Medical Policy

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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: • With nonhealing diabetic lower-extremity ulcers	Interventions of interest are: • Patch or flowable formulation of human amniotic membrane	Comparators of interest are: • Standard wound care • Advanced wound therapies	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With lower-extremity ulcers due to venous insufficiency	Interventions of interest are: • Patch or flowable formulation of human amniotic membrane	Comparators of interest are: • Compression therapy • Advanced wound therapies	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life

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Populations	Interventions	Comparators	Outcomes
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 ophthalmic conditions	Interventions of interest are: • Patch formulation of human amniotic membrane	Comparators of interest are: • Medical therapy	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life

DESCRIPTION

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

Objective

The objective of this evidence review is to evaluate the evidence for the various human amniotic membrane products available for a wide array of indications.

Background

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).

Fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist.[1] There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause 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

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d-HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells both in vitro and in vivo.[2]

HAM is an established treatment for corneal reconstruction and is being evaluated for the treatment of various conditions, including skin wounds, burns, leg ulcers, and prevention of tissue adhesion in surgical procedures.[1] Additional indications studied in preclinical models include tendonitis, tendon repair, and nerve repair. The availability of HAM opens the possibility of regenerative medicine for a wide variety of conditions.

Amniotic fluid surrounds the fetus during pregnancy and provides protection and nourishment. In the second half of gestation, most of the fluid is a result of micturition and secretion from the respiratory tract and gastrointestinal tract of the fetus, along with urea.[1] The fluid contains proteins, carbohydrates, proteins and peptides, fats, amino acids, enzymes, hormones, pigments, and fetal cells. Use of human and bovine amniotic fluid for orthopedic conditions was first reported in 1927.[3] Amniotic fluid has been compared with synovial fluid, containing hyaluronan, lubrican, cholesterol, and cytokines. Injection of amniotic fluid or amniotic fluid–derived cells is currently being evaluated for the treatment of osteoarthritis and plantar fasciitis.

Amniotic membrane and amniotic fluid are also being investigated as sources of pluripotent stem cells.[1] Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type.

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

Product (Supplier)	Preparation	Components			
	Cryopreserved, Dehydrated, or Extracted	Amnion	Chorion	Amniotic Fluid	Umbilical Cord
Patch					
Affinity™ (NuTech Medical)	C	X			
AlloWrap™ (AlloSource)	NS	X			
AmnioBand® Membrane (MTF Wound Care)	D	X	X		
AmnioClear™ (Liventa Bioscience)	NS	X	X		
AmnioExcel® (Derma Sciences)	D	X			
AmnioFix® (MiMedx)	D	X			
AmnioGen™ 45 (US Biologix)[a]	D	X			
AmnioGen™ 200 (US Biologix)[a]	D		X		
AmnioGraft® (BioTissue)	C	X			
AmnioPro® 45 (HRT)[a]	D	X			X
AmnioPro® 200 (HRT)[a]	D		X		X
Artacent® Wound (Tides Medical)	D	X			
BioDDryFlex® (BioD)	D	X			
BioDfence™ (BioD)	D	X	X		
BioRenew 200 (HRT)[a]	D		X		
BioRenew 45 (HRT)[a]	D	X			

