

# Medical Policy



## Title: Amniotic Membrane and Amniotic Fluid

See Also: *Bio-Engineered Skin and Soft Tissue Substitutes*

### Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>With nonhealing diabetic lower-extremity ulcers</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Patch or flowable formulation of human amniotic membrane</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Standard wound care</li> <li>Advanced wound therapies</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 lower-extremity ulcers due to venous insufficiency</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Patch or flowable formulation of human amniotic membrane</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Compression therapy</li> <li>Advanced wound therapies</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>

<b>Populations</b>	<b>Interventions</b>	<b>Comparators</b>	<b>Outcomes</b>
Individuals: • With knee osteoarthritis	Interventions of interest are: • Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid	Comparators of interest are: • Conservative therapy • Corticosteroid injections	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With plantar fasciitis	Interventions of interest are: • Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid	Comparators of interest are: • Conservative therapy • Corticosteroid injections	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative treatment	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With corneal ulcers or melts that do not respond to initial medical therapy	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With bullous keratopathy as a palliative measure in patients who are not candidates for a curative treatment (eg, endothelial or penetrating keratoplasty)	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With moderate or severe Stevens-Johnson syndrome	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With persistent epithelial defects that do not respond to conservative therapy	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life

<b>Populations</b>	<b>Interventions</b>	<b>Comparators</b>	<b>Outcomes</b>
Individuals: • With severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With moderate or severe acute ocular chemical burn	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With corneal perforation when corneal tissue is not immediately available	Interventions of interest are: • Sutured human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft	Interventions of interest are: • Sutured or glued human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life

## **DESCRIPTION**

Several commercially available forms of human amniotic membrane (HAM) and amniotic fluid can be administered by patches, topical application, or injection. Amniotic membrane and amniotic fluid are being evaluated for the treatment of a variety of conditions, including chronic full-thickness diabetic lower extremity ulcers, venous ulcers, knee osteoarthritis, plantar fasciitis, and ophthalmic conditions.

## **OBJECTIVE**

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

## **BACKGROUND**

### **Human Amniotic Membrane**

Human amniotic membrane (HAM) consists of 2 conjoined layers, the amnion, and chorion, and forms the innermost lining of the amniotic sac or placenta. When prepared for use as an allograft, the membrane is harvested immediately after birth, cleaned, sterilized, and either cryopreserved or dehydrated. Many products available using amnion, chorion, amniotic fluid, and umbilical cord are being studied for the treatment of a variety of conditions, including chronic full-thickness diabetic lower-extremity ulcers, venous ulcers, knee osteoarthritis, plantar fasciitis, and ophthalmic conditions. The products are formulated either as patches, which can be applied as wound covers, or as suspensions or particulates, or connective tissue extractions, which can be injected or applied topically (see Table 1).

The fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist.<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.

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

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

Product (Supplier)	Preparation Cryopreserved, Dehydrated, or Extracted	Components			
		Amnion	Chorion	Amniotic Fluid	Umbilical Cord
ReNu™ (NuTech Medical)	D	X		X	
WoundEx® Flow (Skye Biologics) <sup>b</sup>	E	X	X	X	X

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

<sup>a,b</sup> Processed by HRT and marketed by under different tradenames.

## REGULATORY STATUS

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. HAM products and amniotic fluid products are included in these regulations.

In 2003, Prokera™ was cleared for marketing by the Food and Drug Administration through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). The Food and Drug Administration determined that this device was substantially equivalent to the Symblepharon Ring. The Prokera™ device is intended “for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred.” The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

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

**POLICY**

- A. Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered **medically necessary**.
1. AmnioBand Membrane (Q4151)
  2. Biovance (Q4154)
  3. EpiCord (Q4187)
  4. Epifix (Q4186)
  5. Grafix (Q4132, Q4133)
- B. FDA-approved sutured and non-sutured human amniotic membrane grafts may be considered **medically necessary** for the treatment of the following ophthalmic indications:
1. Neurotrophic keratitis
  2. Corneal ulcers and melts
  3. Pterygium repair
  4. Stevens-Johnson syndrome
  5. Persistent epithelial defects (with documented pain for  $\geq 5$  days)
  6. Acid or alkaline burn
- C. FDA approved sutured and non-sutured human amniotic membrane grafts are considered **experimental / investigational** for the treatment of all other ophthalmic conditions including, but not limited to, dry eye syndrome, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy.
- D. Injection of micronized or particulated human amniotic membrane is considered **experimental / investigational** for all indications, including, but not limited to, treatment of osteoarthritis and plantar fasciitis.
- E. Injection of human amniotic fluid is considered **experimental / investigational** for all indications.
- F. All other indications not listed above are considered **experimental / investigational**, including, but not limited to, treatment of lower-extremity ulcers due to venous insufficiency.

**Policy Guidelines**

1. Nonhealing is defined as less than a 20% decrease in wound area with standard wound care for at least 2 weeks based on the entry criteria for clinical trials (eg, Zelen et al, 2015).
2. A persistent epithelial defect is one that failed to close completely after 5 days of conservative treatment or has failed to demonstrate a decrease in size after 2 days of conservative treatment.

3. Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. Failure of multiple modalities should not be required prior to moving to human amniotic membrane grafts. An amniotic membrane graft requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in regard to treatments requiring multiple drops per day.

## **RATIONALE**

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through November 27, 2018.

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

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

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

#### Dehydrated Amniotic Membrane or Placental Membrane

##### Clinical Context and Therapy Purpose

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

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

The following PICOTS were used to select literature to inform this review.

