Membrane Injection as Compared to Saline Placebo Injection in the Treatment of Osteoarthritis of the Knee	466	Oct 2021
NCT04457752 <sup>a</sup>	A Randomised 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	Dec 2021
NCT03390920 <sup>a</sup>	Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions	200	Jun 2022
NCT04612023	A Prospective, Double-Blinded, Randomized Controlled Trial of an Amniotic Membrane Allograft Injection Comparing Two Doses (1 mL and 2mL Injection) and a Placebo (Sterile Saline) in the Treatment of Osteoarthritis of the Knee	90	Jul 2022
NCT04553432 <sup>a</sup>	Dry Eye OmniLenz Application of Omnigen Research Study	70	Jul 2022
NCT04599673	Prospective Analysis of Intraoperative AMNIOGEN® Injection in Patients With Rotator Cuff Tear	100	Sep 2022
NCT04636229 <sup>a</sup>	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
NCT03864939	Randomized Pilot Study to Improve Postprostatectomy Incontinence and Potency by Application of Dried Human Amnion Graft	328	Apr 2025
<b>Unpublished</b>			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02609594 <sup>a</sup>	A Multi-center Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Amnioband Dehydrated Human Amniotic Membrane and Standard of Care vs. Standard of Care Alone in the Treatment of Venous Leg Ulcers	240	Dec 2018 (status unknown)
NCT02838784 <sup>a</sup>	The Efficacy and Safety of Artacent™ for Treatment Resistant Lower Extremity Venous and Diabetic Ulcers: A Prospective Randomized Study	134	Dec 2018 (status unknown)
NCT03441607 <sup>a</sup>	Safety & Efficacy of Micronized Human Amnion Chorion Membrane Biologic (mHACMb) FloGraft (Micronized Human Amnion Chorion Membrane)® in Adults With Pain Due to Osteoarthritis of the Knee	320	Mar 2019 (status unknown)
NCT02318511 <sup>a</sup>	An Investigation of ReNu™ Knee Injection: Monitoring the Response of Knee Function and Pain in Patients With Osteoarthritis	200	Feb 2019 (completed)
NCT03379324 <sup>a</sup>	A Prospective, Randomized Study Comparing Outcomes Following Arthroscopic Double-row Rotator Cuff Repair With and Without the Addition of a Cryopreserved, Liquid, Injectable Amnion Allograft	260	Sep 2019(status unknown)

NCT: national clinical trial.

<sup>a</sup> 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
Q4100	Skin substitute, not otherwise specified
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
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
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

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
Q4237	Cryo-Cord, per square centimeter
Q4238	Derm-maxx, per square centimeter
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 Effective 10-01-2021
Q4252	Vendaje, per square centimeter Effective 10-01-2021
Q4253	Zenith amniotic membrane, per square centimeter. Effective 10-01-2021
Q4254	Novafix dl, per square centimeter
Q4255	Reguard, for topical use only, per square centimeter

- 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.
- 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

### ICD-10 Diagnoses

E08.621	Diabetes mellitus due to underlying condition with foot ulcer
E08.622	Diabetes mellitus due to underlying condition with other skin ulcer (Use additional code to identify site of ulcer limited to the ICD-10 L codes listed in this policy.)
E09.621	Drug or chemical induced diabetes mellitus with foot ulcer
E09.622	Drug or chemical induced diabetes mellitus with other skin ulcer (Use additional code to identify site of ulcer limited to the ICD-10 L codes listed in this policy.)
E10.621	Type 1 diabetes mellitus with foot ulcer
E10.622	Type 1 diabetes mellitus with other skin ulcer (Use additional code to identify site of ulcer limited to the ICD-10 L codes listed in this policy.)
E11.621	Type 2 diabetes mellitus with foot ulcer
E11.622	Type 2 diabetes mellitus with other skin ulcer (Use additional code to identify site of ulcer limited to the ICD-10 L codes listed in this policy.)

E13.621	Other specified diabetes mellitus with foot ulcer
E13.622	Other specified diabetes mellitus with other skin ulcer (Use additional code to identify site of ulcer limited to the ICD-10 L codes listed in this policy.)
H11.001	Unspecified pterygium of right eye
H11.002	Unspecified pterygium of left eye
H11.003	Unspecified pterygium of eye, bilateral
H11.011	Amyloid pterygium of right eye
H11.012	Amyloid pterygium of left eye
H11.013	Amyloid pterygium of eye, bilateral
H11.021	Central pterygium of right eye
H11.022	Central pterygium of left eye
H11.023	Central pterygium of eye, bilateral
H11.031	Double pterygium of right eye
H11.032	Double pterygium of left eye
H11.033	Double pterygium of eye, bilateral
H11.041	Peripheral pterygium, stationary, right eye
H11.042	Peripheral pterygium, stationary, left eye
H11.043	Peripheral pterygium, stationary, bilateral
H11.051	Peripheral pterygium, progressive, right eye
H11.052	Peripheral pterygium, progressive, left eye
H11.053	Peripheral pterygium, progressive, bilateral
H11.061	Recurrent pterygium of right eye
H11.062	Recurrent pterygium of left eye
H11.063	Recurrent pterygium of eye, bilateral
H16.011	Central corneal ulcer, right eye
H16.012	Central corneal ulcer, left eye
H16.013	Central corneal ulcer, bilateral
H16.021	Ring corneal ulcer, right eye
H16.022	Ring corneal ulcer, left eye
H16.023	Ring corneal ulcer, bilateral
H16.031	Corneal ulcer with hypopyon, right eye
H16.032	Corneal ulcer with hypopyon, left eye
H16.033	Corneal ulcer with hypopyon, bilateral
H16.041	Marginal corneal ulcer, right eye
H16.042	Marginal corneal ulcer, left eye
H16.043	Marginal corneal ulcer, bilateral
H16.051	Mooren's corneal ulcer, right eye
H16.052	Mooren's corneal ulcer, left eye
H16.053	Mooren's corneal ulcer, bilateral
H16.061	Mycotic corneal ulcer, right eye
H16.062	Mycotic corneal ulcer, left eye
H16.063	Mycotic corneal ulcer, bilateral
H16.231	Neurotrophic keratoconjunctivitis, right eye
H16.232	Neurotrophic keratoconjunctivitis, left eye
H16.233	Neurotrophic keratoconjunctivitis, bilateral
H18.11	Bullous Keratopathy, Right Eye
H18.12	Bullous Keratopathy, Left Eye
H18.13	Bullous Keratopathy, Bilateral
H18.30	Unspecified Corneal Membrane Change
H18.52	Epithelial (Juvenile) Corneal Dystrophy
H18.831	Recurrent erosion of cornea, right eye
H18.832	Recurrent erosion of cornea, left eye

H18.833	Recurrent erosion of cornea, bilateral
H18.891	Other specified disorders of cornea, right eye
H18.892	Other specified disorders of cornea, left eye
H18.893	Other specified disorders of cornea, bilateral
I87.2	Venous Insufficiency (Chronic) (Peripheral)
L51.1	Stevens-Johnson Syndrome
T26.11XA	Burn of cornea and conjunctival sac, right eye, initial encounter
T26.11XD	Burn of cornea and conjunctival sac, right eye, subsequent encounter
T26.11XS	Burn of cornea and conjunctival sac, right eye, sequela
T26.12XA	Burn of cornea and conjunctival sac, left eye, initial encounter
T26.12XD	Burn of cornea and conjunctival sac, left eye, subsequent encounter
T26.12XS	Burn of cornea and conjunctival sac, left eye, sequela
T26.50XA	Corrosion Of Unspecified Eyelid And Periocular Area, Initial Encounter
T26.50XD	Corrosion Of Unspecified Eyelid And Periocular Area, Subsequent Encounter
T26.50XS	Corrosion Of Unspecified Eyelid And Periocular Area, Sequela
T26.51XA	Corrosion Of Right Eyelid And Periocular Area, Initial Encounter
T26.51XD	Corrosion Of Right Eyelid And Periocular Area, Subsequent Encounter
T26.51XS	Corrosion Of Right Eyelid And Periocular Area, Sequela
T26.52XA	Corrosion Of Left Eyelid And Periocular Area, Initial Encounter
T26.52XD	Corrosion Of Left Eyelid And Periocular Area, Subsequent Encounter
T26.52XS	Corrosion Of Left Eyelid And Periocular Area, Sequela

**REVISIONS**

03-20-2017	Policy added to the bcbsks.com web site.
01-01-2019	<p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item A 1, added "Q4168".</li> <li>▪ In Item A 3, removed "Q4131" and added "Q4145, Q4186".</li> <li>▪ 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.</li> <li>▪ 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."</li> <li>▪ 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."</li> <li>▪ 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."</li> <li>▪ Updated Policy Guidelines.</li> </ul> <p>Updated Rationale section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added CPT codes: 65778, 65779.</li> </ul>