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Product (Supplier)	Preparation	Components			
	Cryopreserved, Dehydrated, or Extracted	Amnion	Chorion	Amniotic Fluid	Umbilical Cord
BioSkin 45 (HRT)[a]	D	X			
BioSkin 45 (HRT)[a]	D		X		
Biovance® (Aliqual Biomedical)	D	X			
Clarix® (Amniox Medical)	C	X			X
Cygnus (Vivex Biomedical)	D	X			
Cygnus Max (Vivex Biomedical)	D				X
Dermavest™ (Aedicell)[a]	C	X	X		X
EpiCord™ (MiMedx)	D				X
EpiFix® (MiMedx)	D	X	X		
Grafix® (Osiris)	C	X	X		
Guardian/AmnioBand® (MTF Wound Care)	D	X	X		
HydraTek® (Human Regenerative Technologies)	D	X			
Neox® 100 (Amniox Medical)	C	X			X
Neox® Cord (Amniox Medical)	C	X			X
Neox® Wound Allograft (Amniox Medical)	C	X			X
NuShield™ (NuTech Medical)	D	X	X		
PalinGen® Membrane (Amnio ReGen Solutions)	C	X			
Plurivest™ (Aedicell)[a]	C	X	X		X
Revitalon™ (Medline Industries)	D	X	X		
WoundEx® 200 (Skye Biologics)[a]	D		X		
WoundEx® 45 (Skye Biologics)[a]	D	X			
Suspension, particulate, or extraction					
AmnioBand® Particulate (MTF Wound Care)	D	X	X		
AmnioGen™-A (US Biologix)[b]	E	X	X	X	X
AmnioGen™-C (US Biologix)[b]	C	X	X	X	X
AmnioMatrix® (Derma Sciences)	D	X		X	
AmnioPro® Flow (HRT)[b]	E	X	X	X	X
AmnioVisc™ (Lattice Biologics)	NS			X	
BioRenew® Flow (HRT)[b]	E	X	X	X	X
BioSkin® Flow (HRT)[b]	E	X	X	X	X
Clarix® Flo (Amniox Medical)	C	X			X
HydraTek® (Human Regenerative Technologies)	D	X			
Interfyl™ (Alliqua Biomedical)	NS	X	X		
Neox® Flo (Amniox Medical)	C	X			X
OrthoFlo™ (MiMedx)	D			X	
PalinGen® Flow (Amnio ReGen Solutions)	C	X		X	
PalinGen® SportFlow (Amnio ReGen Solutions)	C	X		X	

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Product (Supplier)	Preparation	Components			
	Cryopreserved, Dehydrated, or Extracted	Amnion	Chorion	Amniotic Fluid	Umbilical Cord
ProMatrX™ ACF (Amnio ReGen Solutions)	C	X		X	
ReNu™ (NuTech Medical)	D	X		X	
WoundEx® Flow (Skye Biologics)[b]	E	X	X	X	X

C: cryopreserved; D: dehydrated; E: extracted connective tissue; HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation; NS: not specified.
[a,b] Processed by HRT and marketed by under different tradenames.

The preferred outcomes for the healing of lower-extremity ulcers and burn wounds are the percentage of patients with complete wound healing and the time to complete wound healing.[4] The percentage of patients with 50% wound healing and time to 50% wound healing have also been considered appropriate outcomes for these conditions.[5] The percent change in wound area at 4 weeks is predictive of complete healing at 12 weeks in patients with diabetic foot ulcers.[6] Thus, minimal improvement at 30 days can be considered as an indicator that a wound is unlikely to heal in patients with comorbidities known to affect wound healing, but would not be considered a primary outcome measure.

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 (CFR) title 21, parts 1270 and 1271. Human amniotic membrane and amniotic fluid are included in these regulations.

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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. Epifix (Q4131)
   4. Grafix (Q4132, Q4133)

B. Injection of micronized or particulated human amniotic membrane is considered **experimental / investigational** for all indications.

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

D. All other human amniotic membrane products and indications not listed above are considered **experimental / investigational**.

Policy Guidelines

Nonhealing is defined as less than a 20% decrease in wound area with standard wound care for at least 2 weeks.

RATIONALE

This evidence review has been updated regularly with a search of the MEDLINE database. The most recent literature update was performed through November 20, 2016.

For conditions in which subjective measures are the primary outcomes, randomized controlled trials (RCTs) are particularly important due to the expected placebo effect and variable natural history. RCTs are also important because there may be numerous confounders of outcomes, and nonrandomized comparisons are prone to selection bias. For these reasons, RCTs are essential to demonstrate the clinical effectiveness of amniotic membrane and amniotic membrane injections compared with alternatives such as continued medical management or other established treatments.Therefore, the products assessed in this review are those that have RCT evidence. For indications where treatment with some amniotic membrane products has been established, nonrandomized studies that include patients with similar characteristics and have similar magnitude of benefit may be considered sufficient evidence.

