Amniotic Membrane and Amniotic Fluid Grafts

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Medical Policy #: 02.01.60
Original Effective Date: March 2018
Reviewed: March 2022
Revised: November 2022

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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.

Human Amniotic Membrane

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

suspensions or particulates, or connective tissue extractions, which can be injected or applied topically.

Fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist. There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause a substantial immune response. It is believed that these properties are retained in cryopreserved HAM and HAM products, resulting in a readily available tissue with regenerative potential. In support, 1 HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.

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

Amniotic Fluid
Amniotic fluid surrounds the fetus during pregnancy and provides protection and nourishment. In the second half of gestation, most of the fluid is a result of micturition and secretion from the respiratory tract and gastrointestinal tract of the fetus, along with urea. The fluid contains proteins, carbohydrates, peptides, fats, amino acids, enzymes, hormones, pigments, and fetal cells. Use of human and bovine amniotic fluid for orthopedic conditions was first reported in 1927. Amniotic fluid has been compared with synovial fluid, containing hyaluronan, 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.

Diabetic Lower-Extremity Ulcers

Patch or Flowable Amniotic Membrane or Placental Membrane

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

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

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

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

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

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

Review of Evidence
At least 7 randomized controlled trials (RCTs) have evaluated rates of healing with amniotic membrane grafts or placental membrane grafts compared to standard of care (SOC) or an advanced wound therapy in patients with chronic diabetic foot ulcers (see below tables). 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 versus Alginate dressing) to 60% (EpiFix) in the intention-to-treat (ITT) analysis (see Table 2). In a 2018 trial, the cryopreserved placental membrane Grafix was found to be non-inferior to an advanced fibroblast-derived wound therapy (Dermagraft).

Summary of Key RCT Characteristics

Study: Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator
Serena et al (2020)	U.S.	14		76 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers unresponsive	n=38, Affinity	n=38, SOC

				to SOC and extending into dermis, subcutaneous tissue, muscle, or tendon		
Tettelbach et al (2019)	U.S.	14		110 patients with non-healing (4 weeks) lower extremity ulcers	EpiFix	SOC with alginate dressing
Ananian et al (2018)	U.S.	7	2016-2017	75 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers between 1 cm2 and 15 cm2	n=38, Grafix weekly for up to 8 weeks	n=37, Dermagraft (fibroblast-derived) weekly for up to 8 weeks
DiDomenico et al (2018)				80 patients with non-healing (4 weeks) diabetic foot ulcers	AmnioBand Membrane plus SOC	SOC
Tettelbach et al (2018)	U.S.	11	2016-2018	155 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers	n=101 EpiCord plus SOC	n=54 SOC with alginate dressing
Snyder et al (2016)				29 patients with non-healing diabetic foot ulcers	AmnioExcel plus SOC	SOC
Zelen et al (2015, 2016)		4		60 patients with less than 20%	EpiFix	Apligraf or SOC with collagen-

				wound healing in a 2 week run-in period		alginate dressing

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

Summary of Key RCT Results

Study	**Wounds Healed**	**Wounds Healed**	**Time to Complete Healing**	**Adverse Events and Number of Treatments**
Serena et al (2020)	12 Weeks (ITT) (%)	16 Weeks (ITT) (%)	Median	
N	76	76	76	
Affinity	55%	58%	11 weeks	
SOC	29%	29%	not attained by 16 weeks	
p-value	.02	.01		
HR (95% CI)		1.75 (1.16 to 2.70)		
Tettelbach et al (2019)		Wounds Healed at 12 Weeks (ITT) n(%)		
N		110		
EpiFix		38 (81)		
SOC		28 (55)		
p-value				
HR (95% CI)				
Ananian et al (2018)	8 Weeks (PP) n (%)			Patients with Index Ulcer Related Adverse Events n (%)
N	62			75
Grafix	15 (48.4%)			1 (5.9%)
Dermagraft	12 (38.7%)			4 (16.7%)
Diff (95% CI)	9.68% (−10.7 to 28.9)			
Lower bound for non-inferiority	-15%			

DiDomenico et al (2018)	6 Weeks (ITT) n (%)	12 weeks ITT n (%)	Mean Days (95% CI)	
N	80	80	80	
AmnioBand	27 (68)	34 (85)	37.0 (29.5 to 44.4)	
SOC	8 (20)	13 (33)	67.3 (59.0 to 79.6)	
p-value	<.001	<.001	<.001	
HR (95% CI)		4.25 (0.44 to 0.79)		
Tettelbach et al (2018)	12 Weeks (PP) n (%)	12 Weeks (ITT) n (%)		Patients with Adverse Events (% of total)
N	134	155		
EpiCord	81 (81%)	71 (70%)		42 (42%)
SOC	29 (54%)	26 (48%)		33 (61%)
p-value	.001	.009		
Snyder et al (2016)	6 Weeks (PP) Mean (95% CI)			
N	21			
AmnioExcel	45.5% (32.9% to 58.0%)			
SOC	0%			
p-value	.014			
Zelen et al (2015, 2016)	6 Weeks ITT n (%)	Wounds Healed at 12 Weeks		Weekly Treatments
N	60	100		
EpiFix	19 (95%)	NR		3.4
Apligraf	9 (45%)	NR		5.9
SOC	7 (35%)	NR		
p-value	.003	<.001 vs. SOC		.003
HR (95% CI)		5.66; (3.03 to 10.57)		
Difference in wounds healed between amniotic or placental membrane and SOC	Affinity 26% AmnioBand 55% AmnioExcel 33% EpiFix 60%	Affinity 28% EpiCord 22% Grafix 41%		