	<ul style="list-style-type: none"> <li>▪ Added new HCPCS codes: Q4183, Q4184, Q4185, Q4186, Q4187, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4201, Q4204.</li> <li>▪ Removed deleted HCPCS code: Q4131.</li> <li>▪ Revised nomenclature to HCPCS codes: Q4132, Q4133, Q4137, Q4148, Q4156, Q4162, Q4163.</li> <li>▪ 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.</li> </ul> <p>Updated References section.</p>
02-18-2019	<p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item A 3, removed "Q4145".</li> </ul>
03-27-2019	<p>Updated Description section.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item A, added new Item A 3, "Epicord (Q4187)".</li> </ul> <p>Updated Rationale section.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Removed ICD-10 codes: T26.51XA, T26.51XD, T26.51XS, T26.52XA, T26.52XD, T26.52XS.</li> </ul> <p>Updated References section.</p>
05-21-2019	<p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item A 1, removed HCPCS code Q4168.</li> </ul>
09-27-2019	<p>Policy published to the bcbsks.com website on 08-28-2019 with an effective date of 09-27-2019.</p> <p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added ICD-10 codes: H18.891, H18.892, H18.893.</li> </ul> <p>Updated References section.</p>
10-01-2019	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added HCPCS Codes: Q4205, Q4206, Q4208, Q4209, Q4210, Q4211, Q4212, Q4213, Q4214, Q4215, Q4216, Q4217, Q4218, Q4219, Q4221</li> </ul>
07-01-2020	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ 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</li> </ul>
07-16-2021	<p>Updated Description section</p> <p><b>In Policy section</b></p> <p><u>Added item A.1</u></p> <p><u>In Item B</u></p> <ul style="list-style-type: none"> <li>• Removed: "FDA-approved sutured and non-sutured human amniotic membrane grafts may be considered medically necessary for the treatment of the following ophthalmic indications:       <ol style="list-style-type: none"> <li>1. Neurotrophic keratitis</li> <li>2. Corneal ulcers and melts</li> <li>3. Pterygium repair</li> <li>4. Stevens-Johnson syndrome</li> <li>5. Persistent epithelial defects (with documented pain for ≥5 days)</li> </ol> </li> </ul>

	<p>6. Acid or alkaline burn”</p> <ul style="list-style-type: none"> <li>• 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:             <ol style="list-style-type: none"> <li>1. Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy;</li> <li>2. Corneal ulcers and melts that do not respond to initial conservative therapy;</li> <li>3. Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment;</li> <li>4. Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty);</li> <li>5. Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient;</li> <li>6. Moderate or severe Stevens-Johnson syndrome;</li> <li>7. Persistent epithelial defects that do not respond as stated in policy guideline #2;</li> <li>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</li> <li>9. Moderate or severe acute ocular chemical burn.”</li> <li>10. Corneal perforation when corneal tissue is not immediately available; or</li> <li>11. Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft</li> </ol> </li> </ul> <p><u>In Item C</u></p> <ul style="list-style-type: none"> <li>• Removed: “FDA approved sutured and non-sutured human amniotic membrane grafts are considered <b>experimental / investigational</b> 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.”</li> <li>• Added: “Human amniotic membrane grafts with or without suture are considered <b>experimental / investigational</b> for all ophthalmic indications not outlined above.”</li> </ul> <p><u>Added</u></p> <ul style="list-style-type: none"> <li>• <u>Item F</u></li> <li>• <u>Policy Guidelines</u></li> </ul> <p>Updated Rationale section</p> <p>In Coding section:</p> <ul style="list-style-type: none"> <li>• Added HCPCS Codes: Q4180, Q4220, Q4238, Q4249, Q4250, Q4254, Q4255</li> <li>• 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</li> <li>• 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</li> </ul> <p>Updated Reference section</p> <p>Added Appendix</p>
<p>10-08-2021</p>	<p>In Coding section: Effective 10-01-2021                  Added HCPCS codes: Q4251, Q4252, Q4253                  Deleted HCPCS codes: Q4228, Q4236 (no longer being manufactured)</p>

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### Other References

1. Blue Cross and Blue Shield of Kansas Ophthalmology / Optometry Liaison Committee Consent Ballot, November 2018, May 2021.
2. Blue Cross and Blue Shield of Kansas Ophthalmology / Optometry Liaison Committee, May 2011, May 2012, May 2018; August 2019, May 2021.

## **Appendix**

### **2019 Clinical 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.

### **Respondents**

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

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

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide a review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA nor any Blue Plan.



Identified by Mass Society of Eye Physicians and Surgeons					
2	Mark Latina	MD	Tufts University School of Medicine	Ophthalmology	Ophthalmology, Glaucoma Fellowship trained

**Respondent Conflict of Interest Disclosure**

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

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

**Responses**

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

#	Indications	Rationale
1	Neurotrophic keratitis	Sutured and non-sutured human amniotic membrane HAM are both accepted and effective treatments for neurotrophic keratopathy that does not respond to conservative therapy in patients with corneal staining or an epithelial defect that (1) has failed to completely close after 5 days of conservative treatment, or (2) has failed to demonstrate a decrease in size after 2 days of conservative treatment. Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. Failure of multiple modalities should not be required prior to moving to HAM. HAM requires less effort on the part of the patient to adhere to a treatment regimen and has a



#	Indications	Rationale
		<p>significant advantage in that regard over treatments that require multiple drops per day. Non-sutured HAM is the preferred initial treatment because it can be performed rapidly in an office setting, bypassing the delay associated with scheduling a procedure in an outpatient facility. It also avoids the facility fees associated with the sutured HAM procedure. Patients that are responding to non-sutured HAM may need a second or third application if healing is not yet complete. Those who show a poor response or poorly tolerate a non-sutured HAM device are candidates for sutured HAM.</p> <p>Khokhar (Cornea 2005;24:654. PMID 16015082) found an increased but nonsignificant rate of epithelial healing with sutured HAM compared to more invasive interventions such as tarsorrhaphy for neurotrophic corneal ulceration in a small randomized clinical trial (RCT). A larger trial might have demonstrated a significant difference but the disease is uncommon enough to make such a trial difficult to perform. For the same reason, there have been no trials directly comparing sutured and non-sutured HAM for neurotrophic keratopathy. This reflects not only the uncommon nature of the disease but also the lack of interest in subjecting patients to the more invasive and expensive sutured HAM procedure when clinical experience indicates that non-sutured HAM is effective in a significant number of patients.</p> <p>Other uncontrolled series and case reports supporting effectiveness of HAM for neurotrophic keratopathy:  Chen HJ. Br J Ophthalmol 2000;84:63. PMID 10906085  Ivekovic B. Coll Anthropol 2002;26:47. PMID 12137322  Suri K. Eye Contact Lens 2013;39:341. PMID 23945524  Uhlig CE. Acta Ophthalmol 2015;93:e481. PMID 25773445</p>
2	Neurotrophic keratitis	<p>Neurotrophic keratitis is a degenerative corneal disease induced by an impairment of corneal innervation and often manifested by corneal persistent epithelial defects (PED). Neurotrophic PED is characterized by painless epithelial breakdown, inflammation of the underlying stroma, and poor healing. The disease progression often leads to spontaneous corneal melting and perforation. In my practice, conventional treatments including topical medications, bandage contact lens, eye patching, and tarsorrhaphy usually fail to promote healing. If delayed healing was achieved, there is still a high risk of corneal scarring.</p> <p>Cryopreserved amniotic membrane (AM) has successfully been used to enhance healing in patients with Neurotrophic keratitis. [1-8] Besides the known actions of the AM in controlling inflammation and promoting healing, it is also rich in nerve growth factors that facilitate the recovery of the corneal nerves and enhancement of corneal wound healing.</p> <p>In my opinion and based on the literature, the use of AM (with or without sutures) for treating neurotrophic keratoconjunctivitis is medically necessary when the standard therapy fails. It interrupts the disease process by controlling inflammation, preventing further damage and restoring ocular surface integrity. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.</p>