##### Patients

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

### Interventions

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

### Comparators

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

### Outcomes

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

- Incidence of complete wound closure.
- Time to complete wound closure (reflecting accelerated wound closure).
- Incidence of complete wound closure following surgical wound closure.
- Pain control.

### Timing

Complete ulcer healing with advanced wound therapies may be measured at 6 to 12 weeks.

### Setting

The setting is outpatient care by a wound care specialist.

### Review of Evidence

At least six RCTs have evaluated rates of healing with amniotic membrane grafts or placental membrane graft compared to SOC or an advanced wound therapy in patients with chronic diabetic foot ulcers (see Table 2). The number of patients in these studies ranged from 25 to 155. Human amniotic membrane (HAM) or placental membrane grafts improved healing compared to SOC by 22% (EpiCord vs Alginate dressing) to 60% (EpiFix) in the intention-to-treat (ITT) analysis (see Table 3). In a 2018 trial, the cryopreserved placental membrane Grafix was found to be non-inferior to an advanced fibroblast-derived wound therapy (Dermagraft).

**Table 2.** Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator
Ananian et al (2018) <sup>4</sup>	US	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>11</sup>	US	11	2016-2018	155 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers	n=101 EpiCord plus SOC	n=54 SOC with alginate dressing

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator
DiDomenico et al (2016) <sup>11</sup> ,				40 patients with non-healing (4 weeks) diabetic foot ulcers	AmnioBand Membrane plus SOC	SOC
Snyder et al (2016) <sup>11</sup> ,				29 patients with non-healing diabetic foot ulcers	AmnioExcel plus SOC	SOC
Zelen et al (2015, 2016) <sup>8,9</sup> ,				60 patients with less than 20% wound healing in a 2 week run-in period	EpiFix	Apligraf or SOC with collagen-alginate dressing
Lavery et al (2014) <sup>10</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 3.** Summary of Key RCT Results

Study	Wounds Healed at 6 Weeks (ITT)	Wounds Healed	Wounds Healed	Days to Complete Healing	Adverse Events and Number of Treatments
Ananian et al (2018) <sup>4</sup>		<b>8 Weeks (PP) n (%)</b>			<b>Patients with Index Ulcer Related Adverse Events n (%)</b>
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>11</sup> ,		<b>12 Weeks (PP) n (%)</b>	<b>12 Weeks (ITT) n (%)</b>		<b>Patients with Adverse Events (% of total)</b>
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 (2016) <sup>11</sup> ,	<b>n (%)</b>			Mean (95% CI)	
N	40		40	40	
AmnioBand	14 (70%)		17 (85%)	36 (27 to 46)	
SOC	3 (15%)		5 (25%)	70 (59 to 81)	
OR/NNT (95% CI)	OR: 17 (3.1 to 93)		NNT: 1.7 (1.2 to 2.8)		
P Value	0.001			<0.001	
Snyder et al (2016) <sup>11</sup> ,	<b>Mean (95% CI)</b>	<b>6 Weeks (PP) Mean (95% CI)</b>			
N	29	21			

Study	Wounds Healed at 6 Weeks (ITT)	Wounds Healed	Wounds Healed	Days to Complete Healing	Adverse Events and Number of Treatments
AmnioExcel	33% (25.0% to 46.4%)	45.5% (32.9% to 58.0%)			
SOC	0%	0%			
P Value	0.017	0.014			
Zelen et al (2015, 2016) <sup>8,9</sup> ,	<b>n (%)</b>		<b>Wounds Healed at 12 Weeks</b>		<b>Weekly Treatments</b>
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
Lavery et al (2014) <sup>10</sup> ,			<b>Wounds Healed at 12 Weeks</b>		<b>Patients With Adverse Events</b>
N			97 <sup>a</sup>	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	AmnioBand 55% AmnioExcel 33% EpiFix 60%		EpiCord 22% Grafix 41%		

HAM: human amniotic membrane; CI: confidence interval; HR: hazard ratio; ITT: intention-to-treat; NNT: number needed to treat; NR: not reported; PP: per protocol; RCT: randomized controlled trial; RR.

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.

Gaps in study design and conduct are shown in Table 4. Studies without notable gaps 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>11</sup>, preclude conclusions for this product.

**Table 4.** Study Design and Conduct Gaps

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>
Ananian et al (2018) <sup>4</sup> ,		2, 3. No blinding for outcomes assessment				
Tettelbach et al (2018) <sup>11</sup> ,		1, 2, 3. No blinding				
DiDomenico et al (2016) <sup>11</sup> ,						
Snyder et al (2016) <sup>11</sup> ,				1. There was high loss to follow-up with discontinuation of 8 of 29 participants	1. Power analysis was not reported	

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>
Zelen et al (2015, 2016) <sup>8,9</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.		
Lavery et al (2014) <sup>10</sup>						

The evidence gaps 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.

### Prospective Single-arm or Registry Studies

Prospective single-arm or registry studies are described in Tables 5 and 6.

Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about a third (n=47) were diabetic foot wounds.<sup>11</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.

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

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

Study	Study Design	Participants	Treatment Delivery
Smiell et al (2015) <sup>11</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>12</sup>	Prospective multi-center single-arm study	31 patients with chronic complex diabetic foot wounds with exposed tendon or bone	Graftax weekly until closure or 16 weeks

**Table 6.** 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>11</sup>	Biovance	41.6%	8 weeks	2.4
Frykberg et al (2016) <sup>12</sup>	Graftax	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 (ie, 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 used power analysis, blinded assessment of wound healing, and ITT analysis. For the HAM products that have been sufficiently evaluated (ie, AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix), results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries.