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

1. Incidence of complete wound closure.
2. Time to complete wound closure (reflecting accelerated wound closure).
3. Incidence of complete wound closure following surgical wound closure.
4. Pain control.

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DIABETIC LOWER-EXTREMITY ULCERS

Dehydrated Amniotic Membrane or Placental Membrane

AmnioBand vs Standard Care

AmnioBand Membrane was compared with standard of care (SOC) for the treatment of nonhealing (minimum 4 weeks) diabetic foot ulcers in an industry-sponsored, multicenter study by DiDomenico et al (2016).[7] Forty patients were randomized to SOC or SOC plus weekly applications of the dehydrated placental allograft for up to 12 weeks. Healing was determined by the principal investigator at each institution and confirmed by an independent and blinded panel of 6 physicians. This study was adequately powered to detect a difference of 45% between groups in the primary outcome, the proportion of wounds healed at 6 weeks. Complete healing by 6 weeks was observed for 70% (14/20) of wounds treated with the dehydrated placental matrix compared with 15% (3/20) of wounds treated by SOC alone (p=0.001). The odds ratio for healing was 17 (95% confidence interval [CI], 3.1 to 93; p=0.001). At 12 weeks, complete healing was observed for 85% (17/20) of wounds in the AmnioBand group compared with 25% (5/20) in the SOC group. Mean time to heal for wounds treated with amniotic membrane was 36 days (95% CI, 27 to 46 days) compared to 70 days (95% CI, 59 to 81 days; p<0.001) with standard care. The number needed to treat to achieve healing at 12 weeks was 1.7 (95% CI, 1.2 to 2.8). Strengths of this study included power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and intention-to-treat (ITT) analysis.

AmnioExcel vs Standard Care

AmnioExcel dehydrated human amniotic membrane (d-HAM) was compared with standard care in an industry-sponsored, open-label multicenter RCT (N=29) by Snyder et al (2016).[8] Randomization was performed by computer module and stratified by site and wound area. The primary outcome was the percentage of patients with complete wound closure at 6 weeks. The per protocol population included 11 patients in the AmnioExcel group and 10 in the SOC group. For the ITT population, 33% (95% CI, 25.0% to 46.4%) of patients in the AmnioExcel group achieved wound closure by 6 weeks compared to 0% of the SOC group (p=0.017). In the per protocol analysis, 45.5% of patients treated with AmnioExcel achieved wound closure by 6 weeks compared to 0% in the SOC arm (p=0.008) with a 95% confidence interval of the responder ratio of 32.9% to 58.0% (p=0.014). Power analysis was not described and there were 8 early withdrawals (4 in each group), raising questions about the reliability of the effect size.

Biovance Registry

In 2015, Smiell et al reported an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types, including 47 diabetic foot wounds, 20 pressure ulcers, and 89 venous ulcers.[9] This study showed the effectiveness of d-HAM in a real-world setting. The size of the wounds at baseline ranged from less than 2 cm^2 (35.4% of wounds) to over 25 cm^2 (9.0% of wounds). Ninety-eight percent were on the lower extremities. Twenty-eight ulcers had failed prior treatment with advanced biologic therapies (Apligraf, Dermagraft, or Regranex), including 10 diabetic foot wounds. For all wound types, 41.6% closed with a mean time to closure of 8 weeks and a mean of 2.4 amniotic membrane applications. In the subgroup of 112 patients who practiced good wound care, including offloading or compression therapy as indicated, 49.6% of wounds closed by a mean of 7.4 weeks. Wounds that had not closed during the observation period decreased in size by a mean of 46.6%.