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

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

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Serena et al (2020)	3. The randomization process and allocation concealment were not described	1, 2. No blinding of patients or investigators. Assessors were blinded		1. Although ITT analysis, there was substantial missing data for depth and volume with the digital analysis system.		
Tettelbach et al (2019)		1, 2. No blinding of patients or investigators. Assessors were blinded				
Ananian et al (2018)		2, 3. No blinding for outcomes assessment				
DiDomenico et al (2018)						
Tettelbach et al (2018)		1, 2, 3. No blinding				
Snyder et al (2016)				1. There was high loss to follow-up with discontinuation	1. Power analysis was not reported	

				of 8 of 29 participants		
Zelen et al (2015, 2016)				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.		

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

Prospective Single-arm or Registry Studies

Prospective single-arm or registry studies are described in the below Tables.

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. Of those treated, 28 ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of 8 weeks and a mean of 2.4 amniotic membrane applications.

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

Summary of Prospective Single-arm Studies or Registry Characteristics

Study	Study Design	Participants	Treatment Delivery
Smiell et al (2015)	Multicenter Registry	Various chronic wounds: 47 diabetic	Biovance

		foot wounds, 20 pressure ulcers, and 89 venous ulcers; 28 had failed prior treatment with advanced biologic therapies (Apligraf, Dermagraft, or Regranex)	
Frykberg et al (2016)	Prospective multi-center single-arm study	31 patients with chronic complex diabetic foot wounds with exposed tendon or bone	Grafix weekly until closure or 16 weeks

Summary of Prospective Single-arm Studies or Registry Results

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

Section Summary: Diabetic Lower-Extremity Ulcers

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

Lower-Extremity Ulcers Due to Venous Insufficiency

Amniotic Membrane

Clinical Context and Therapy Purpose

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Review of Evidence

A second industry-sponsored, multicenter, open-label randomized controlled trial (RCT) (Bianchi et al [2018; 2019]) evaluated the time to complete ulcer healing following weekly treatment with EpiFix d-HAM plus compression therapy or compression wound therapy alone. Patients treated with EpiFix had a higher probability of complete healing by 12 weeks, as adjudicated by blinded outcome assessors (hazard ratio, 2.26; 95% CI, 1.25 to 4.10; p=.01), and improved time to complete healing, as assessed by Kaplan-Meier analysis. In per-protocol analysis, healing within 12 weeks was reported for 60% of patients in the EpiFix group and 35% of patients in the control group (p<.013) (see Table 8). Intent-to-treat analysis found complete healing in 50% of patients in the EpiFix group compared to 31% of patients in the control group (p=.0473). There were several limitations of this trial (see Tables 8 and 9). In the per-protocol analysis, 19 (15%) patients were excluded from the analysis, and the proportion of patients excluded differed

between groups (19% from the EpiFix group vs. 11% from the control group). There was also a difference between the groups in how treatment failures at 8 weeks were handled. Patients in the control group who did not have a 40% decrease in wound area at 8 weeks were considered study failures and treated with advanced wound therapies. The ITT analysis used last-observation-carried-forward for these patients and sensitivity analysis was not performed to determine how alternative methods of handling the missing data would affect results. Kaplan-Meier analysis suggested a modest improvement in the time to heal when measured by ITT analysis but may be subject to the same methodological limitations.

As described above, Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about half (n=89) were venous ulcers.[15,] Of the 179 treated, 28 (16%) ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of 8 weeks and a mean of 2.4 amniotic membrane applications. However, without a control group, the percentage of wounds that would have healed with SOC is unknown.

Section Summary: Lower-Extremity Ulcers Due to Venous Insufficiency
The evidence on human amniotic membrane (HAM) for the treatment of venous leg ulcers includes 2 multicenter randomized controlled trials (RCTs) with EpiFix. One RCT reported a larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure at 4 weeks did not differ between EpiFix and the SOC. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression. Although a significant difference in complete healing was reported, interpretation is limited by the differential loss to follow-up and exclusions between groups. Although a subsequent publication reported ITT analysis, the handling of missing data differed between the groups and sensitivity analysis was not performed. The methodological flaws in the design, execution, and reporting of both of these RCTs limit inference that can be drawn from the results. Two additional studies with other HAM products have been completed but not published, raising further questions about the efficacy of HAM for lower-extremity ulcers due to venous insufficiency. Therefore, corroboration with well-designed and well-conducted RCTs evaluating wound healing in patients with venous leg ulcers is needed to demonstrate efficacy. The corroborating RCTs should report ITT and sensitivity analysis, with analysis of all patients, including those who were off treatment or had protocol deviations and exclusions.

Osteoarthritis
ReNu Knee Injection in Patients with Osteoarthritis
In 2016, a feasibility study (N=6) was reported of cryopreserved human amniotic membrane (c-HAM) suspension with amniotic fluid-derived cells for the treatment of knee osteoarthritis. A single intra-articular injection of the suspension was used, with follow-up at 1 and 2 weeks and at 3-, 6-, and 12-months posttreatment. Outcomes included the Knee Injury and Osteoarthritis Outcome Score, International Knee

Documentation Committee scale, and a numeric pain scale. Statistical analyses were not performed for this small sample. No adverse events, aside from a transient increase in pain, were noted. RCTs are in progress.