#	Indications	Rationale
		<ol style="list-style-type: none"> <li>1. Chen H-J, Pires RTF, Tseng SCG. Amniotic membrane transplantation for severe neurotrophic corneal ulcers. <i>Br. J. Ophthalmol.</i> 2000; 84:826–833. [PubMed: 10906085]</li> <li>2. IvekoviÄ± B, Tedeschi-Reiner E, Petric I, et al. Amniotic membrane transplantation for ocular surface reconstruction in neurotrophic corneal ulcer a. <i>Coll Antropol.</i> 2002;26(1):47-54. [PMID: 12137322]</li> <li>3. Khokhar S, Natung T, Sony P, et al. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. <i>Cornea.</i> 2005;24:654–660. [PMID: 16015082]</li> <li>4. Pachigolla G, Prasher P, Di Pascuale MA, et al. Evaluation of the role of ProKera in the management of ocular surface and orbital disorders. <i>Eye Contact Lens.</i> 2009; 35(4):172-175 [PMID: 19474753]</li> <li>5. Suri K, Kosker M, Raber I, et al. Sutureless Amniotic Membrane ProKera for Ocular Surface Disorders. Short-Term Results. <i>Eye Contact Lens.</i> 2013;39:341-347 [PMID: 23945524]</li> <li>6. Uhlig CE, Frings C, Rohloff N, et al. Long-term efficacy of glycerine-processed amniotic membrane transplantation in patients with corneal ulcer. <i>Acta Ophthalmol.</i> 2015;93(6):e481-7. [PMID:25773445]</li> <li>7. Röck T, Bartz-Schmidt KU, Röck D. Management of a neurotrophic deep corneal ulcer with amniotic membrane transplantation in a patient with functional monocular vision: A case report. <i>Medicine (Baltimore).</i> 2017;96(50):e8997. [PMID: 29390295]</li> <li>8. Morkin, M. I. and P. Hamrah. "Efficacy of self-retained cryopreserved amniotic membrane for treatment of neuropathic corneal pain." <i>Ocul Surf</i> 2018, 16(1): 132-138. [PMID: 29032001]</li> </ol>
1	Corneal ulcers and melts	<p>Corneal ulcers and melts comprise a wide range of disorders with varying etiologies. Common to many of these are an underlying inflammatory component. HAM has been shown to reduce inflammation and promote epithelial healing. These properties make HAM an effective adjunct in treating these conditions while the primary etiology is addressed with targeted therapy (e.g. corticosteroids, antibiotics, biologic immunomodulators). HAM is typically employed when there is a lack of response to initial medical treatment or where HAM can offer some degree of tectonic support in cases where there is significant stromal tissue loss.</p> <p>The varied and uncommon nature of the etiology of ulcers and melts makes it unlikely that there will ever be significantly-sized RCTs comparing HAM to conventional therapy or sutured vs. non-sutured HAM. There are numerous small series and case reports without controls showing improvement after HAM placement in cases that were not responding to conventional therapy. A number of these were summarized in a review by Bouchard (<i>Ocul Surf</i> 2004;2:201. PMID 17216092).</p> <p>Cited below are selected reports supporting the efficacy of HAM for the treatment of corneal ulcers and melts, including several published since Bouchard's review:</p> <p>Kruse FE. <i>Ophthalmology</i> 1999;106:1504. PMID: 10442895  Hanada K. <i>Am J Ophthalmol</i> 2001;131:324. PMID 11239864  Chen HC. <i>Cornea</i> 2006;25:564. PMID 16783145  Sheha H. <i>Cornea</i> 2009;28:1118. PMID 19770726  Tok OY. <i>Int J Ophthalmol</i> 2015;18:938. PMID 26558205</p>

#	Indications	Rationale
		<p>Sharma N. Indian J Ophthalmol 2018;66:816. PMID 29785990  Prabhasawat P. Br J Ophthalmol 2001;85:1455. PMID 11734521  Solomon A. Ophthalmology 2002;109:694. PMID 11927426  Uhlig CE. Am J Ophthalmol Case Rep 2018;10:296. PMID 29780958</p>
2	Corneal ulcers and melts	<p>Cryopreserved amniotic membrane (AM) has successfully been used to control inflammation and promote healing in corneal ulcers of varying etiology. [1-9] Based on my experience, the use of AM at an early stage of the disease would prevent any unexpected complications such as infection, scarring, melt and perforation. Particularly, using AM without suture for this indication provides the advantage of in-office treatment without any delay. Furthermore, it avoids potential sight-threatening complications and achieves a clinically meaningful improvement in net visual outcome.</p> <ol style="list-style-type: none"> <li>1. Kruse FE, Rohrschneider K, Völcker HE. Multilayer amniotic membrane transplantation for reconstruction of deep corneal ulcers. Ophthalmology. 1999;106(8):1504-10; discussion 1511. [PMID: 10442895]</li> <li>2. Hanada K, Shimazaki J, Shimmura S, et al. Multilayered amniotic membrane transplantation for severe ulceration of the cornea and sclera. Am. J. Ophthalmol. 2001; 131(3):324-331. [PubMed: 11239864]</li> <li>3. Chen HC, Tan HY, Hsiao CH, et al. Amniotic membrane transplantation for persistent corneal ulcers and perforations in acute fungal keratitis. Cornea. 2006 Jun;25(5):564-72. [PMID: 16783145]</li> <li>4. Barequet IS, Habot-Wilner Z, Keller N, Smollan G, Ziv H, Belkin M, Rosner M. Effect of amniotic membrane transplantation on the healing of bacterial keratitis. Invest Ophthalmol Vis Sci. 2008 Jan;49(1):163-7. [PMID: 18172088]</li> <li>5. Sheha H, Liang L, Li J, et al. Sutureless amniotic membrane transplantation for severe bacterial keratitis. Cornea 2009; 28(10): 1118-1123. [PMID: 19770726]</li> <li>6. Tok OY, Tok L, Atay IM, et al. Toxic keratopathy associated with abuse of topical anesthetics and amniotic membrane transplantation for treatment. Int J Ophthalmol. 2015; 18;8(5):938-44. [PMID: 26558205]</li> <li>7. Sheha H, Tighe S, Cheng AMS, et al. A stepping stone in treating dendritic keratitis. Am J Ophthalmol Case Rep. 2017; 6(7):55-58. [PMID: 29260079]</li> <li>8. Zhong J, Wang B, Li S, et al. Full-thickness conjunctival flap covering surgery combined with amniotic membrane transplantation for severe fungal keratitis. Exp Ther Med. 2018;15(3):2711-2718. [PMID: 29456673]</li> <li>9. Sharma N, Singhal D, Maharana PK, et al. Continuous intraoperative optical coherence tomography-guided shield ulcer debridement with tuck in multilayered amniotic membrane transplantation. Indian J Ophthalmol. 2018;66(6):816-819. [PMID: 29785990]</li> </ol>
1	Corneal perforation	<p>Multilayered sutured HAM has been performed in some cases of corneal perforation. While it offers some tectonic support, corneal tissue is the preferred graft material in these cases. HAM alone may be a reasonable temporizing alternative when corneal tissue is not immediately available. Non-sutured HAM would not offer significant tectonic support in these cases.</p> <p>Both sutured and non-sutured HAM reduces inflammation and promotes epithelial healing. It is therefore a useful adjunct in addition to corneal transplantation in those patients with active inflammation and perforation.</p>

#	Indications	Rationale
		<p>The rare nature of these cases guarantees that there will be no large RCTs performed for this indication. A number of clinical series and case reports supporting the efficacy of HAM for corneal perforation are cited here:</p> <p>Prabhasawat P. Br J Ophthalmol 2001;85:1455. PMID 11734521  Solomon A. Ophthalmology 2002;109:694. PMID 11927426  Rodriguez-Ares MT. Cornea 2004;23:577. PMID 15256996  Hick S. Cornea 2005;24:369. PMID 15829790  Uhlig CE. Am J Ophthalmol Case Rep 2018;10:296. PMID 29780958</p>
2	Corneal perforation	<p>Depending on the size and location of the corneal perforation, treatment options include gluing, amniotic membrane transplantation, and corneal transplantation. The success rate of using AM to repair corneal perforation is reported to be as high as 93%. [1-7] Kim et al [7] used multiple layers of AM with tissue glue in 10 patients with large corneal perforations up to 5 mm and noted 90% success in complete closure of perforation. AM offers the advantage of avoiding potential corneal graft rejection and postoperative astigmatism of tectonic corneal grafts. I personally did not use AM for this indication, but based on the literature, multiple layers of AM for this indication provides a clinically meaningful improvement in net health outcome.</p> <ol style="list-style-type: none"> <li>1. Prabhasawat P, Tesavibul N, Komolsuradej W. Single and multilayer amniotic membrane transplantation for persistent corneal epithelial defect with and without stromal thinning and perforation. Br J Ophthalmol. 2001;85(12):1455-63. [PMID: 11734521]</li> <li>2. Solomon A, Meller D, Prabhasawat P, et al. Amniotic membrane grafts for nontraumatic corneal perforations, descemetoceles, and deep ulcers. Ophthalmology. 2002; 109(4):694–703. [PubMed: 11927426]</li> <li>3. Rodriguez-Ares MT, Tourino R, Lopez-Valladares MJ, et al. Multilayer amniotic membrane transplantation in the treatment of corneal perforations. Cornea. 2004; 23(6):577–583. [PubMed: 15256996]</li> <li>4. Hick S, Demers PE, Brunette I, et al. Amniotic membrane transplantation and fibrin glue in the management of corneal ulcers and perforations: a review of 33 cases. Cornea. 2005; 24(4):369–377. [PubMed: 15829790]</li> <li>5. Xie HT, Zhao D, Liu Y, et al. Umbilical Cord Patch Transplantation for Corneal Perforations and Descemetoceles. J Ophthalmol. 2017;2017:2767053. [PMID: 28660079]</li> <li>6. Uhlig CE, Müller VC. Resorbable and running suture for stable fixation of amniotic membrane multilayers: A useful modification in deep or perforating sterile corneal ulcers. Am J Ophthalmol Case Rep. 2018; 19 (10):296-299. [PMID: 29780958]</li> <li>7. Kim HK, Park HS. Fibrin glue-assisted augmented amniotic membrane transplantation for the treatment of large noninfectious corneal perforations. Cornea 2009; 28(2), 170–176.[PMID: 19158560]</li> </ol>
1	Bullous keratopathy	<p>HAM is one of several modalities for treatment of bullous keratopathy due to corneal endothelial dysfunction. HAM does not address the underlying endothelial disease, so it is considered palliative rather than curative therapy. It is a reasonable alternative for patients who are not candidates for curative endothelial or penetrating keratoplasty. Sutured HAM has been shown to be as effective for bullous keratopathy as anterior stromal puncture (Paris F. Br J Ophthalmol 2013;97:980. PMID 23723410) and phototherapeutic keratectomy (Chawla B. Cornea 2010;29:976. PMID 20517149). Non-sutured HAM is a</p>