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EpiFix vs Standard Care

In 2013, Zelen et al reported an industry-sponsored, nonblinded, RCT comparing use of EpiFix d-HAM (n=13) with standard of care (SOC; n=12) for diabetic foot ulcers of at least 4 weeks in duration.[10] EpiFix was applied every 2 weeks if the wound had not healed, with weekly dressing changes comprised of nonadherent dressing, moisture retentive dressing, and a compression dressing. Standard moist wound dressing was changed daily. After 4 weeks of treatment, EpiFix-treated wounds had reduced in size by a mean of 97% compared with 32% for the SOC group. Healing rate, defined as complete epithelialization of the open area of the wound, was 77% for EpiFix compared with 0% for SOC. After 6 weeks of treatment, wounds were reduced by 98.4% with EpiFix treatment compared with -1.8% for SOC. The healing rate was 92% with EpiFix compared with 8% with SOC alone. At trial conclusion, unhealed wounds from the control group were treated with EpiFix.[11] The mean duration of foot ulcers at the beginning of treatment was 19.4 weeks (range, 6.0-54 weeks) for the combined group. Follow-up was available at 9 to 12 months after primary healing in 18 of 22 eligible patients. Examination of these 18 patients found that 17 (94.4%) wounds remained fully healed.

EpiFix vs Apligraf

EpiFix d-HAM was compared with Apligraf (living cell therapy) in a multicenter RCT published by Zelen et al (2015).[12] Sixty patients were randomized to treatment with Epifix, Apligraf, or standard wound care. Although patients and site investigators could not be blinded due to differences in products, wound healing was verified by 3 independent physicians who evaluated photographic images. Median wound size was 2.0 cm^2 (range, 1.0-9.0 cm^2) and median duration of the index ulcer was 11 weeks (range, 5-54 weeks). After 6 weekly treatments, the mean percent wound area healed was 97.1% for EpiFix, 80.9% for Apligraf, and 27.7% for SOC; 95% of wounds had healed completely in the EpiFix group compared with 45% treated with Apligraf and 35% who received standard wound care ($p \leq 0.003$). The estimated median time to wound closure, based on Kaplan-Meier analysis, was 13 days for EpiFix compared with 49 days for both Apligraf and SOC ($p \leq 0.001$).

In 2015, Kirsner et al reported an industry-sponsored observational study comparing the effectiveness of Apligraf and EpiFix in a real-world setting.[13] Data were obtained from a wound care–specific database from 3000 wound care facilities. The database included 1458 diabetic ulcers treated for the first time in 2014 with Apligraf (n=994) or EpiFix (n=464). Using the same criteria as the 2015 study by Zelen (described above), data were included on the treatment of 226 diabetic foot ulcers from 99 wound care centers. Foot wounds were included with size between 1 cm^2 and 25 cm^2, duration of 1 year or less, and wound reduction of 20% or less in the 14 days prior to treatment. Although wounds for the 2 groups were comparable at baseline, the rationale for using a particular product was not reported. There were 163 wounds treated with Apligraf (mean, 2.5 applications) and 63 treated with EpiFix (mean, 3.5 applications, p=0.003). By week 24, 72% of wounds treated with Apligraf and 47% of wounds treated with EpiFix had closed (p=0.01). Median time to closure was 13.3 weeks for Apligraf and 26.0 weeks for EpiFix (p=0.01). This study is limited by the possibility of selection bias in determining treatment assignment.

Cryopreserved Placental Membrane

Grafix vs Standard Care

Grafix cryopreserved placental membrane was compared with standard wound care in a 2014 multicenter RCT.[14] Strengths of this study included power analysis, blinded assessment of wound

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healing, evaluation of wound closure as the primary outcome measure, and ITT analysis. Ninety-seven patients with chronic diabetic foot ulcers were randomized to Grafix or to standard wound therapy, both administered once a week for up to 12 weeks. Power analysis indicated that 94 patients per arm would be needed for adequate power. However, after prespecified interim analysis at 50% enrollment, the blinded review committee recommended that the trial be stopped due to efficacy of the treatment. ITT analysis from the blinded evaluation phase showed a significant increase in the proportion of patients achieving the primary outcome of wound closure by 12 weeks (62.0% vs 21.3%, p<0.001) and a decrease in the median time to complete wound closure (42.0 days vs 69.5 days, p=0.019). Safety evaluation found that fewer Grafix-treated patients experienced at least 1 adverse event (44.0% vs 66.0%, p=0.031) or had wound-related infections (18.0% vs 36.2%, p=0.044), with a trend toward fewer hospitalizations related to infections (6% vs 15%, p=0.15).