A trial with 200 participants was completed in February 2019, however, no publications from this trial have been identified.

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

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

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

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

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

Outcomes

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

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

Review of Evidence
Systematic Reviews
A 2016 network meta-analysis of 22 randomized controlled trials (RCTs) (total N=1216 patients) compared injection therapies for plantar fasciitis. In addition to c-HAM (human amniotic membrane) and micronized d-HAM/chorionic membrane, treatments included corticosteroids, botulinum toxin type A, autologous whole blood, platelet-rich plasma, nonsteroidal anti-inflammatory drugs, dry needling, dextrose prolotherapy, and polydeoxyribonucleotide. Placebo arms included normal saline, local anesthetic, sham dry needling, and tibial nerve block. Analysis indicated d-HAM had the highest

probability for improvement in pain and composite outcomes in the short-term, however, this finding was based only on a single RCT. Outcomes at 2 to 6 months (7 RCTs) favored botulinum toxin for pain and patient recovery plan for composite outcomes.

Randomized Controlled Trials
Zelen et al (2013) reported a preliminary study with 15 patients per group (placebo, 0.5 cc, and 1.25 cc) and 8-week follow-up. A subsequent randomized controlled trial (RCT) by Cazell et al (2018) enrolled 145 patients and reported 3-month follow-up. In Cazzell et al (2018) amniotic membrane injection led to greater improvements in the VAS for pain and the Foot Functional Index between baseline and 3 months 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.

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-human amniotic membrane (HAM) and placebo control. Injection of micronized amniotic membrane resulted in greater improvements in VAS for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is this is an interim report of 3 months' results. The authors noted that 12-month follow-up will be reported in a subsequent publication. No additional publications have been identified

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

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

Clinical Context and Therapy Purpose
The purpose of human amniotic membrane (HAM) in patients who have neurotrophic keratitis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

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

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

Outcomes
The general outcomes of interest are eye pain and epithelial healing.
Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

Review of Evidence
Suri et al (2013) reported on 11 eyes of 11 patients with neurotrophic keratopathy that had not responded to conventional treatment. 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.

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

Section Summary: Neurotrophic Keratitis with Ocular Surface Damage and Inflammation that Does Not Respond to Conservative Therapy
An randomized controlled trial (RCT) of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. Another trial reported on 11 eyes of 11 patients with neurotrophic keratopathy that had not responded to conventional treatment. 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.

Corneal Ulcers and Melts that do not Respond to Initial Medical Therapy

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

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

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

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

Outcomes
The general outcomes of interest are eye discomfort and epithelial healing.
Changes in symptoms may be measured in days, while changes in ocular surface would be measured at 1 to 3 months.

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

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

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

Section Summary: Corneal Ulcers and Melts That Do Not Respond to Initial Medical Therapy
Corneal ulcers and melts are uncommon and variable and additional randomized controlled trials (RCTs) are not expected. A systematic review of 1 RCT and case series showed healing in 97% of patients with an improvement of vision in 53% of eyes. One

retrospective comparative study with 22 patients found more rapid and complete epithelialization and more patients with a clinically significant improvement in visual acuity following early treatment with self-retained amniotic membrane when compared to historical controls. These results support the use of non-sutured amniotic membrane for corneal ulcers and melts that do not respond to initial medical therapy.

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

Clinical Context and Therapy Purpose
The purpose of human amniotic membrane (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.

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

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

Comparators
The following therapies are currently being used: medical therapy.

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

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

Review of Evidence
No evidence was identified for this indication.

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

Clinical Context and Therapy Purpose
The purpose of human amniotic membrane (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.

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

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

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

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

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

Review of Evidence
Dos Santos Paris et al (2013) published a randomized controlled trial (RCT) that compared fresh human amniotic membrane (HAM) with stromal puncture for the management of pain in patients with bullous keratopathy. Forty patients with pain from bullous keratopathy who were either waiting for a corneal transplant or had no potential for sight in the affected eye were randomized to the 2 treatments. Symptoms had been present for approximately 2 years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with use of HAM only if the pain did not resolve.

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

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

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

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

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

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

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

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

Review of Evidence
No randomized controlled trials (RCTs) were identified on human amniotic membrane (HAM) for limbal stem cell deficiency.

Keirkhah et al (2008) reported on the use of HAM in 11 eyes of 9 patients who had limbal stem cell deficiency. Patients underwent superficial keratectomy to remove the conjunctivalized pannus followed by HAM transplantation using fibrin glue. An additional ProKera patch was used in 7 patients. An improvement in visual acuity was observed in all but 2 patients. Pachigolla et al (2009) reported a series of 20 patients who received a ProKera implant for ocular surface disorders; 6 of the patients had limbal stem cell deficiency with a history of chemical burn. Following treatment with ProKera, 3 of the 6 patients had a smooth corneal surface and improved vision to 20/40. The other 3 patients had final visual acuity of 20/400, counting fingers, or light perception.

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

Moderate or Severe Stevens-Johnson Syndrome

Clinical Context and Therapy Purpose
The purpose of human amniotic membrane (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.

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

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

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

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

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

Review of Evidence
One randomized controlled trial (RCT) by Sharma et al (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or medical therapy alone. The c-HAM was prepared locally and applied with fibrin glue rather than sutures. Application of c-HAM in the early stages of SJS resulted in improved visual acuity (p=.042), better tear breakup time (p=.015), improved Schirmer test results (p<.001), and less conjunctival congestion (p=.03). In the c-HAM group at 180 days, there were no cases of corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. These outcomes are dramatically better than those in the medical therapy alone group, which had 11 (44%) cases with corneal haze (p=.001), 6 (24%) cases of corneal vascularization and conjunctivalization (p=.03), and 6 (24%) cases of trichiasis and metaplastic lashes.