#	Indications	Rationale
		<p>reasonable alternative to anterior stromal puncture as it is faster and simpler to perform. Sutured HAM in an operating room setting and non-sutured HAM in the office are of particular value in patients who have difficulty holding still for office procedures such as anterior stromal puncture in which there is a risk of increased corneal scarring or globe perforation with patient movement. HAM typically offers long-lasting pain relief in these cases, obviating the need for corneal transplantation with its associated increased risks (rejection, infection) and costs.</p> <p>There are additional reports demonstrating the efficacy of HAM for bullous keratopathy:</p> <p>Pires RTF. Arch Ophthalmol 1999;117:1291. PMID 10532436  Espana EM. J Cataract Refract Surg 2003;29:279. PMID 12648638  Chansanti O. J Med Assoc Thai 2005;9:S57. PMID 16681053  Srinivas S. Eur J Ophthalmol 2007;17:7. PMID 17294377  Georgiadis NS. Clin Exp Ophthalmol 2008;36:130. PMID 18352868  Chawla B. Eur J Ophthalmol 2008;18:998. PMID 18988175  Altiparmak UE. Am J Ophthalmol 2009;147:442. PMID 19019342  Stefaniu GI. J Med Life 2014;7:88. PMID 25870682  Siu GD. Int Ophthalmol 2015;35:777. PMID: 255866</p>
2	Bullous keratopathy	<p>Cryopreserved amniotic membrane (AM) is recommended for Bullous keratopathy with poor visual potential. AM achieves immediate pain relief, reduced inflammation, and complete healing. [1-12] Chansanti et al [4] noted postoperative relief of pain in 14 eyes (82.4%) and complete corneal epithelial healing in 15 eyes (88.2%) after AMT. Sonmez et al. [5] performed anterior stromal micropuncture and AMT in 5 eyes with painful bullous keratopathy [40]. All showed an intact, smooth corneal epithelial surface 1 month after the procedure, and there were no patients that developed recurrent bullae formation during an average follow-up period of 21 months. Siu et al [12] reported a long term symptomatic relief of bullous keratopathy with amniotic membrane transplant in a total of 21 eyes of 20 patients. The majority of eyes experienced pain reduction (94 %), with a significant mean pain score difference of <math>6.8 \pm 2.6</math>, 2-tail <math>p &lt; 0.001</math> (99 % CI 4.9-8.7). The mean preoperative and postoperative pain scores were <math>7.3 \pm 2.9</math> and <math>0.5 \pm 1.0</math>, respectively. 16 eyes (76 %) were completely pain free, and 10 eyes (47 %) remained symptom free after a mean follow-up of <math>39.0 \pm 36.3</math> months (range 5-171 months). The median epithelial healing time was 2 weeks (range 1-20 weeks). Based on the literature, AM is considered as a longer-term treatment for bullous keratopathy patients with poorer visual prognosis. AM without sutures may also be used as an interim measure for patients awaiting corneal transplant. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.</p> <ol style="list-style-type: none"> <li>Pires RTF, Tseng SCG, Prabhasawat P et al. Amniotic membrane transplantation for symptomatic bullous keratopathy. Arch.Ophthalmol. 1999; 117, 1291-1297.[PMID: 10532436]</li> <li>Mrukwa-Kominek E, Gierek-Ciaciura S, Rokita-Wala I, et al. Use of amniotic membrane transplantation for treating bullous keratopathy. Klin Oczna. 2002;104(1):41-6. Polish. [PMID: 12046309]</li> </ol>

#	Indications	Rationale
		<ol style="list-style-type: none"> <li>3. Espana EM, Grueterich M, Sandoval H et al. Amniotic membrane transplantation for bullous keratopathy in eyes with poor visual potential. <i>J.Cat.Refract.Surg.</i> 2003; 29, 279-284.</li> <li>4. Chansanti O, Horatanaruang O. The results of amniotic membrane transplantation for symptomatic bullous keratopathy. <i>J Med.Assoc.Thai.</i> 88 Suppl 2005; 9, S57-S62.</li> <li>5. Sonmez B, Kim BT, Aldave AJ. Amniotic membrane transplantation with anterior stromal micropuncture for treatment of painful bullous keratopathy in eyes with poor visual potential. <i>Cornea</i> 26(2), 227–229 (2007).</li> <li>6. Srinivas S, Mavrikakis E, Jenkins C. Amniotic membrane transplantation for painful bullous keratopathy. <i>Eur J Ophthalmol.</i> 2007;17(1):7-10. [PMID: 17294377]</li> <li>7. Georgiadis NS, Ziakas NG, Boboridis KG, et al. Cryopreserved amniotic membrane transplantation for the management of symptomatic bullous keratopathy. <i>Clin Exp Ophthalmol.</i> 2008;36(2):130-5. [PMID: 18352868]</li> <li>8. Chawla B, Tandon R. Sutureless amniotic membrane fixation with fibrin glue in symptomatic bullous keratopathy with poor visual potential. <i>Eur J Ophthalmol.</i> 2008;18(6):998-1001. [PMID: 18988175]</li> <li>9. Altiparmak UE, Oflu Y, Yildiz EH, et al. Prospective comparison of two suturing techniques of amniotic membrane transplantation for symptomatic bullous keratopathy. <i>Am J Ophthalmol.</i> 2009;147(3):442-446.e1. [PMID:19019342]</li> <li>10. Gregory ME, Spiteri-Cornish K, Hegarty B, et al. Combined amniotic membrane transplant and anterior stromal puncture in painful bullous keratopathy: clinical outcome and confocal microscopy. <i>Can J Ophthalmol.</i> 2011;46(2):169-74. [PMID: 21708086]</li> <li>11. Stefaniu GI, Chiotoroiu SM, Secureanu FA, et al. Use of amniotic membrane in bullous keratopathy palliative care. <i>J Med Life.</i> 2014;7 Spec No. 2:88-91. [PMID: 25870682]</li> <li>12. Siu GD, Young AL, Cheng LL. Long-term symptomatic relief of bullous keratopathy with amniotic membrane transplant. <i>Int Ophthalmol.</i> 2015;35(6):777-83. [PMID: 25586624]</li> </ol>
1	Pterygium repair	<p>Sutured HAM has been fairly extensively studied as an alternative to conjunctival autograft or bare sclera technique in pterygium surgery (Kaufman SC. <i>Ophthalmology</i> 2013;120:201. PMID 23062647. Clearfield, <i>Cochrane Database Syst Rev</i> 2016;2:CD011349. PMID 26867004). While HAM is more effective at preventing recurrences than bare sclera technique, and subject to fewer serious complications than mitomycin C, conjunctival autograft has been shown to be more effective than HAM in terms of reducing recurrences. However, there are patients with extensive, double, or recurrent pterygia in which there is insufficient healthy tissue to create a conjunctival autograft. In these patients, sutured or non-sutured (glued) HAM is the material of choice for covering the conjunctival defect left after removal of the pterygium as the recurrence rate is lower than if the sclera is left bare. Sutured and glued HAM should be covered for these cases.</p> <p>Non-sutured HAM is effective at promoting epithelial healing in patients who have persistent epithelial defects (see below) after pterygium surgery and should be covered in these cases.</p>