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

### Dehydrated Amniotic Membrane

#### Clinical Context and Therapy Purpose

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

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

The following PICOTS were used to select literature to inform this review.

#### Patients

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

#### Interventions

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

#### Comparators

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

#### Outcomes

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

- Incidence of complete wound closure.
- Time to complete wound closure (reflecting accelerated wound closure).
- Incidence of complete wound closure following surgical wound closure.
- Pain control.

#### Timing

Complete ulcer healing with advanced wound therapies may be measured at 6 to 12 weeks.

### Setting

The setting is outpatient care by a wound care specialist.

Two RCTs, both with EpiFix, were identified on amniotic membrane grafts for venous leg ulcers. Serena et al (2014) reported on an industry-sponsored multicenter open-label RCT that compared EpiFix d-HAM plus compression therapy with compression therapy alone for venous leg ulcers (see Table 7).<sup>13</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 four week study. There was no significant difference in healing for wounds given 1 vs 2 applications of amniotic membrane (62% vs 63%, respectively). Strengths of this trial included adequate power and ITT analysis with last observation carried forward. Limitations included the lack of blinding for wound evaluation and use of 40% closure rather than complete closure. A 2015 retrospective study of 44 patients from this RCT (31 treated with amniotic membrane) found that wounds with at least 40% closure at 4 weeks (n=20) had a closure rate of 80% by 24 weeks; however, this analysis did not take into account additional treatments after the 4-week randomized trial period.

A second industry-sponsored multicenter open-label RCT, (Bianchi et al [2017]), evaluated the time to complete ulcer healing following weekly treatment with EpiFix d-HAM and compression therapy or compression therapy with standard dressing (see Table 7).<sup>14</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. Healing within 12 weeks was reported for 60% of patients in the EpiFix group and 35% of patients in the control group (see Table 8). There were several limitations of this trial. Nineteen (15%) patients were excluded from the analysis, and the proportion of patients excluded differed between groups (19% from the EpiFix group vs 11% from the control group). Also, the trial did not use the ITT analysis. Had all excluded patients been considered treatment failures, the difference between groups would have been 17% (48% wound healing for EpiFix vs 31% for controls). There was also a difference between the groups in how treatment failures at eight weeks were handled. Patients in the control group who did not have a 40% decrease in wound area at eight weeks were considered study failures and treated with advanced wound therapies. Although the trialists noted that only 1 patient from this group had healed by weeks 12 and 16, reporting is unclear about how many patients from the d-HAM group would have been considered treatment failures at 8 weeks using the same cutoff.

**Table 7.** Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Serena et al (2014) <sup>13</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 compression (n=53)	Compression therapy alone (n=31)
Bianchi et al (2017) <sup>14</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; 52 analyzed)	Moist wound therapy plus compression (n=64; 57 analyzed)

RCT: randomized controlled trial; VLU: venous leg ulcer.

**Table 8.** Summary of Key RCT Results

Study	Percent With 40% Wound Closure at 4 Weeks	Percent with Complete Wound Closure at 4 Weeks	Percent with Complete Wound Closure at 12 Weeks	Percent with Complete Wound Closure at 16 Weeks
Serena et al (2014) <sup>13</sup> ,				
EpiFix	62	11.3		
Control	32	12.9		
P Value	0.005			
Bianchi et al (2017) <sup>14</sup> ,				
EpiFix			60	71
Control			35	44
P Value			0.013	0.007

RCT: randomized controlled trial.

### Biovance

As described above, Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about half (n=89) were venous ulcers.<sup>11</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 the SOC is unknown.

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

The evidence on HAM for the treatment of venous leg ulcers includes two multicenter RCTs with EpiFix. One RCT reported a larger percent wound closure at four weeks, but the percentage of patients with complete wound closure at four weeks did not differ between EpiFix and the SOC. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression. Although a significant difference in complete healing was reported, data interpretation is limited by the differential loss to follow-up and exclusions between groups and the lack of ITT analysis. Corroboration with well-designed and well-conducted RCTs evaluating wound healing is needed to demonstrate efficacy. The corroborating RCTs should report ITT analysis, with analysis of all patients, including those who were off

treatment or had protocol deviations and exclusions. While per protocol analysis can supplement the results, it is not sufficient to determine the effect of the treatment on health outcomes.

## **Osteoarthritis**

### ReNu

A feasibility study (n=6) of cryopreserved (c-HAM) suspension with amniotic fluid–derived cells for the treatment of knee osteoarthritis was reported in 2016.<sup>15</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.

### *Section Summary: Osteoarthritis*

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

## Plantar Fasciitis

### *Clinical Context and Therapy Purpose*

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

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

The following PICOTS were used to select literature to inform this review.

### Patients

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

### Interventions

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

### Comparators

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

### Outcomes

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

### Timing

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

Setting

The setting is outpatient care by a primary care physician or foot specialist.

Review of Evidence

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

Systematic Review

A 2016 network meta-analysis of 22 RCTs (total n=1216 patients) compared injection therapies for plantar fasciitis.<sup>16</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 two to six months (seven RCTs) favored botulinum toxin for pain and patient recovery plan for composite outcomes.