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

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

Clinical Context and Therapy Purpose
The purpose of human amniotic membrane (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.

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

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

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

Outcomes
The general outcomes of interest are epithelial closure.

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

Review of Evidence
Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease. They noted that c-HAM has been available since 1995 and has become an established treatment for persistent epithelial defects and ulceration refractory to conventional therapy. However, there was a lack of controlled studies due to the rarity of the diseases and the absence of standard therapy. They identified 661 reported cases in the peer-reviewed literature. Most cases reported assessed the conjunctival indications of pterygium, scars and symblepharon, and corneal indications of acute chemical injury and postinfectious keratitis.

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

Severe Dry Eye Disease with Ocular Surface Damage and Inflammation that Does Not Respond to Conservative Therapy

Clinical Context and Therapy Purpose
The purpose of human amniotic membrane (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.

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

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

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

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

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

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

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. The c-HAM was applied for an average of 3.4 days (range, 3-5 days), while the control group continued treatment with artificial tears, cyclosporine A, serum tears, antibiotics, steroids, and nonsteroidal anti-inflammatory medications. The primary outcome was an increase in corneal nerve density. Signs and symptoms of dry eye disease improved at both 1-month and 3-month follow-ups in the c-HAM group but not in the conventional treatment group. For example, pain scores decreased from 7.1 at baseline to 2.2 at 1 month and 1.0 at 3 months in the c-HAM group. In vivo confocal microscopy, reviewed by masked readers, showed a significant increase in corneal nerve density in the study group at 3 months, with no change in nerve density in the controls. Corneal sensitivity was similarly increased in the c-HAM group but not in controls.

Section Summary: Severe Dry Eye with Ocular Surface Damage and Inflammation that Does Not Respond to Conservative Therapy
The evidence on human amniotic membrane (HAM) for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective

series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months.

Moderate or Severe Acute Ocular Chemical Burns
Clinical Context and Therapy Purpose
The purpose of human amniotic membrane (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.

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

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

Comparators
The following therapies are currently being used: medical therapy (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.

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

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

A second randomized controlled trial (RCT) that compared amniotic membrane plus medical therapy (30 eyes) to medical therapy alone (30 eyes) for grade IV ocular burn was reported by Eslani et al (2018). Medical therapy at this tertiary referral hospital included topical preservative-free lubricating gel and drops, chloramphenicol, betamethasone, homatropine, oral vitamin C, and doxycycline. There was no significant difference in the time to epithelial healing (amniotic membrane: 75.8 vs. 72.6 days) or in visual acuity between the 2 groups (2.06 logMAR for both groups). There was a trend for

a decrease in corneal neovascularization (p=.108); the study was not powered for this outcome.

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

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

Corneal Perforation When Corneal Tissue is Not Immediately Available

Clinical Context and Therapy Purpose
The purpose of human amniotic membrane (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.

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

Interventions
The therapy being considered is sutured HAM.

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

Outcomes
The general outcomes of interest are eye pain.

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

Review of Evidence
No randomized controlled trials (RCTs) were identified on corneal perforation.

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

Following Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft
Clinical Context and Therapy Purpose
The purpose of human amniotic membrane (HAM) in patients who have pterygium repair is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Interventions
The therapy being considered is sutured or glued HAM.

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

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

Pterygium recurrence would be measured at 1 to 3 months.

Review of Evidence
Randomized controlled trials (RCTs) have been reported on the use of amniotic membrane following pterygium repair. In 2013, the American Academy of Ophthalmology published a technology assessment on options and adjuvants for pterygium surgery. Reviewers identified 4 RCTs comparing conjunctival or limbal autograft procedure with amniotic membrane graft, finding that conjunctival or limbal autograft was more effective than human amniotic membrane (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

Section Summary: Following Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft
Clinical Context and Therapy Purpose
The purpose of repair with human amniotic membrane (HAM) in patients who have undergone Mohs microsurgery for skin cancer is to provide a treatment option that is an alternative to or an improvement on existing procedures.

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

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

Comparators
Comparators of interest include surgical repair using autologous tissue (eg, local flaps and full-thickness skin grafts) and healing without surgery. Second intention healing (i.e., the wound is left open to heal by granulation, contraction, and epithelialization) is a nonsurgical option for certain defects.

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

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

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

Review of Evidence
No RCTs were identified for this indication.

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

experienced zero complications (97.9% vs. 71.3%; p<.0001; relative risk 13.67; 95% CI 4.33 to 43.12). Placental allograft reconstructions developed less infection (p=.004) and were less likely to experience poor scar cosmesis (P <.0001). Confidence in these findings is limited, however, by the study's retrospective design and potential for bias due to missing data. Additionally, the study's relevance is limited due to a lack of diversity in the study population and no comparison to non-surgical treatment options.

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

Clinical Input
In 2019, BCBSA sought clinical input to help determine whether the use of human amniotic membrane graft either without or with suture fixation for several ophthalmic conditions would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 2 respondents, including 1 specialty society-level response and 1 physician-level response identified through specialty societies including physicians with academic medical center affiliations.