#	Indications	Rationale
2	Pterygium repair	<p>The most daunting challenge of pterygium surgery is the high rate of recurrence, as high as 88%. Surgical techniques in more recent years, in which scleral defects are covered with conjunctival autograft or cryopreserved amniotic membrane (AM) with or without mitomycin C (MMC), have resulted in much better outcomes, with less recurrence rates and minimal complications. [1-16]</p> <p>However, some debate still continues regarding which graft offers the better outcome. In a prospective study, Prabhasawat et al [1] first reported a recurrence rate of 10.9% in primary pterygium (n = 54) after excision and AMT. Solomon et al [2] subsequently modified the technique of AMT and achieved a low recurrence rate of 3% in 33 cases of primary pterygium. Another surgical parameter is the use of MMC. Rosen et al [16] reported a considerably low recurrence rate (3.6%) when used AM graft without sutures along with reduced exposure to MMC. In my opinion, AM is as effective as conjunctival autograft in preventing pterygium recurrence and can be considered as a preferred grafting procedure for pterygium repair. The use of AM provides the following benefits: save donor conjunctiva, minimize surgical trauma, reduce surgery time, reduce postoperative pain, reduce inflammation, facilitate faster recovery and healing. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.</p> <ol style="list-style-type: none"> <li>1. Prabhasawat P, Barton K, Burkett G, et al. Comparison of conjunctival autografts, amniotic membrane grafts and primary closure for pterygium excision. <i>Ophthalmology</i> 1997; 104, 974-985. [PMID: 9186439]</li> <li>2. Ma DH-K, See L-C, Liao S-B, et al. Amniotic membrane graft for primary pterygium: comparison with conjunctival autograft and topical mitomycin C treatment. <i>Br.J.Ophthalmol.</i> 2000; 84, 973-978.[PMID: 10966947]</li> <li>3. Solomon A, Espana EM, Tseng SCG. Amniotic membrane transplantation for reconstruction of the conjunctival fornices. <i>Ophthalmology.</i> 2003; 110:93-100. [PubMed: 12511352]</li> <li>4. Jain S, Rastogi A. Evaluation of the outcome of amniotic membrane transplantation for ocular surface reconstruction in symblepharon. <i>Eye.</i> 2004; 18(12):1251-1257. [PubMed: 15184952]</li> <li>5. Zhou SY, Chen JQ, Chen LS, et al. Long-term results of amniotic membrane transplantation for conjunctival surface reconstruction. <i>Zhonghua Yan. Ke. Za Zhi.</i> 2004; 40(11):745-749. [PubMed: 15634481]</li> <li>6. Keklikci U, Celik Y, Cakmak SS, et al. Conjunctival-limbal autograft, amniotic membrane transplantation, and intraoperative mitomycin C for primary pterygium. <i>Ann Ophthalmol (Skokie).</i> 2007;39(4):296-301. [PMID: 18025649]</li> <li>7. Kucukerdonmez C, Akova YA, Altinors DD. Comparison of conjunctival autograft with amniotic membrane transplantation for pterygium surgery: surgical and cosmetic outcome. <i>Cornea.</i> 2007;26(4):407-413. [PMID: 17457187]</li> <li>8. Kucukerdonmez C, Akova YA, Altinors DD. Vascularization is more delayed in amniotic membrane graft than conjunctival autograft after pterygium excision. <i>Am.J.Ophthalmol</i> 2007; 143(2), 245-249. [PMID: 17173849]</li> <li>9. Fallah MR, Golabdar MR, Amozadeh J, et al. Transplantation of conjunctival limbal autograft and amniotic membrane vs mitomycin C and amniotic membrane in treatment of recurrent pterygium. <i>Eye</i> 2008; 22(3), 420-424. [PMID: 17159974]</li> </ol>

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		<ol style="list-style-type: none"> <li>10. Kheirkhah A, Casas V, Sheha H, et al. Role of conjunctival inflammation in surgical outcome after amniotic membrane transplantation with or without fibrin glue for pterygium. <i>Cornea</i> 2008; 27(1), 56-63. [PMID: 18245968]</li> <li>11. Kheirkhah A, Blanco G, Casas V, et al. Surgical strategies for fornix reconstruction based on symblepharon severity. <i>Am. J. Ophthalmol.</i> 2008; 146(2):266– 275. [PubMed: 18514608]</li> <li>12. Park JH, Jeoung JW, Wee WR, et al. Clinical efficacy of amniotic membrane transplantation in the treatment of various ocular surface diseases. <i>Cont Lens Anterior Eye.</i> 2008 Apr;31(2):73-80. [PMID: 18249149]</li> <li>13. KatÄ±rcÄ±oglu YA, Altiparmak U, Engur Goktas S, et al. Comparison of Two Techniques for the Treatment of Recurrent Pterygium: Amniotic Membrane vs Conjunctival Autograft Combined with Mitomycin C. <i>Semin Ophthalmol.</i> 2015;30(5-6):321-7. [PMID: 24506693]</li> <li>14. Zhao D, Yin HY, Cheng A, et al. Sealing of the gap between the conjunctiva and tenon capsule to improve symblepharon surgery. <i>Am J Ophthalmol.</i> 2015;160(3):438-446.e1. [PMID: 26093286]</li> <li>15. Tanaka TS, Demirci H. Cryopreserved Ultra-Thick Human Amniotic Membrane for Conjunctival Surface Reconstruction After Excision of Conjunctival Tumors. <i>Cornea.</i> 2016;35(4):445-50. [PMID: 26807897]</li> <li>16. Rosen R. Amniotic Membrane Grafts to Reduce Pterygium Recurrence. <i>Cornea.</i> 2018;37(2):189-193. [PMID: 28976415]</li> </ol>
1	Limbic stem cell deficiency	<p>Limbic stem cell deficiency is an uncommon, serious disorder leading to conjunctivalization, irregularity, and opacity of the corneal surface. Total limbic stem cell deficiency typically requires a limbic stem cell transplant to restore the ocular surface. These vascularized transplants require prolonged systemic immunosuppression and the attendant risks to support graft survival and prevent recurrence of the disease. Partial limbic stem cell deficiency may respond to selective removal of the diseased tissue without a transplant when a limited portion of the ocular surface is involved. In more extensive cases where selective removal alone is not sufficient, HAM in conjunction with superficial keratectomy to remove the diseased tissue can provide long-term restoration of a smooth and transparent ocular surface and improved visual acuity without having to resort to a transplant (Kheirkhah AV. <i>Am J Ophthalmol</i> 2008;145:787. PMID 18329626). Due to the rarity of this disease, it is unlikely that RCTs will ever be performed. Comparisons to limbic stem cell transplants are unlikely to be performed because of the risks of systemic immune suppression.</p> <p>HAM should be covered in conjunction with superficial keratectomy for cases of limbic stem cell deficiency.</p>
2	Limbic stem cell deficiency	<p>Patients with Limbic stem cell deficiency (LSCD) suffer from severe loss of vision due to vascularized cornea scarring and non-healing epithelial defect. Their vision cannot be corrected by conventional penetrating keratoplasty. Previous studies have shown that in eyes with partial LSCD, AM promotes expansion of remaining limbic epithelial stem cells [1-4]. To avoid suture-related disadvantages and complications, Kheirkhah et al. [5] recently reported successful reconstruction of the corneal surface in nine patients with nearly total LSCD using fibrin glue. Kheirkhah et al. [56] further reported successful use of minimal conjunctival limbic autograft in conjunction with AM for total limbic stem cell deficiency.</p> <ol style="list-style-type: none"> <li>1. Tseng SCG, Prabhasawat P, Barton K, et al. Amniotic membrane transplantation with or without limbic allografts for corneal surface</li> </ol>



#	Indications	Rationale
		<p>reconstruction in patients with limbal stem cell deficiency. Arch. Ophthalmol. 1998;116, 431–441. [PMID: 9565039]</p> <ol style="list-style-type: none"> <li>2. Anderson DF, Ellies P, Pires RT, et al. Amniotic membrane transplantation for partial limbal stem cell deficiency. Br. J. Ophthalmol. 2001; 85(5), 567–575. [PMID: 11316719 ]</li> <li>3. Gomes JA, dos Santos MS, Cunha MC, et al. Amniotic membrane transplantation for partial and total limbal stem cell deficiency secondary to chemical burn. Ophthalmology 2003; 110(3), 466–473. [PMID: 12623806]</li> <li>4. Sangwan VS, Matalia HP, Vemuganti GK, et al. Amniotic membrane transplantation for reconstruction of corneal epithelial surface in cases of partial limbal stem cell deficiency. Indian J. Ophthalmol. 2004; 52(4), 281–285. [PMID: 15693318]</li> <li>5. Kheirkhah A, V. Casas V. Raju K et al. Sutureless amniotic membrane transplantation for partial limbal stem cell deficiency. Am.J.Ophthalmol. 2008; 145(5): 787-794. [PMID: 18329626]</li> <li>6. Kheirkhah, A., Raju VK and S. C. Tseng. "Minimal conjunctival limbal autograft for total limbal stem cell deficiency." Cornea 2008; 27(6): 730-733. [PMID: 18580269]</li> </ol>
1	Stevens-Johnson	<p>Sutureless HAM plus medical therapy has been demonstrated in a small RCT to be more effective than medical therapy alone in treatment of Stevens-Johnson syndrome (Sharma N. Ophthalmology 2016;123:484. PMID 26686968). Sutureless or sutured HAM, depending on the severity of the disease, in conjunction with medical therapy has become the accepted management technique for the treatment of moderate or severe Stevens-Johnson. Both should be covered for this indication. The severity of the disease and its infrequency makes it unlikely that a large RCT will be performed. Additional literature demonstrating good visual outcomes with both sutured and sutureless HAM in a disease that prior to introduction of HAM was typically blinding includes:</p> <p>Shammas MC. Am J Ophthalmol 2010;149:203. PMID 20005508  Gregory DM. Ocular Surf 2008;6:40. PMID 18418506  Shay E. Surv Ophthalmol 2009;54:686. PMID 19699503  Gregory DM. Ophthalmology 2011;118:908. PMID 21440941  Shay E. Cornea 2010;29:359. PMID 20098313  Tomlins PJ. Cornea 2013;32:365. PMID 22677638  Kolomeyer AM. Eye Contact Lens 2013;39:e7. PMID 22683916  Ma KN. Ocular Surf 2016;14:31. PMID 26387869</p>
2	Stevens-Johnson	<p>Amniotic membrane with sutures has been used to suppress inflammation, promote healing, and prevent scarring in patients with acute Stevens Johnson Syndrome (SJS) with or without toxic epidermal necrolysis (TEN) [1-6]. The conventional management at intensive care and burn units are usually reserved for life-threatening problems, and thus are frequently inadequate to address ocular inflammation and ulceration. As a result, patients suffering are frequently left with a blinding disease owing to scarring-induced late complications. Gregory et al. [7] and Shay et al. [8] have reviewed the literature and found that AMT performed within 2 weeks after the onset of disease effectively aborts inflammation and facilitates rapid healing in AM-covered areas, thus preventing pathogenic cicatricial complications at the chronic stage in 12 eyes. Several case reports and case series [6-12] demonstrated the effectiveness of AM without sutures (ProKera) at the acute stage of SJS/ TEN, and noted restoration of</p>