Section Summary: Diabetic Lower-Extremity Ulcers

The evidence on amniotic and placental membrane products for the treatment of diabetic lower-extremity ulcers includes several RCTs compared HAM to SOC or to an established advanced wound care product. All of these industry-sponsored studies included evaluation of wound closure as the primary outcome measure, and some included power analysis, blinded assessment of wound healing, and ITT analysis. For the amniotic membrane products evaluated in RCTs (eg, AmnioBand Membrane, EpiFix, Grafix), results indicated improved outcomes compared to SOC, and outcomes that are at least as good as the advanced wound care product Apligraf. In addition, a registry study for Biovance showed improved health outcomes with a magnitude of benefit similar to that observed in the RCTs for other products.

LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

Dehydrated Amniotic Membrane

EpiFix

In 2014, Serena et al reported on an industry-sponsored multicenter open-label RCT that compared EpiFix dehydrated amniotic membrane plus compression therapy to compression therapy alone for venous leg ulcers.[15] Ulcers were included if they were chronic (>1 month in duration); extended through the full thickness of the skin but not down to muscle, tendon, or bone; and had been treated with compression therapy for at least 14 days. Eighty-four participants were enrolled and assigned to a single EpiFix allograft (n=26), 2 allografts (n=27), or compression therapy alone (n=31). The primary outcome (proportion of patients with 40% wound closure at 4 weeks) was achieved by 62% in the combined EpiFix groups and by 32% in the control group (p=0.005). During the 4-week study period, 6 (11.3%) patients in the combined EpiFix group and 4 (12.9%) in the control group achieved complete wound closure. Secondary outcomes, which evaluated the use of 1 versus 2 applications of amniotic membrane, showed no significant difference in outcomes (62% vs 63%). Strengths of this study 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 report 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 retrospective study did not take into account additional treatments after the 4-week randomized trial period.[16]

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Biovance

As described above, in 2015, Smiell et al reported on an industry-sponsored, multicenter registry study of Biovance dehydrated amniotic membrane for the treatment of various chronic wound types; about half (n=89) were venous ulcers.[9] 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

Given the lack of difference between 1 and 2 applications of EpiFix and the lack of difference between the experimental and control groups in complete wound closure at 4 weeks, and because no HAM products have been shown to improve healing of venous ulcers in comparative trials, additional study is needed to evaluate the effect of this treatment on health outcomes.

OSTEOARTHRITIS

ReNu

A feasibility study (N=6) of cryopreserved HAM (c-HAM) suspension with amniotic fluid–derived cells (ReNu) for the treatment of knee osteoarthritis was reported in 2016.[17] 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 effects, aside from a transient increase in pain, were noted. An RCT is in progress.

PLANTAR FASCIITIS

One systematic review and 2 randomized pilot studies were identified on the treatment of plantar fasciitis with injection of micronized HAM.

Systematic Review

A 2016 network meta-analysis of 22 RCTs (total N=1216 patients) compared injection therapies for plantar fasciitis.[18] In addition to c-HAM and micronized d-HAM/chorionic membrane, treatments included corticosteroids, botulinum toxin type A, autologous whole blood, platelet-rich plasma (PRP), nonsteroidal anti-inflammatory drugs, dry needling, dextrose prolotherapy, and polydeoxyribonucleotide. Placebo arms included normal saline, local anesthetic, sham dry needling, and tibial nerve block. The minimum clinically important difference (MCID) was defined as -9 mm on a visual analog scale (VAS), which is substantially lower than the more typically used 30% or 20-mm decrease in VAS score for pain. Secondary outcomes included total and subscores for the Foot Health Status Questionnaire (FHSQ), with an MCID defined as 7 on the FHSQ function and 9 on the FHSQ general foot health subscales. Overall, risk of bias was low for randomization and blinding of participants, high for blinding of personnel, and uncertain for allocation concealment and outcome reporting. Analysis found d-HAM had the highest probability for improvement in pain and composite outcomes in the short term. However, this finding was based on only 1 RCT. When the efficacy of d-HAM was compared to corticosteroid injections, the mean difference in VAS score was a modest -7.32 out of 100 (95% CI, -11.2 to -3.38) and the mean difference in the FHSQ score was 31.2 (95% CI, 13.9 to 48.6). Outcomes at 2-to-6 months (7 RCTs) favored botulinum toxin for pain and PRP for composite outcomes.