Clinical input supported the use of amniotic membrane in individuals with the following indications:

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.
- Corneal ulcers and melts that do not respond to initial medical therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment.
- Bullous keratopathy and who are not candidates for curative treatment (eg, endothelial or penetrating keratoplasty) as an alternative to stromal puncture.
- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient.
- Persistent epithelial defects and ulcerations that do not respond to conservative therapy.
- Severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy.
- Moderate or severe acute ocular chemical burn.
- Corneal perforation when corneal tissue is not immediately available.

- Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

Summary of Evidence

Practice Guideline and Position Statements

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

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

Step 1:

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

Step 2:
If above options are inadequate consider:

- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)

- In-office, physical heating and expression of the meibomian glands
- In-office intense pulsed light therapy for meibomian gland dysfunction
- Prescription drugs to manage dry eye disease
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited duration)
- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3:
If above options are inadequate consider:

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

Step 4:
If above options are inadequate consider:

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

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

Regulatory Status
The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, Title 21, parts 1270 and 1271. In 2017, the FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps).

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

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

1. "The HCT/P is minimally manipulated;
2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

1. Either:
    i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
    iii. Is for autologous use;
    iv. Is for allogeneic use in a first-degree or second-degree blood relative; or
    v. Is for reproductive use."

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

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

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

In 2003, Prokera was cleared for marketing by the FDA through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104). The FDA determined that this device was substantially equivalent to the Symblepharon Ring. The Prokera device is intended "for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred."[5,] The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

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

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policy

- 02.01.17 Bio-Engineered Skin and Soft Tissue Substitutes

Human Amniotic Member (HAM) Grafts for Non-Ophthalmic Conditions
Treatment of chronic non-infected diabetic lower-extremity ulcer(s) using the following human amniotic membrane (HAM) grafts may be considered **medically necessary** when the ulcer(s) have not healed with standard conservative management (such as surgical debridement, complete off loading, and standard dressing changes) attempted for at least 2 to 4 weeks (past start of therapy) with the following supporting documentation: the ulcer(s) has failed to decrease in size and depth, or there is no change in baseline size or depth with no sign of improvement, or no indication that improvement is likely:

- Affinity (Q4159)
- AmnioBand Membrane (Q4151)
- Biovance (Q4154)
- EpiCord Q4187
- EpiFix (Q4186)
- Grafix (GrafixCore, GrafixPrime) (Q4132, Q4133)

The use of human amniotic membrane (HAM) grafts when the above criteria are not met and for any use not listed above, including but not limited to the following is considered **investigational** due to a lack of clinical evidence demonstrating an impact on improved health outcomes:

- Lower extremity ulcers due to venous insufficiency
- Osteoarthritis
- Plantar fasciitis

Human Amniotic Membrane Grafts for Ophthalmic Conditions
Human amniotic membrane (HAM) grafts with or without suture (AmbioDisk, AmnioGraft, Artacent Ocular, Prokera, Vendja Optic [A4100 or Q4100]) may be considered **medically necessary** for the treatment of the following ophthalmic indications:

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy.
- Corneal ulcers and melts that do not respond to initial conservative therapy.
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment.
- Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial, or penetrating keratoplasty).
- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient.
- Moderate or severe Stevens-Johnson syndrome (corneal ulceration, uveitis [inflammation of the uvea, middle layer of the eye], and possibly blindness).
- Persistent epithelial defects that do not respond within 2 days to conservative therapy.
- Severe dry eye (DEWS 3 or 4) with ocular surface damage and inflammation that remains symptomatic after Steps 1, 2, and 3 of the dry eye disease management algorithms (*see Policy Guidelines below*).
- Moderate or severe acute ocular chemical burn.

Human amniotic membrane (HAM) grafts with suture or glue may be considered **medically necessary** for the treatment of the following ophthalmic indications:

- Corneal perforation when corneal tissue is not immediately available; **or**
- Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

The use of human amniotic membrane (HAM) grafts included above not meeting the above criteria and for all other ophthalmic conditions is considered **investigational** due to a lack of clinical evidence demonstrating an impact on improved health outcomes.

Investigational

All Other human amniotic membrane (HAM) grafts (products) including are considered **investigational** for all indications, including but not limited to the following, due to a lack of clinical evidence demonstrating an impact on improved net health outcomes:

- Allogen
- AlloWrap
- AmbioDry5
- AmnioAMP-MP
- AmnioArmor

- Amniobind
- AmnioClear
- Amniocore
- Amniocyte plus
- AmnioExcel
- AmnioFill
- AmnioFix
- Amnio-maxx or Amnio-maxx lite
- Amniorepair or altiply
- Amniotext
- Amniotic serum drops/umbilical cord serum drops (e.g., Regener-Eyes, Genesis)
- Amniowound
- Amnio Wrap2
- Amniply
- Artacent Wound
- Arthrex Amnion Matrix
- Ascent
- Axolotl Ambien or Axolotl Cryo
- BioDDryFlex
- BioDExcel
- BioDFactor
- BioDfence
- BioNextPATCH
- BioSkin (thin - 45 microns)
- BioSkin (thick - 200 microns)
- CarePATCH
- Celera Dual Layer or Celera Dual Membrane
- Cellesta
- Clarix
- Cogenex
- Cogenex Flowable
- Corecyte
- Corplex P
- Coretext
- Cryo-cord
- Cygnus
- Cygnus Max
- Dermacyte
- Derm-maxx
- Dermavest
- Enverse
- Essence Viable Amnion Matrix
- Floweramniopatch