Randomized Controlled Trials

Zelen et al (2013) reported a preliminary study with 15 patients per group (placebo, 0.5 cc, and 1.25 cc) and 8-week follow-up.<sup>17</sup> A subsequent RCT by Cazzell et al (2018) enrolled 145 patients and reported 3-month follow-up (see Table 9).<sup>18</sup> In the Cazzell et al (2018) RCT, amniotic membrane injection led to greater improvements in the VAS for pain and the Foot Functional Index between baseline and 3 months (see Table 10) compared to controls. VAS at 3 months had decreased to 17.1 in the AmnioFix group compared to 38.8 in the placebo control group, which would be considered a clinically significant difference.

**Table 9.** Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator Intervention
Cazzell et al (2018) <sup>18</sup> ; AIPF004 (NCT02427191)	US	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

RCT: randomized controlled trial; VAS: visual analog score.

**Table 10.** 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>18</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.

Gaps in relevance and design and conduct of this publication are described in Tables 11 and 12. The major limitation of the study is the short-term follow-up, which the authors note is continuing to 12 months. The extended follow-up will be reported in a separate publication.

**Table 11.** Relevance Gaps

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>18</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 months will be reported in a subsequent publication.

The evidence gaps 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 12.** Study Design and Conduct Gaps

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>d</sup>	Statistical <sup>f</sup>
Cazzell et al (2018) <sup>18</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 evidence gaps 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 three months' results. The authors note that 12-month follow-up will be reported in a subsequent publication.

## **HAM for Ophthalmologic Conditions**

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

### Neurotrophic Keratitis with Ocular Surface Damage or Inflammation That Does Not Respond to Conservative Treatment

#### Clinical Context and Therapy Purpose

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

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

The following PICOTS were used to select literature to inform this review.

#### Patients

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

#### Interventions

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

#### Comparators

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

#### Outcomes

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

#### Timing

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

#### Setting

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

#### Review of Evidence

Khokhar et al (2005) reported on an RCT of 30 patients (30 eyes) with refractory neurotrophic corneal ulcers who were randomized to HAM transplantation (n=15) or conventional treatment with tarsorrhaphy or bandage contact lens.<sup>19</sup> 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>20</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.

Clinical input recommended HAM for neurotrophic keratitis that did not respond to conservative therapy. Input recommended non-sutured HAM as the preferred initial treatment "because it can be performed rapidly in an office setting, avoiding the delay associated with scheduling a procedure in an outpatient surgical facility."

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

An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.

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

*Clinical Context and Therapy Purpose*

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

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

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

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

Comparators

The following therapies are currently being used: medical therapy.

Outcomes

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

Timing

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

### Setting

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

### Review of Evidence

No evidence was identified for this indication.

Clinical input indicated that "both sutured and non-sutured HAM reduces inflammation and promotes epithelial healing. It is, therefore, a useful adjunct in addition to corneal transplantation in those patients with active inflammation and perforation."

### *Section Summary: Corneal Perforation When There is Active Inflammation After Corneal Transplant Requiring Adjunctive Treatment*

No evidence was identified for this indication. Clinical input supported the use of HAM to reduce inflammation and promote epithelial healing with active inflammation following corneal transplant.

### Bullous Keratopathy in Patients Who Are Not Candidates for a Curative Treatment (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 PICOTS were used to select literature to inform this review.

#### Patients

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

#### Interventions

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

#### Comparators

The following therapies are currently being used: stromal puncture.

#### Outcomes

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

#### Timing

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

### Setting

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

### Review of Evidence

Dos Santos Paris et al (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy.<sup>21</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 two treatments. Symptoms had been present for approximately two years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with the use of HAM only if the pain did not resolve.

Clinical input recommended HAM as a palliative measure in patients who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) Input recommended HAM as a reasonable alternative to stromal puncture.

### *Section Summary: Bullous Keratopathy in Patients Who Are Not Candidates for a Curative Treatment and Who Are Unable to Remain Still for Stromal Puncture*

An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. Based on clinical input, non-sutured HAM could be used as an alternative to stromal puncture.

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

#### Clinical Context and Therapy Purpose

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

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

The following PICOTS were used to select literature to inform this review.

#### Patients

The relevant population of interest are patients who have LSCD with extensive diseased tissue where selective removal alone is not sufficient.

#### Interventions

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

#### Comparators

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

#### Outcomes

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

### Timing

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

### Setting

*Review of Evidence:* The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

No RCTs were identified on HAM for LSCD.

Keirkhah et al (2008) reported on the use of HAM in 11 eyes of 9 patients who had LSCD.<sup>22</sup> Patients underwent superficial keratectomy to remove the conjunctivalized pannus followed by HAM transplantation using fibrin glue. An additional Prokera patch was used in seven patients. An improvement in visual acuity was observed in all but two patients. Pachigolla et al (2009) reported a series of 20 patients who received a Prokera implant for ocular surface disorders; 6 of the patients had limbal stem cell deficiency with a history of chemical burn. Following treatment with Prokera, 3 of the 6 patients had a smooth corneal surface and improved vision to 20/40.<sup>30</sup> The other 3 patients had final visual acuity of 20/400, counting fingers, or light perception.

Clinical input recommended HAM for patients with LSCD in conjunction with superficial keratectomy, noting that due to the rarity of this disease, it is unlikely that RCTs will ever be performed. Input also noted that "comparisons to limbal stem cell transplants are unlikely to be performed because of the risks of systemic immune suppression."

### *Section Summary: Partial LSCD with Extensive Diseased Tissue Where Selective Removal Alone is Not Sufficient*

No RCTs were identified on HAM for LSCD. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. Clinical input noted the limitations of performing an RCT and supported the use of HAM for this indication.