#	Indications	Rationale
		<p>normal vision. Gregory et al [9] further reported restoration of vision in 10 consecutive cases using AM with and without sutures. However, because this devastating ocular surface disease usually elicits inflammation and ulceration in such hidden areas as the lid margin, the tarsus, and the fornix, AM extended to cover the entire ocular surface is necessary.[10] Ma et al [13] developed a novel technique for using large AM graft without suture to cover the entire ocular surface in patients with acute SJS. In my opinion, and based on the literature, the use of AM with sutures is preferred to prevent long term lid related complications. The use of AM without suture is still helpful in emergency settings when the patient condition does not allow for surgical intervention. Collectively, the use of AM for this indication provides a clinically meaningful improvement in net health outcome.</p> <ol style="list-style-type: none"> <li>1. John T, Foulks GN, John ME, et al. Amniotic membrane in the surgical management of acute toxic epidermal necrolysis. <i>Ophthalmology</i> 2002; 109(2), 351–360. [PMID: 11825823]</li> <li>2. Kobayashi A, Yoshita T, Sugiyama K et al. Amniotic membrane transplantation in acute phase of toxic epidermal necrolysis with severe corneal involvement. <i>Ophthalmology</i> 2006; 113(1), 126–132. [PMID: 16324747]</li> <li>3. Di Pascuale MA, Espana EM, Liu DT et al. Correlation of corneal complications with eyelid cicatricial pathologies in patients with Steven-Johnson syndrome and toxic epidermal necrolysis syndrome. <i>Ophthalmology</i> 2005; 112(5), 904–912. [PMID: 15878074]</li> <li>4. Muqit MM, Ellingham RB, Daniel C. Technique of amniotic membrane transplant dressing in the management of acute Stevens–Johnson syndrome. <i>Br. J. Ophthalmol.</i> 2007; 91(11), 1536. [PMID: 17947270]</li> <li>5. Tandon A, Cackett P, Mulvihill A, et al. Amniotic membrane grafting for conjunctival and lid surface disease in the acute phase of toxic epidermal necrolysis. <i>J. AAPOS</i> 2007; 11(6), 612–613. [PMID: 17681814]</li> <li>6. Shamma MC, Lai EC, Sarkar JS, et al. Management of acute Stevens–Johnson syndrome and toxic epidermal necrolysis utilizing amniotic membrane and topical corticosteroids. <i>Am. J. Ophthalmol.</i> 2010; 149(2), 203–213. [PMID: 20005508]</li> <li>7. Gregory DG. The ophthalmologic management of acute Stevens–Johnson syndrome. <i>Ocul. Surf.</i> 2008; 6(2), 87–95. [PMID: 18418506]</li> <li>8. Shay E, Kheirkhah A, Liang L, et al. Amniotic membrane transplantation as a new therapy for the acute ocular manifestations of Stevens–Johnson syndrome and toxic epidermal necrolysis. <i>Surv. Ophthalmol.</i> 2009; 54(6), 686–696. [PMID: 19699503]</li> <li>9. Gregory, DG. Treatment of Acute Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis Using Amniotic Membrane: A Review of 10 Consecutive Cases. <i>Ophthalmology</i> 2011; 118:908–914. [PMID: 21440941]</li> <li>10. Shay E, Khadem JJ and Tseng SC. Efficacy and limitation of sutureless amniotic membrane transplantation for acute toxic epidermal necrolysis. <i>Cornea</i> 2010; 29(3): 359-361. [PMID: 20098313]</li> <li>11. Tomlins, P.J., Parulekar MV, and Rauz S. ""Triple-TEN" in the Treatment of Acute Ocular Complications From Toxic Epidermal Necrolysis." <i>Cornea</i> 2013; 32(3): 365-369. [PMID: 22677638]</li> <li>12. Kolomeyer AM, Do BK, Tu Y, et al. Placement of ProKera in the management of ocular manifestations of acute Stevens-Johnson syndrome in an outpatient. <i>Eye Contact Lens.</i> 2013;39: e7-11. [PMID: 22683916]</li> </ol>

#	Indications	Rationale
		<p>13. Ma KN, Thanos A, Chodosh J, et al. A Novel Technique for Amniotic Membrane Transplantation in Patients with Acute Stevens-Johnson Syndrome. <i>Ocul Surf.</i> 2016;14(1):31-6. [PMID: 26387869]</p>
1	Persistent epithelial defects	<p>HAM is an effective treatment for persistent epithelial defects due to a number of underlying causes. While not a first-line treatment, both sutured and non-sutured HAM are appropriate in patients with epithelial defects that fail to show a response within 2 days of initiation of conservative therapy. Conservative therapy is considered to be any one or more of the following: topical lubricants and/or antibiotics, therapeutic contact lens, or patching. If there is a failure to respond to any one of these modalities, HAM is an appropriate second step.</p> <p>Persistent epithelial defects are often a precursor to corneal stromal melting and ulceration. Many of the comments and citations in the above "Section b. corneal ulcers and melts" are applicable here. The uncommon nature of the diseases associated with persistent epithelial defects and the lack of a standard therapeutic regimen account for the lack of RCTs. However, the following publications demonstrate the effectiveness of HAM for this indication.</p> <p>Prabhasawat P. <i>Br J Ophthalmol</i> 2001;85:1455. PMID 11734521  Lee SH. <i>Am J Ophthalmol</i> 97;123:303. PMID 9063239  Letko E. <i>Arch Ophthalmol</i> 2001;119:659. PMID 11346392  Gris O. <i>Cornea</i> 2002;21:22. PMID 11805502  Seitz B. <i>Eye (London)</i> 2009;23:840. PMID 18535612  Dekaris I. <i>Coll Antropol</i> 2010;34 Suppl 2:15. PMID 21305721</p>
2	Persistent epithelial defects	<p>Persistent epithelial defect (PED) is often caused by microtrauma, neurotrophic keratopathy and exposure. Conventional treatment includes correcting the underlying condition, suppressing the inflammation, and promoting the healing process using tears. If conventional treatment fails after 2 weeks, these patients are prone to further complications and corneal scarring and haze. Because PED also be 'neurotrophic', please refer to Neurotrophic keratitis indication. As stated above, conventional treatments usually fail to promote prompt healing in these conditions and the eyes are prone to delayed healing, corneal ulceration, scarring, and infection. These complications in turn result in poor patient outcomes, visual detriment, and a greater frequency of office visits and associated costs. The following publications [1-6] show the effectiveness of AM with and without sutures in promoting healing in PEDs. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.</p> <ol style="list-style-type: none"> <li>1. Lee SH, Tseng SC. Amniotic membrane transplantation for persistent epithelial defects with ulceration. <i>Am J Ophthalmol.</i> 1997;123(3):303-12. [PMID:9063239]</li> <li>2. Letko E, Stechschulte SU, Kenyon KR, et al. Amniotic membrane inlay and overlay grafting for corneal epithelial defects and stromal ulcers. <i>Arch Ophthalmol.</i> 2001;119(5):659-63. [PMID: 11346392]</li> <li>3. Gris O, del Campo Z, Wolley-Dod C, et al. Amniotic membrane implantation as a therapeutic contact lens for the treatment of epithelial disorders. <i>Cornea.</i> 2002;21(1):22-7. [PMID: 11805502]</li> <li>4. Seitz B, Das S, Sauer R, et al. Amniotic membrane transplantation for persistent corneal epithelial defects in eyes after penetrating keratoplasty. <i>Eye (Lond).</i> 2009;23(4):840-8. [PMID: 18535612]</li> </ol>