- Genesis Amniotic Membrane
- Human Health Factor 10 Amniotic Patch (hhf10-p)
- Innovamatrix
- Matrion
- Microderm Acellular Wound Matrix
- Mlg-complete
- NeoPatch
- NeoPly
- Neox 100
- Neox Cord
- Neox Wound Allograft
- Novachor
- NuDyn
- NuShield
- PalinGen Membrane
- Plurivest
- PolycyteProcenta
- Protext
- Relese
- ReNu
- Restorigin
- Revita
- Revitalon
- Signature APatch
- Stravix Cryopreserved Placental Tissue
- Stravix PL
- Surfactor
- SurgiGraft
- SurGraft tl
- TAG
- Therion
- WoundEx (45 microns)
- WoundEx (200 microns)
- XCellerate
- XWRAP

Micronized or particulated human amniotic membrane products are considered **investigational** for all indications including but not limited to the following due to a lack of clinical evidence demonstrating an impact on improved health outcomes:

- AmnioBand Particulate
- AmnioFill
- AmnioMatrix
- AmnioVisc

- Artacent AC Powder
- BioDMatrix
- BioSkin Flow
- Clarix Flo
- EpiFix injectable
- Interfyl
- Neox Flo
- OrthoFlo
- PalinGen Flow
- PalinGen SportFlow
- ProMatrX
- ReNu
- WoundEx Flow

Injection of amniotic fluid is considered **investigational** for all indications due to lack of clinical evidence demonstrating an impact on improved health outcomes.

Policy Guidelines

Required Documentation
Diabetic Lower-Extremity Ulcer(s)

- Documentation that conservative measures have failed, or the medical record supports that the wound is so clinically severe that it requires immediate, aggressive therapy.
- Documentation that the ulcer has failed to decrease in size and depth, or that there has been no change in baseline size or depth with no sign of improvement, or no indication that improvement is likely.
- The individual's medical record must reflect the frequency of skin substitute application, and this should be consistent with each individual's history and response to the skin substitute application and product safety criteria. Repeated application to the same wound within the same treatment period without signs of improvement may be denied.
- Documentation that the skin substitute product was appropriately applied and immobilized in accordance with the manufacturer’s label instructions.

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

Step 1:

- Education regarding the condition, its management, treatment, and prognosis
- Modification of local environment

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

Step 2:
If above options are inadequate consider:

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

Step 3:
If above options are inadequate consider:

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

Step 4:
If above options are inadequate consider:

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

Dry eye severity level DEWS 3 to 4

Discomfort, severity, and frequency - Severe frequent or constant

Visual symptoms - chronic and/or constant, limiting to disabling

Conjunctival Injection - +/- or +/+

Conjunctive Staining - moderate to marked

Corneal Staining - marked central or severe punctate erosions

Corneal/tear signs - Filamentary keratitis, mucus clumping, increase in tear debris

Lid/meibomian glands - Frequent

Tear film breakup time - < 5

Schirmer score (mm/5 min) - < 5

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- A2001 Innovamatrix ac, per square centimeter
- A2013 Innovamatrix fs, per square centimeter
- A4100 Skin substitute, FDA cleared as a device, not otherwise specified
- 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, 1cc
- Q4140 BioDFence, per sq cm
- Q4145 Epifix, injectable, 1mg
- 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 NeoxFlo or ClarixFlo, 1mg
- 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, 05.cc
- Q4163 WoundEx, BioSkin, per sq cm
- Q4168 AmnioBand, 1mg
- Q4169 Artacent wound, per sq cm
- Q4170 Cygnus, per sq cm
- Q4171 Interfyle, 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 square centimeter
- Q4177 FlowerAmnioFlo, 0.1cc
- Q4178 FlowerAmnioPatch, per sq cm
- Q4180 Revita, per sq cm
- Q4181 Amnio wound, per sq cm
- Q4183 Surgigraft, per sq cm
- Q4184 Cellesta or Cellesta Duo, 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, 1mg
- Q4190 Artacent AC, per sq cm
- Q4191 Restorigin, per sq cm
- Q4192 Restorigin, 1cc
- Q4194 Novachor, per sq cm
- Q4198 Genesis Amniotic Membrane, per sq cm
- Q4199 Cygnus matrix, per sq cm
- Q4201 Matrion, per sq cm
- Q4202 Keroxx (2.5g/cc), 1cc
- Q4204 XWRAP, per sq cm
- Q4205 Membrane graft or membrane wrap, per sq cm
- Q4206 Fluid flow or fluid GF, 1 cc
- Q4208 Novafix, per sq cm
- Q4209 SurGraft, per sq cm
- Q4210 Axolotl Graft or Axolotl Dualgraft, per sq cm
- Q4211 Amnion Bio or AxoBioMembrane, per sq cm
- Q4212 AlloGen, per cc
- Q4213 Ascent, 0.5 mg
- Q4214 Cellesta cord, per sq cm
- Q4215 Axolotl Mmbient or Axolotl Cryo, 0.1 mg
- Q4216 Artacent cord, per sq cm
- Q4217 Woundfix, BioWound, Woundfix Plus, BioWound Plus, Woundfix Xplus or BioWound Xplus, per sq cm
- Q4218 SurgiCORD, per sq cm