### Moderate or Severe Stevens-Johnson Syndrome

#### Clinical Context and Therapy Purpose

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

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

The following PICOTS were used to select literature to inform this review.

### Patients

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

### Interventions

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

### Comparators

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

### Outcomes

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

### Timing

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

### Setting

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

### Review of Evidence

One RCT from India by Sharma et al (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or medical therapy alone.<sup>24</sup> The c-HAM was prepared locally and applied with fibrin glue rather than sutures. Application of c-HAM in the early stages of Stevens-Johnson syndrome resulted in improved visual acuity ( $p=0.042$ ), better tear breakup time ( $p=0.015$ ), improved Schirmer test results ( $p<0.001$ ), and less conjunctival congestion ( $p=0.03$ ). In the c-HAM group at 180 days, there were no cases of corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. These outcomes are dramatically better than those in the medical therapy alone group, which had 11 (44%) cases with corneal haze ( $p=0.001$ ), 6 (24%) cases of corneal vascularization and conjunctivalization ( $p=0.03$ ), and 6 (24%) cases of trichiasis and metaplastic lashes. Clinical input recommended HAM for moderate-to-severe Stevens-Johnson noting that "the severity of the disease and its infrequency makes it unlikely that a large RCT will be performed." Sutured HAM would be preferred to prevent lid-related complications, but non-sutured HAM "is still helpful in emergency settings when the patient condition does not allow for surgical intervention."

### *Section Summary: Moderate or Severe Stevens-Johnson Syndrome*

The evidence on HAM for the treatment of Stevens-Johnson syndrome includes 1 RCT with 25 patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone. Clinical input indicated that large RCTs are unlikely due to the severity and rarity of the disease, supported the use of HAM for moderate or severe Stevens-Johnson.

### Persistent Epithelial Defects and Ulcerations That Do Not Respond to Conservative Therapy

#### Clinical Context and Therapy Purpose

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

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

The following PICOTS were used to select literature to inform this review.

#### Patients

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

#### Interventions

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

#### Comparators

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

#### Outcomes

The general outcomes of interest are epithelial closure.

#### Timing

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

#### Setting

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

#### Review of Evidence

Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease.<sup>25</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. Clinical input recommended HAM for persistent epithelial defects that do not respond to conservative therapy (eg, topical lubricants and/or antibiotics, therapeutic contact lens, or patching), noting that "the uncommon nature of the diseases associated with persistent epithelial defects and the lack of a standard therapeutic regimen account for the lack of RCTs."

#### *Section Summary: Persistent Epithelial Defects and Ulceration That Do Not Respond to Conservative Therapy*

No RCTs were identified on persistent epithelial defects and ulceration. Clinical input noted the difficulty in conducting RCTs for this indication and supported the use of amniotic membrane for persistent epithelial defects and ulceration that does not respond to conservative therapy.

## Severe Dry Eye Disease with Ocular Surface Damage and Inflammation that does not Respond to Conservative Therapy

### Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: does the use of sutured or self-retained HAM improve the net health outcome in patients who have severe dry eye with ocular surface damage and inflammation?

The following PICOTS were used to select literature to inform this review.

### Patients

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

### Interventions

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

### Comparators

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

### Outcomes

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

### Timing

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

### Setting

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

### Review of Evidence

John et al (2017) reported on an RCT with 20 patients with moderate-to-severe dry eye disease who were treated with Prokera c-HAM or maximal conventional treatment.<sup>26</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 one-month and three-month follow-ups

in the c-HAM group but not in the conventional treatment group. For example, pain scores decreased from 7.1 at baseline to 2.2 at 1 month and 1.0 at 3 months in the c-HAM group. In vivo confocal microscopy, reviewed by masked readers, showed a significant increase in corneal nerve density in the study group at three months, with no change in nerve density in the controls. Corneal sensitivity was similarly increased in the c-HAM group but not in controls.

The treatment outcomes in the DRy Eye Amniotic Membrane study (McDonald et al [2018]) was a retrospective series of 84 patients (97 eyes) with severe dry eye despite maximal medical therapy who were treated with Prokera self-retained c-HAM.<sup>27</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.

Clinical input recommended HAM in cases of severe dry eye with ocular surface damage and inflammation.

*Section Summary: Severe Dry Eye with Ocular Surface Damage and Inflammation that does not Respond to Conservative Therapy*

The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. Clinical input supported the use of HAM in cases of severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy.

Moderate or Severe Acute Ocular Chemical Burns

Clinical Context and Therapy Purpose

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

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

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

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

### Comparators

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

### Outcomes

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

### Timing

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

### Setting

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

### Review of Evidence

An RCT of 100 patients with chemical or thermal ocular burns was published by Tandon et al (2011).<sup>28</sup> Half of the patients (n=50) had moderate ocular burns and the remainder (n=50) had severe ocular burns. All but eight of the patients had alkali or acid burns. Patients were randomized to HAM transplantation plus medical therapy or medical therapy alone. Epithelial healing, which was the primary outcome, was improved in the group treated with HAM, but there was no significant difference between the two groups for the final visual outcome, symblepharon formation, corneal clarity or vascularization.

Use of the Prokera self-retained implant was reported by Kheirkhah et al (2008) in a series of 5 patients with acute alkaline burns.<sup>29</sup>

Clinical input recommended HAM for acute ocular chemical burn, noting that "ocular chemical burns represent a diverse array of clinical conditions and severity, making high-quality RCTs difficult or impossible to perform."