#	Indications	Rationale
		<p>5. Dekaris I, MraviciÄ± I, BarisiÄ± A, et al. Amniotic membrane transplantation in the treatment of persistent epithelial defect on the corneal graft. <i>Coll Antropol.</i> 2010;34 Suppl 2:15-9. [PMID: 21305721]</p> <p>6. Nguyen, P., K. Rue, M. Heur, et al. "Ocular surface rehabilitation: Application of human amniotic membrane in high-risk penetrating keratoplasties." <i>Saudi J Ophthalmol</i> 2014; 28(3): 198-202. [PMID: 25278797]</p>
1	Severe dry eye	<p>As noted in the BCBS review, non-sutured HAM has been demonstrated in an RCT to be more effective than conservative therapy in patients with moderate to severe dry eye disease (John T. <i>J Ophthalmol</i> 2017;2017:6404918. PMID 28894606). Also noted in the review was a small series of 10 patients with moderate to severe dry eye that were non-responsive to conventional therapy (Cheng <i>AM. Ocul Surf</i> 2016;14:56. PMID 26387870). These patients improved with placement of non-sutured HAM. A more recent, larger retrospective review of patients with severe dry eye disease unresponsive to traditional therapy and then treated with non-sutured HAM showed that 88% of subjects demonstrated significant improvement of symptoms extending beyond the period of treatment with HAM (McDonald MD. <i>Clin Ophthalmol</i> 2018;12:677. PMID 29670328).</p> <p>Traditional dry eye therapy typically consists of frequent application of lubricants, hot compresses, and environmental controls to increase humidity. Patients may not respond to traditional dry eye therapy due to the severity of the disease or due to inability to control the environment or administer drops frequently. Topical drugs such as cyclosporine and lifitegrast may be helpful in these cases but they may take months to take effect. If the patient's daily activities are significantly affected by dry eye signs and symptoms, HAM may provide rapid relief while waiting for long-term medications to take effect. HAM is unlikely to be of benefit for mild dry eye disease or disease that responds to conservative therapy. Because HAM limits acuity it is only viable as a short-term therapy. Sutured HAM is not typically used for severe dry eye alone, but may be necessary in the face of one or more concomitant diseases discussed in the other sections.</p> <p>Our recommendation is that non-sutured HAM be covered in patients with persistent symptoms or persistent corneal staining that does not respond to traditional dry eye therapy.</p>
2	Severe dry eye	<p>Dry eye disease (DED) is a multifactorial disease comprised of tear film insufficiency and associated ocular surface disorder such as superficial epithelial defect. Treatment of DED depends on the etiology and the level of severity. Although artificial tears, immunosuppressants, and punctal occlusion are commonly used for tear film insufficiency, ocular surface involvement with a defect are usually refractory and may require eye protection devices and/ or surgical intervention.</p> <p>In fact, Prokera has been reported to manage ocular signs and symptoms of DED. In a retrospective study by Cheng et al,[1] Prokera was placed for 5 days (Range: 2-8 days) in 15 eyes of 10 patients with moderate to severe DED. The dry eye severity ranged from Grade 1 to 4 according to the Report of the International Dry Eye Work Shop (DEWS) 2007.[2] All patients experienced symptomatic relief for a mean period of 4.2 months (Range: 0.3-6.8). Such improvement was accompanied by reduction of Ocular Surface Disease Index (OSDI) symptom scores, the use of topical medications, conjunctival hyperemia,</p>

#	Indications	Rationale
		<p>and corneal staining as well as improvement in the quality of vision.<sup>11</sup> In a single site prospective, randomized, and controlled study conducted by John et al [3], Prokera together with standard of care was placed in 10 patients for <math>3.4 \pm 0.7</math> days (Range: 3-5 days) while standard of care was instituted in another 10 patients as the control. All 20 patients presented with moderate to severe DED with DEWS Grade 2-4. Compared to the control arm of 10 patients receiving standard of care, the treatment arm of 10 patients receiving Prokera together with standard of care resulted in reduction of symptoms based on SPEED score and signs such as superficial punctate keratitis (SPK) measured by fluorescein staining, leading to an overall reduction of the mean DEWS severity score from <math>2.9 \pm 0.3</math> at baseline to <math>1.1 \pm 0.3</math> at 1 month and <math>1.0 \pm 0.0</math> at 3 months, respectively (both <math>p \leq 0.001</math>). These palliative benefits are correlated with an increase of corneal nerve density measured by in vivo confocal microscopy from <math>12,241 \pm 5,083 \mu\text{m}/\text{mm}^2</math> at baseline to <math>16,364 \pm 3,734 \mu\text{m}/\text{mm}^2</math> at 1 month, and <math>18,827 \pm 5,453 \mu\text{m}/\text{mm}^2</math> at 3 months (both <math>p=0.015</math>). The increase of corneal nerve density is also correlated with an increase of corneal sensitivity measured by a monofilament in the Bonnet-Crochet esthesiometer. A lasting benefit for more than 3 months after one placement of Prokera was also demonstrated in a retrospective study by McDonald et al [4] in 97 eyes of 84 of patients with moderate to severe DED (DEWS 2-4), of which the majority presented with symptoms of ocular discomfort, blurry vision, ocular pain, redness, and light sensitivity. Most of the cases manifested the ocular sign of SPK due to exposure keratitis, filamentary keratitis, epithelial defect, and neurotrophic keratitis. A single placement of Prokera for <math>5.4 \pm 2.8</math> days leads to notable improvement of DED symptoms and reduction of ocular signs in 74 subjects (88%) as evidenced by notable reduction of the mean DEWS severity score from 3.25 to 1.44 at 1 week, 1.45 at 1 month, and 1.47 at 3 months.</p> <p>In my practice, a single placement of Amniotic Membrane (non-sutured) was also effective in reducing signs and symptoms of DED for a period lasting more than three months. Therefore, amniotic membrane without sutures should be considered for severe dry eye with ocular surface damage and inflammation.</p> <ol style="list-style-type: none"> <li>1. Cheng AM, Zhao D, Chen R, et al. Accelerated Restoration of Ocular Surface Health in Dry Eye Disease by Self-Retained Cryopreserved Amniotic Membrane. <i>Ocul Surf.</i> 2016 Jan;14(1):56-63. [PMID: 26387870]</li> <li>2. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). <i>Ocul Surf.</i> 2007; 5: 75-92.</li> <li>3. John T, Tighe S, Sheha H, et al. Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease. <i>J Ophthalmol.</i> 2017;6404918. [PMC5574308]</li> <li>4. McDonald MB, Sheha H, Tighe S, et al. Treatment outcomes in the Dry Eye Amniotic Membrane (DREAM) study. <i>Clin Ophthalmol.</i> 2018 Apr 9;12:677-681. [PMID: 29670328]</li> </ol>
1	Acute ocular chemical burn	<p>Ocular chemical burns represent a diverse array of clinical conditions and severity, making high quality RCTs difficult or impossible to perform. The Cochrane review cited in the BCBS review (Clare G. Cochrane Database Syst Rev 2012;9:CD009379. PMID 22972141) reflects this difficulty. However, it is clear that there are subsets of patients that respond to either sutured or non-sutured HAM based in its ability to reduce inflammation and promote epithelial healing.</p>

#	Indications	Rationale
		<p>Particularly in moderate and severe burns where the prognosis with traditional therapy is poor, sutured and non-sutured HAM are important alternatives that should be covered. There are multiple reports of good outcomes in these cases. Though control groups are lacking, several of these reports are fairly large series and were not addressed directly in the BCBS review:</p> <p>Westekemper H. Br J Ophthalmol 2017;101:103. PMID 27150827  Meller D. Ophthalmology 2000;107:980. PMID 10811094  Ucakan OO. Cornea 2002;21:169. PMID 11862088  Arora R. Eye 2005;19:273. PMID 15286672  Tamhane A. Ophthalmology 2005;112:1963. PMID: 16198422  Tejwani S. Cornea 2007;26:21. PMID 17198009  Prabhasawat P. J Med Assoc Thai 2007;90:319. PMID 17375638  Kheirkhah A. Arch Ophthalmol 2008;126:1059. PMID 18695099  Tandon R. Br J Ophthalmol 2011;95:199. PMID: 20675729</p>
2	Acute ocular chemical burn	<p>Previous studies have demonstrated the importance of early intervention with cryopreserved amniotic membrane (AM) in mild and moderate chemical burns.[1-10] Specifically, Miller et al [7] used AM as a patch graft with sutures in 13 eyes of patients with acute chemical burn grade II-IV (within 2 weeks of the injury) and epithelial healing occurred within 2-5 weeks. Prabhasawat et al [8] also showed that AM as a patch graft performed within 5 days of grades II and III chemical burns promoted faster epithelial healing and less corneal haze than if performed after 5 days. These results were confirmed by Tandon et al [9] who demonstrated the efficacy of sutured AM in eyes with acute ocular burns in a prospective, randomized, controlled clinical trial of 100 patients with grade II to IV acute ocular burns. Patients were randomized to receive AM or conventional medical treatment. The rate of epithelial healing was significantly better in the AM group than the group with standard medical therapy alone. Kheirkhah et al [10] noted a similar positive outcome when AM without sutures (Prokera) was used within 8 days of chemical burn injury. Based on the above, the use of AM with or without sutures in acute chemical burn is considered a medical necessity to control inflammation, prevent further damage, reduce scarring and restore visual function. In my opinion, and based on the literature, the use of AM without sutures is preferred to prevent surgical trauma and suture related complications in such compromised eyes. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.</p> <ol style="list-style-type: none"> <li>1. Kim JS, Kim JC, Na BK, et al. Amniotic membrane patching promotes healing and inhibits protease activity on wound healing following acute corneal alkali burns. Exp Eye Res. 2000;70:329Y337. [PMID: 10712819]</li> <li>2. Sridhar MS, Bansal AK, Sangwan VS, et al. Amniotic membrane transplantation in acute chemical and thermal injury. Am J Ophthalmol. 2000;130:134Y137. [PMID: 10712819]</li> <li>3. Ucakan OO, Koklu G, Firat E. Nonpreserved human amniotic membrane transplantation in acute and chronic chemical eye injuries. Cornea. 2002;21:169Y172.</li> <li>4. Arora R, Mehta D, Jain V. Amniotic membrane transplantation in acute chemical burns. Eye. 2005;19:273Y278. [PMID: 11862088]</li> <li>5. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared</li> </ol>