- Q4219 SurgiGRAFT-DUAl, per sq cm
- Q4220 BellaCell HD or Surederm, per sq cm
- Q4221 Amnio Wrap2, per sq cm
- Q4224 Human health factor 10 amniotic patch (hhf10-p), per square centimeter
- Q4225 Amniobind, per square centimeter
- Q4227 AmnioCore TM, per sq cm
- Q4229 Cogenex Amniotic Membrane, per sq cm
- Q4230 Cogenex Flowable Amnion, per 0.5 cc
- Q4231 Corplex P, per cc
- Q4232 Corplex, per sq cm
- Q4233 SurFactor or NuDyn, per 0.5 cc
- Q4234 XCellerate, per sq cm
- Q4235 AMNIOREPAIR or AltiPly, per sq cm
- Q4236 CarePATCH per sq cm
- Q4237 Cryo-Cord, per sq cm
- Q4238 Derm-maxx per sq cm
- Q4239 Amnio-Maxx or Amnio-Maxx Lite, per sq cm
- Q4240 CoreCyte, for topical use only, per 0.5 cc
- Q4241 PoluCyte, for topical use only, per 0.5 cc
- Q4242 AmnioCyte Plus, per 0.5 cc
- Q4244 Procenta, per 200 mg
- Q4245 AmnioText, per cc
- Q4246 CoreText or ProText, per cc
- Q4247 Amniotext patch, per sq cm
- Q4248 Dermacyte Amniotic Membrane allograft, per sq cm
- Q4249 AMNIPLY, for topical use only, per sq cm
- Q4250 AmnioAmp-MP,per sq cm
- Q4251 Vim, per sq cm
- Q4252 Vendaje, per sq cm
- Q4253 Zenith Amniotic Membrane, per sq cm
- Q4254 Novafix DL, per sq cm
- Q4255 REGUaRD, for topical use only, per sq cm
- Q4256 Mlg-complete, per sq cm
- Q4257 Relese, per sq cm
- Q4258 Enverse, per sq
- Q4259 Celera Dual Layer or Celera Dual Membrane per sq cm
- Q4260 Signature APatch per sq cm
- Q4261 TAG per sq cm
- Q4263 Surgraft tl, per sq cm
- V2790 Amniotic Membrane for Surgical Reconstruction, per procedure
- 15271 Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area

- 15272 Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
- 15273 Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
- 15274 Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15275 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
- 15276 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
- 15277 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
- 15278 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 65778 Placement of amniotic membrane on the ocular surface, without sutures
- 65779 Placement of amniotic membrane on the ocular surface, single layer, sutured
- 65780 Ocular surface reconstruction; amniotic membrane transplantation, multiple layers

SELECTED REFERENCES

- Parolini O, Soncini M, Evangelista M, et al. Amniotic membrane and amniotic fluid-derived cells: potential tools for regenerative medicine?. Regen Med. Mar 2009; 4(2): 275-91. PMID 19317646
- Koob TJ, Rennert R, Zabek N, et al. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. Int Wound J. Oct 2013; 10(5): 493-500. PMID 23902526
- Shimberg M, Wadsworth K. The use of amniotic-fluid concentrate in orthopaedic conditions. J Bone Joint Surg. 1938;20(I):167-177.
- U.S. Food and Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use Guidance for Industry and Food and Drug Administration Staff.

2017 https://www.regulations.gov/document?D=FDA-2017-D-6146-0003 Accessed January 10, 2022
- Food and Drug Administration. 510(k) Summary: ProKeraTM Bio-Tissue Inc. (K032104). 2003; https://www.accessdata.fda.gov/cdrh_docs/pdf3/K032104.pdf. Accessed January 10, 2022.
- Serena TE, Yaakov R, Moore S, et al. A randomized controlled clinical trial of a hypothermically stored amniotic membrane for use in diabetic foot ulcers. J Comp Eff Res. Jan 2020; 9(1): 23-34. PMID 31691579
- Ananian CE, Dhillon YS, Van Gils CC, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. Wound Repair Regen. May 2018; 26(3): 274-283. PMID 30098272
- Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. Int Wound J. Feb 2019; 16(1): 122-130. PMID 30246926
- DiDomenico LA, Orgill DP, Galiano RD, et al. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients. Int Wound J. Dec 2018; 15(6): 950-957. PMID 30019528
- Snyder RJ, Shimozaki K, Tallis A, et al. A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcer. Wounds. Mar 2016; 28(3): 70-7. PMID 26978860
- Zelen CM, Gould L, Serena TE, et al. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. Int Wound J. Dec 2015; 12(6): 724-32. PMID 25424146
- Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. Int Wound J. Apr 2016; 13(2): 272-82. PMID 26695998
- Tettelbach W, Cazzell S, Reyzelman AM, et al. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. Int Wound J. Feb 2019; 16(1): 19-29. PMID 30136445
- Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix((R)) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. Int Wound J. Oct 2014; 11(5): 554-60. PMID 25048468