### *Section Summary: Moderate or Severe Acute Ocular Chemical Burns*

Evidence includes an RCT of 100 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Patients in the HAM group had a faster rate of epithelial healing, without a significant benefit for other outcomes. Clinical input was in support of HAM for acute ocular chemical burn.

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

#### Clinical Context and Therapy Purpose

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

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

The following PICOTS were used to select literature to inform this review.

### Patients

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

### Interventions

The therapy being considered is sutured HAM.

### Comparators

The following therapies are currently being used: conservative management.

### Outcomes

The general outcomes of interest are eye pain.

### Timing

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

### Setting

The setting is outpatient care by an ophthalmologist for self-retained HAM or in a surgical suite for sutured HAM.

### Review of Evidence

No RCTs were identified on corneal perforation.

Clinical input noted that multiple layers of HAM have been shown to promote healing of corneal perforation and recommended sutured HAM for tectonic support when corneal tissue is not immediately available.

### *Section Summary: Corneal Perforation When Corneal Tissue is not Immediately Available*

The standard treatment for corneal perforation is corneal transplantation. Based on clinical input, sutured HAM may be used as a temporary measure when corneal tissue is not immediately available.

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

#### Clinical Context and Therapy Purpose

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

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

The following PICOTS were used to select literature to inform this review.

### Patients

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

### Interventions

The therapy being considered is sutured or glued HAM.

### Comparators

The following therapies are currently being used: conjunctival autograft.

### Outcomes

The general outcomes of interest are a recurrence of pterygium.

### Timing

Pterygium recurrence would be measured at one to three months.

### Setting

The setting is in a surgical suite for pterygium repair.

### Review of Evidence

RCTs have been reported on the use of amniotic membrane following pterygium repair. The American Academy of Ophthalmology (2013) published a technology assessment on options and adjuvants for pterygium surgery.<sup>30</sup> Reviewers identified four RCTs comparing conjunctival or limbal autograft procedure with amniotic membrane graft, finding that conjunctival or limbal autograft was more effective than HAM graft in reducing the rate of pterygium recurrence. A 2016 Cochrane review of 20 RCTs (total n=1866 patients) arrived at the same conclusion.<sup>31</sup> Clinical input recommended sutured or glued HAM for pterygium repair when there was insufficient healthy tissue to create a conjunctival autograft (eg, extensive, double, or recurrent pterygium).

### *Section Summary: Following Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft*

Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence. Based on clinical input, sutured or glued HAM may be considered when there is insufficient healthy tissue to create a conjunctival autograft (eg, extensive, double, or recurrent pterygium).

## **SUMMARY OF EVIDENCE**

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

For individuals who have non-healing diabetic lower-extremity ulcers who receive a patch or flowable formulation of HAM (ie, AmnioBand Membrane, Biovance, EpiFix, Grafix), the evidence includes RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing (<20% healing with  $\geq 2$  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 ITT analysis. For the HAM products that have been sufficiently evaluated (ie, AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix), results have

shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have lower-extremity ulcers due to venous insufficiency who receive a patch or flowable formulation of HAM, the evidence includes two RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for the treatment of lower-extremity venous ulcers includes two multicenter RCTs with EpiFix. One RCT reported larger percent wound closure at four weeks but the percentage of patients with complete wound closure did not differ between EpiFix and the SOC. A second multicenter RCT reported a significant difference in complete healing at 12 weeks, but the interpretation is limited by methodologic concerns. Well-designed and well-conducted RCTs that compare HAM with the SOC for venous insufficiency ulcers are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Osteoarthritis**

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

### **Plantar Fasciitis**

For individuals who have plantar fasciitis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes two small RCTs. The relevant outcomes are symptoms, functional outcomes, QOL, and treatment-related morbidity. Research on HAM injections for plantar fasciitis is at an early stage. The evidence includes a small (n=23) double-blind comparison with corticosteroid and a patient-blinded (n=45) comparison of 2 different doses of dehydrated HAM with saline. Additional controlled trials with larger sample sizes and longer follow-up are needed to permit conclusions on the effect of HAM and amniotic fluid injections on plantar fasciitis pain. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Ophthalmic Conditions**

#### Neurotrophic Keratitis with Ocular Surface Damage and Inflammation That does not Respond to Conservative Therapy

For individuals who have neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment. The

evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

#### Corneal Ulcers and Melts That 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 is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. Based on clinical input, HAM might be considered for patients who did not respond to conservative therapy. Clinical input indicated that non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No comparative evidence was identified for this indication. Clinical input supported the use of HAM to reduce inflammation and promote epithelial healing with active inflammation following corneal transplantation.

#### Bullous Keratopathy as a Palliative Measure in Patients Who are not Candidates for a Curative Treatment (eg, endothelial or penetrating keratoplasty)

For individuals who have bullous keratopathy and who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. Based on clinical input, non-sutured HAM could be used as an alternative to stromal puncture.

#### Partial LSCD with Extensive Diseased Tissue Where Selective Removal Alone is not Sufficient

For individuals who have partial LSCD with extensive diseased tissue where selective removal alone is not sufficient who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No RCTs were identified on HAM for LSCD. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. Clinical input noted the limitations of performing an RCT and supported the use of HAM for this indication.