#	Indications	Rationale
		<p>with medical therapy alone in acute ocular burns. Ophthalmology. 2005;112:1963Y1969. [PMID: 16198422]</p> <p>6. Tejwani S, Kolari RS, Sangwan VS, et al. Role of amniotic membrane graft for ocular chemical and thermal injuries. Cornea. 2007;26:21Y26. [PMID: 17198009]</p> <p>7. Meller D, Pires RTF, Mack RJS, et al. Amniotic membrane transplantation for acute chemical or thermal burns. Ophthalmology. 2000;107:980Y990. [PMID: 10811094]</p> <p>8. Prabhasawat P, Tesavibul N, Prakairungthong N, et al. Efficacy of amniotic membrane patching for acute chemical and thermal ocular burns. J Med Assoc Thai. 2007;90:319Y326. PMID: [17375638]</p> <p>9. Tandon R, Gupta N, Kalaivani M, et al. Amniotic Membrane Transplantation as an Adjunct to Medical Therapy in Acute Ocular Burns. Br J Ophthalmol. 2011;95(2):199-204. [PMID: 20675729]</p> <p>10. Kheirkhah A, Johnson DA, Paranjpe DR, et al. Temporary sutureless amniotic membrane patch for acute alkaline burns. Arch Ophthalmol. 2008;126:1059Y1066. [PMID: 18695099]</p>

NR = not reported

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

#	Indications	YES / NO	Low Confidence	Intermediate Confidence	High Confidence		
			1	2	3	4	5
1	Neurothrophic keratitis	Yes					X
2	Neurothrophic keratitis	Yes				X	
1	Corneal ulcers and melts	Yes					X
2	Corneal ulcers and melts	Yes					X
1	Corneal perforation	Yes					X
2	Corneal perforation	Yes					X
1	Bullous keratopathy	Yes					X
2	Bullous keratopathy	Yes				X	
1	Pterygium repair	Yes					X
2	Pterygium repair	Yes					X
1	Limbal stem cell deficiency	Yes					X
2	Limbal stem cell deficiency	Yes				X	
1	Stevens-Johnson	Yes					X

#	Indications	YES / NO	Low Confidence	Intermediate Confidence	High Confidence
2	Stevens-Johnson	Yes			X
1	Persistent epithelial defects	Yes			X
2	Persistent epithelial defects	Yes			X
1	Severe dry eye	Yes			X
2	Severe dry eye	Yes			X
1	Acute ocular chemical burn	Yes			X
2	Acute ocular chemical burn	Yes			X

NR = not reported

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

#	Indications	YES / NO	Low Confidence	Intermediate Confidence	High Confidence		
			1	2	3	4	5
1	Neurotrophic keratitis	Yes					X
2	Neurotrophic keratitis	Yes				X	
1	Corneal ulcers and melts	Yes					X
2	Corneal ulcers and melts	No				X	
1	Corneal perforation	Yes					X
2	Corneal perforation	Yes					X
1	Bullous keratopathy	Yes					X
2	Bullous keratopathy	No				X	
1	Pterygium repair	Yes					X
2	Pterygium repair	Yes					X
1	Limbal stem cell deficiency	Yes				X	
2	Limbal stem cell deficiency	Yes					X
1	Stevens-Johnson	Yes					X
2	Stevens-Johnson	Yes					X
1	Persistent epithelial defects	Yes					X
2	Persistent epithelial defects	No				X	
1	Severe dry eye	Yes				X	



#	Indications	YES / NO	Low Confidence	Intermediate Confidence	High Confidence
2	Severe dry eye	No			X
1	Acute ocular chemical burn	Yes			X
2	Acute ocular chemical burn	Yes			X

NR = not reported

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

#	Indications	YES / NO	Low Confidence	Intermediate Confidence	High Confidence		
			1	2	3	4	5
1	Neurotrophic keratitis	Yes					X
2	Neurotrophic keratitis	Yes					X
1	Corneal ulcers and melts	Yes					X
2	Corneal ulcers and melts	Yes					X
1	Corneal perforation	No					X
2	Corneal perforation	No				X	
1	Bullous keratopathy	Yes					X
2	Bullous keratopathy	Yes					X
1	Pterygium repair	Yes					X
2	Pterygium repair	Yes			X		
1	Limbal stem cell deficiency	Yes				X	
2	Limbal stem cell deficiency	Yes					X
1	Stevens-Johnson	Yes					X
2	Stevens-Johnson	Yes					X
1	Persistent epithelial defects	Yes					X
2	Persistent epithelial defects	Yes					X
1	Severe dry eye	Yes				X	
2	Severe dry eye	Yes					X
1	Acute ocular chemical burn	Yes					X
2	Acute ocular chemical burn	Yes					X

NR = not reported

- Based on the evidence and your clinical experience for using human amniotic membrane without suture fixation for the clinical indications described below:
  - Respond YES or NO for each clinical indication whether this intervention is consistent with generally accepted medical practice; AND
  - Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	Indications	YES / NO	Low Confidence	2	Intermediate Confidence	3	High Confidence	4	5
			1	2	3			4	5
1	Neurotrophic keratitis	Yes							X
2	Neurotrophic keratitis	Yes						X	
1	Corneal ulcers and melts	Yes							X
2	Corneal ulcers and melts	Yes							X
1	Corneal perforation	No							X
2	Corneal perforation	No						X	
1	Bullous keratopathy	Yes							X
2	Bullous keratopathy	Yes						X	
1	Pterygium repair	Yes							X
2	Pterygium repair	No						X	
1	Limbal stem cell deficiency	Yes						X	
2	Limbal stem cell deficiency	Yes						X	
1	Stevens-Johnson	Yes							X
2	Stevens-Johnson	Yes							X
1	Persistent epithelial defects	Yes							X
2	Persistent epithelial defects	Yes						X	
1	Severe dry eye	Yes						X	
2	Severe dry eye	Yes							X
1	Acute ocular chemical burn	Yes							X
2	Acute ocular chemical burn	Yes							X

NR = not reported

- Additional narrative rationale or comments regarding clinical pathway and/or any relevant scientific citations (including the PMID) supporting your clinical input on this topic.

#	Additional Comments
1	Specific citations are included above in the comments for each of the individual indications.
2	Amniotic Membrane is available either as an outpatient clinic based only protective bandage contact lens AM patch, or as an ASC or hospital based operating room surgical inlay tissue

#	Additional Comments
	<p>substitute and is an established treatment for several severe ocular surface diseases. It is most commonly used in patients whose condition is refractory to conventional therapies, such as Corneal Ulcers and Melts, Neurotrophic Keratitis, severe anterior basement membrane dystrophy, and especially difficult-to-heal Persistent Epithelial Defects (PED).</p> <p>I use Prokera (BioTissue) to treat ocular surface diseases because based on the clinical presentation and the failure of conventional therapy, it is medically necessary in order to achieve the best clinical outcome. Prokera is a cryopreserved (not dehydrated) sutureless AM and is the only such AM cleared by the FDA (2003). It is indicated for use "where the ocular surface is damaged, or the underlying corneal stroma is inflamed." The Prokera self-retaining ring makes it possible to non-surgically insert AM into the eye like a very large contact lens and thereby secure the membrane in place. As such, Prokera represents a significant improvement over the use of AM grafts that require the more invasive, time consuming, and costly suturing procedure.</p> <p>Clinically, use of amniotic membranes serve two primary roles: reduction of inflammation and promotion of wound healing. These are critical functions to accelerating and facilitating optimal clinical outcomes for the patient. Other therapies that provide these mechanisms do exist but either come with drawbacks (side effects such as thinning of the conjunctiva, time to effect) or address one function but not the other (in some cases, therapies may be counterproductive for the other critical clinical need).</p>

NR = not reported

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

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