- Smiell JM, Treadwell T, Hahn HD, et al. Real-world Experience With a Decellularized Dehydrated Human Amniotic Membrane Allograft. Wounds. Jun 2015; 27(6): 158-69. PMID 26061491
- Frykberg RG, Gibbons GW, Walters JL, et al. A prospective, multicentre, open-label, single-arm clinical trial for treatment of chronic complex diabetic foot wounds with exposed tendon and/or bone: positive clinical outcomes of viable cryopreserved human placental membrane. Int Wound J. Jun 2017; 14(3): 569-577. PMID 27489115
- Serena TE, Carter MJ, Le LT, et al. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. Wound Repair Regen. Nov-Dec 2014; 22(6): 688-93. PMID 25224019
- Bianchi C, Cazzell S, Vayser D, et al. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix (R)) allograft for the treatment of venous leg ulcers. Int Wound J. Feb 2018; 15(1): 114-122. PMID 29024419
- Bianchi C, Tettelbach W, Istwan N, et al. Variations in study outcomes relative to intention-to-treat and per-protocol data analysis techniques in the evaluation of efficacy for treatment of venous leg ulcers with dehydrated human amnion/chorion membrane allograft. Int Wound J. Jun 2019; 16(3): 761-767. PMID 30864259
- Vines JB, Aliprantis AO, Gomoll AH, et al. Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis. J Knee Surg. Aug 2016; 29(6): 443-50. PMID 26683979
- Tsikopoulos K, Vasiliadis HS, Mavridis D. Injection therapies for plantar fasciopathy ('plantar fasciitis'): a systematic review and network meta-analysis of 22 randomised controlled trials. Br J Sports Med. Nov 2016; 50(22): 1367-1375. PMID 27143138
- Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. Foot Ankle Int. Oct 2013; 34(10): 1332-9. PMID 23945520
- Cazzell S, Stewart J, Agnew PS, et al. Randomized Controlled Trial of Micronized Dehydrated Human Amnion/Chorion Membrane (dHACM) Injection Compared to Placebo for the Treatment of Plantar Fasciitis. Foot Ankle Int. Oct 2018; 39(10): 1151-1161. PMID 30058377
- Suri K, Kosker M, Raber IM, et al. Sutureless amniotic membrane ProKera for ocular surface disorders: short-term results. Eye Contact Lens. Sep 2013; 39(5): 341-7. PMID 23945524
- Liu J, Li L, Li X. Effectiveness of Cryopreserved Amniotic Membrane Transplantation in Corneal Ulceration: A Meta-Analysis. Cornea. Apr 2019; 38(4): 454-462. PMID 30702468
- Yin HY, Cheng AMS, Tighe S, et al. Self-retained cryopreserved amniotic membrane for treating severe corneal ulcers: a comparative, retrospective control study. Sci Rep. Oct 12 2020; 10(1): 17008. PMID 33046729

- Paris Fdos S, Goncalves ED, Campos MS, et al. Amniotic membrane transplantation versus anterior stromal puncture in bullous keratopathy: a comparative study. Br J Ophthalmol. Aug 2013; 97(8): 980-4. PMID 23723410
- Kheirkhah A, Casas V, Raju VK, et al. Sutureless amniotic membrane transplantation for partial limbal stem cell deficiency. Am J Ophthalmol. May 2008; 145(5): 787-94. PMID 18329626
- Pachigolla G, Prasher P, Di Pascuale MA, et al. Evaluation of the role of ProKera in the management of ocular surface and orbital disorders. Eye Contact Lens. Jul 2009; 35(4): 172-5. PMID 19474753
- Sharma N, Thenarasun SA, Kaur M, et al. Adjuvant Role of Amniotic Membrane Transplantation in Acute Ocular Stevens-Johnson Syndrome: A Randomized Control Trial. Ophthalmology. Mar 2016; 123(3): 484-91. PMID 26686968
- Bouchard CS, John T. Amniotic membrane transplantation in the management of severe ocular surface disease: indications and outcomes. Ocul Surf. Jul 2004; 2(3): 201-11. PMID 17216092
- John T, Tighe S, Sheha H, et al. Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease. J Ophthalmol. 2017; 2017: 6404918. PMID 28894606
- McDonald MB, Sheha H, Tighe S, et al. Treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study. Clin Ophthalmol. 2018; 12: 677-681. PMID 29670328
- Tandon R, Gupta N, Kalaivani M, et al. Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns. Br J Ophthalmol. Feb 2011; 95(2): 199-204. PMID 20675729
- Eslani M, Baradaran-Rafii A, Cheung AY, et al. Amniotic Membrane Transplantation in Acute Severe Ocular Chemical Injury: A Randomized Clinical Trial. Am J Ophthalmol. Mar 2019; 199: 209-215. PMID 30419194
- Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. Ophthalmology. Nov 2005; 112(11): 1963-9. PMID 16198422
- Kaufman SC, Jacobs DS, Lee WB, et al. Options and adjuvants in surgery for pterygium: a report by the American Academy of Ophthalmology. Ophthalmology. Jan 2013; 120(1): 201-8. PMID 23062647
- Clearfield E, Muthappan V, Wang X, et al. Conjunctival autograft for pterygium. Cochrane Database Syst Rev. Feb 11 2016; 2: CD011349. PMID 26867004
- Toman J, Michael GM, Wisco OJ, et al. Mohs Defect Repair with Dehydrated Human Amnion/Chorion Membrane. Facial Plast Surg Aesthet Med. Jan-Feb 2022; 24(1): 48-53. PMID 34714143
- Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg. Feb 2016; 63(2 Suppl): 3S-21S. PMID 26804367

- Lavery LA, Davis KE, Berriman SJ, et al. WHS guidelines update: Diabetic foot ulcer treatment guidelines. Wound Repair Regen. Jan-Feb 2016; 24(1): 112-26. PMID 26663430

POLICY HISTORY		
Date	Reason	Action
November 2022	Interim Review	Policy Revised
March 2022	Annual Review	Policy Revised
March 2021	Annual Review	Policy Revised
March 2020	Annual Review	Policy Revised
March 2019	Annual Review	Policy Revised
March 2018		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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