#### Moderate or Severe Stevens-Johnson Syndrome

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

#### Persistent Epithelial Defects and Ulceration That does not Respond to Conservative Therapy

For individuals who have persistent epithelial defects that does not respond to conservative therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No RCTs were identified on persistent epithelial defects and ulceration. Clinical input noted the difficulty in conducting RCTs for this indication and supported the use of amniotic membrane for persistent epithelial defects and ulcerations that does not respond to conservative therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

#### Severe Dry Eye with Ocular Surface Damage and Inflammation That does not Respond to Conservative Therapy

For individuals who have severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy, who receive HAM, the evidence includes an RCT and a large case series. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. Clinical input supported HAM in cases of severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy.

#### Moderate or Severe Acute Ocular Chemical Burns

For individuals who have moderate or severe acute ocular chemical burn who receive HAM, the evidence includes an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Evidence includes an RCT of 100 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Patients in the HAM group had a faster rate of epithelial healing, without a significant benefit for other outcomes. Clinical input was in support of HAM for acute ocular chemical burn. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

#### Corneal Perforation When Corneal Tissue is not Immediately Available

For individuals who have corneal perforation when corneal tissue is not immediately available who receive sutured HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The standard treatment for corneal perforation is corneal transplantation. Based on clinical input, sutured HAM may be used as a temporary measure when corneal tissue is not immediately available.

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

For individuals who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft who receive HAM, the evidence includes RCTs and systematic reviews of RCTs. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence. Based on clinical input, sutured or glued HAM may be considered when there is insufficient healthy tissue to create a conjunctival autograft (eg, extensive, double, or recurrent pterygium). The evidence is

sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

### **CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS**

#### 2019

In response to requests while this policy was under review in 2018-2019, clinical input on the use of human amniotic membrane graft either without or with suture fixation for several ophthalmic conditions was received from 2 respondents, including 1 specialty society-level response and 1 physician-level response identified through specialty societies including physicians with academic medical center affiliations.

Evidence from clinical input is integrated within the Rationale section summaries and the Summary of Evidence.

### **PRACTICE GUIDELINES AND POSITION STATEMENTS**

#### Tear Film and Ocular Surface Society

The Tear Film and Ocular Surface Society (2017) published the DEWS [Dry Eye Workshop] II management and therapy report.<sup>32</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 (eg tarsorrhaphy, salivary gland transplantation)

### Society for Vascular Surgery et al

The Society for Vascular Surgery (2016) in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine made the following recommendation: "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amniotic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."<sup>33</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 13.

**Table 13.** Summary of Key Trials

<b>NCT No.</b>	<b>Trial Name</b>	<b>Planned Enrollment</b>	<b>Completion Date</b>
<b>Ongoing</b>			
NCT03441607 <sup>a</sup>	Safety & Efficacy of Micronized Human Amnion Chorion Membrane Biologic (mHACMb) FloGraft (Micronized Human Amnion Chorion Membrane) <sup>®</sup> in Adults with Pain Due to Osteoarthritis of the Knee	320	Mar 2019
NCT02318511 <sup>a</sup>	An Investigation of ReNu <sup>™</sup> Knee Injection: Monitoring the Response of Knee Function and Pain in Patients With Osteoarthritis	200	Dec 2019
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 Tendinitis	158	Dec 2019
NCT03414268a	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	164	Oct 2019

NCT No.	Trial Name	Planned Enrollment	Completion Date
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
NCT02322554	The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers	50,000	Jan 2020
NCT03390920	Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions Musculoskeletal Conditions	200	Jun 2022
<b>Unpublished</b>			
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
NCT02880592 <sup>a</sup>	A Multi-center, Randomized Controlled Clinical Trial Evaluating the Effect of Fresh Amniotic Membrane in the Treatment of Diabetic Foot Ulcers	100	Jan 2019
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

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. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

### CPT/HCPCS

65778	Placement of amniotic membrane on the ocular surface; without sutures
65779	Placement of amniotic membrane on the ocular surface; single layer, sutured
Q4100	Skin substitute, not otherwise specified
Q4132	Grafix Core and GrafixPL Core, per sq cm
Q4133	Grafix PRIME, 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
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
Q4221	Amniowrap2, per square centimeter
Q4227	Corplex, per square centimeter
Q4228	BioNextPATCH per sq centimeter
Q4229	Cogenex Amniotic Membrane
Q4230	Cogenex Flowable Amnion, per 0.5 cc
Q4231	Corplex P, per cubic centimeter
Q4232	Corplex, per square centimeter
Q4233	SurFactor or NuDyn, per 0.5 cc
Q4234	XCellerate, per square centimeter
Q4235	Amniorepair, altiPLY, per square centimeter
Q4236	carePATCH per sq centimeter
Q4237	Cryo-Cord, 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

- 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 (eg, 20550), the unlisted general musculoskeletal system code (20999), or if subcutaneous or intramuscular, the therapeutic injection code (96372).
- There are codes for the placement of amniotic membrane on the ocular surface: 65778, 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
H16.121	Filamentary keratitis, right eye
H16.122	Filamentary keratitis, left eye
H16.123	Filamentary keratitis, bilateral
H16.231	Neurotrophic keratoconjunctivitis, right eye
H16.232	Neurotrophic keratoconjunctivitis, left eye
H16.233	Neurotrophic keratoconjunctivitis, bilateral
H18.831	Recurrent erosion of cornea, right eye
H18.832	Recurrent erosion of cornea, left eye
H18.833	Recurrent erosion of cornea, bilateral
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
L97.212	Non-pressure chronic ulcer of right calf with fat layer exposed
L97.213	Non-pressure chronic ulcer of right calf with necrosis of muscle
L97.214	Non-pressure chronic ulcer of right calf with necrosis of bone
L97.222	Non-pressure chronic ulcer of left calf with fat layer exposed
L97.223	Non-pressure chronic ulcer of left calf with necrosis of muscle
L97.224	Non-pressure chronic ulcer of left calf with necrosis of bone
L97.312	Non-pressure chronic ulcer of right ankle with fat layer exposed
L97.313	Non-pressure chronic ulcer of right ankle with necrosis of muscle
L97.314	Non-pressure chronic ulcer of right ankle with necrosis of bone
L97.322	Non-pressure chronic ulcer of left ankle with fat layer exposed
L97.323	Non-pressure chronic ulcer of left ankle with necrosis of muscle
L97.324	Non-pressure chronic ulcer of left ankle with necrosis of bone
L97.412	Non-pressure chronic ulcer of right heel and midfoot with fat layer exposed
L97.413	Non-pressure chronic ulcer of right heel and midfoot with necrosis of muscle
L97.414	Non-pressure chronic ulcer of right heel and midfoot with necrosis of bone
L97.422	Non-pressure chronic ulcer of left heel and midfoot with fat layer exposed
L97.423	Non-pressure chronic ulcer of left heel and midfoot with necrosis of muscle

L97.424	Non-pressure chronic ulcer of left heel and midfoot with necrosis of bone
L97.512	Non-pressure chronic ulcer of other part of right foot with fat layer exposed
L97.513	Non-pressure chronic ulcer of other part of right foot with necrosis of muscle
L97.514	Non-pressure chronic ulcer of other part of right foot with necrosis of bone
L97.522	Non-pressure chronic ulcer of other part of left foot with fat layer exposed
L97.523	Non-pressure chronic ulcer of other part of left foot with necrosis of muscle
L97.524	Non-pressure chronic ulcer of other part of left foot with necrosis of bone
L97.812	Non-pressure chronic ulcer of other part of right lower leg with fat layer exposed
L97.813	Non-pressure chronic ulcer of other part of right lower leg with necrosis of muscle
L97.814	Non-pressure chronic ulcer of other part of right lower leg with necrosis of bone
L97.822	Non-pressure chronic ulcer of other part of left lower leg with fat layer exposed
L97.823	Non-pressure chronic ulcer of other part of left lower leg with necrosis of muscle
L97.824	Non-pressure chronic ulcer of other part of left lower leg with necrosis of bone
T26.11XA	Burn of cornea and conjunctival sac, right eye, initial encounter
T26.11XD	Burn of cornea and conjunctival sac, right eye, subsequent encounter
T26.11XS	Burn of cornea and conjunctival sac, right eye, sequela
T26.12XA	Burn of cornea and conjunctival sac, left eye, initial encounter
T26.12XD	Burn of cornea and conjunctival sac, left eye, subsequent encounter
T26.12XS	Burn of cornea and conjunctival sac, left eye, sequela
T26.31XA	Burns of other specified parts of right eye and adnexa, initial encounter
T26.31XD	Burns of other specified parts of right eye and adnexa, subsequent encounter
T26.31XS	Burns of other specified parts of right eye and adnexa, sequela
T26.32XA	Burns of other specified parts of left eye and adnexa, initial encounter
T26.32XD	Burns of other specified parts of left eye and adnexa, subsequent encounter
T26.32XS	Burns of other specified parts of left eye and adnexa, sequela
T26.61XA	Corrosion of cornea and conjunctival sac, right eye, initial encounter
T26.61XD	Corrosion of cornea and conjunctival sac, right eye, subsequent encounter
T26.61XS	Corrosion of cornea and conjunctival sac, right eye, sequela
T26.62XA	Corrosion of cornea and conjunctival sac, left eye, initial encounter
T26.62XD	Corrosion of cornea and conjunctival sac, left eye, subsequent encounter
T26.62XS	Corrosion of cornea and conjunctival sac, left eye, sequela
T26.81XA	Corrosions of other specified parts of right eye and adnexa, initial encounter
T26.81XD	Corrosions of other specified parts of right eye and adnexa, subsequent encounter
T26.81XS	Corrosions of other specified parts of right eye and adnexa, sequela
T26.82XA	Corrosions of other specified parts of left eye and adnexa, initial encounter
T26.82XD	Corrosions of other specified parts of left eye and adnexa, subsequent encounter
T26.82XS	Corrosions of other specified parts of left eye and adnexa, sequela

## REVISIONS

03-20-2017	Policy added to the bcbsks.com web site.
01-01-2019	Updated Description section. In Policy section: <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</li> </ul>

	<p>other ophthalmic conditions including but not limited to dry eye syndrome, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy."</p> <ul style="list-style-type: none"> <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> </ul> <ul style="list-style-type: none"> <li>▪ Updated Policy Guidelines.</li> </ul>
	Updated Rationale section.
	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added CPT codes: 65778, 65779.</li> <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>
	Updated References section.
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	Updated Description section.
	<p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item A, added new Item A 3, "Epicord (Q4187)".</li> </ul>
	Updated Rationale section.
	<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>
	Updated References section.
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>
	Updated References section.
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	In Coding section: ▪ Added HCPCS Codes: Q4176, Q4177, Q4178, Q4181, Q4227, Q4228, Q4229, Q4230, Q4231, Q4232, Q4233, Q4234, Q4235, Q4236, Q4237, Q4239, Q4240, Q4241, Q4242, Q4244, Q4245, Q4246, Q4247, Q4248
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