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Clarix Flo

One 2015 small (N=23), industry-sponsored, double-blind study found similar improvements with injection of c-HAM (Clarix Flo) compared with corticosteroid injection.[19] Another industry-sponsored, patient-blinded study by Zelen et al in 2013 (N=45) compared injection of saline to d-HAM (AmnioFix) 0.5 mL or 1.25 mL in patients with symptoms recalcitrant to conservative treatment.[20] In the 2 d-HAM groups, scores on the American Orthopaedic Foot and Ankle Society Hindfoot Scale improved by about 50 points over the 8 weeks of the study compared with 10 points for controls ($p<0.001$). FACES pain scores decreased from 8.7 of 10 at baseline to 0.8 at 8 weeks with d-HAM, compared with a decrease from 8.0 to 4.6 for controls ($p<0.001$). Longer follow-up is ongoing.

Section Summary: Plantar Fasciitis

Evidence on injection of particulated amniotic membrane and amniotic fluid for the treatment of plantar fasciitis is limited. Evidence includes a small (N=23) double-blind comparison with corticosteroid and a patient-blinded (N=45) comparison of 2 different doses of d-HAM with saline. Power analysis was not reported. A network meta-analysis, which identified only the Zelen et al trial, concluded that d-HAM was more effective than corticosteroid. However, these 2 small studies are not sufficient to demonstrate an improvement in health outcomes for this common condition. Additional study in a larger number of patients is needed to demonstrate consistency in results.

OPHTHALMIC CONDITIONS

Ocular Burns

A 2012 Cochrane review evaluated the evidence on amniotic membrane transplantation (AMT) for acute ocular burns.[21] Included in the review was a single RCT from India of 68 patients with acute ocular burns who were randomized to c-HAM plus medical therapy or to medical therapy alone. In the subset of 36 patients with moderate ocular burns who were treated within 7 days, 13 (65.0%) of 20 control eyes and 14 (87.5%) of 16 AMT-treated eyes had complete epithelialization by 21 days. There was a trend ($p=0.09$) toward a reduced relative risk of failure of epithelization in the treatment group. Mean logarithm of the minimum angle of resolution (LogMAR) final visual acuities were 0.06 in the treatment group and 0.38 in the control group. In the subset of patients with severe ocular burns treated within 7 days, 1 (5.9%) of 17 AMT-treated eyes and 1 (6.7%) of 15 control eyes were epithelialized by day 21. Final visual acuity was 1.77 logMAR in the treated eyes and 1.64 in the control group ($p=NS$). The risk of bias was considered to be high because of differences between the groups at baseline and because outcome assessors could not be masked to treatment. Reviewers determined that conclusive evidence supporting the treatment of acute ocular surface burns with AMT is lacking. It should also be noted that the amniotic membrane used in this study was fresh frozen and is not commercially available.

Stevens-Johnson Syndrome

Another RCT from India (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or to medical therapy alone.[22] 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 ($p=0.042$), tear breakup time ($p=0.015$), 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

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of corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. These outcomes compared dramatically with the medical therapy alone group, which had 11 (44%) of 25 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.

Dry Eye Disease

The Prokera c-HAM device was evaluated in a 2016 series by Cheng et al.[23] The senior author of the study (S.C.G. Tseng) holds the patent on Prokera. This retrospective review assessed 10 patients treated with the self-retained device for moderate-to-severe dry eye disease. In this study, these 10 patients had moderate-to-severe dry eye syndrome despite conventional medical treatment. The c-HAM device was placed in 15 eyes (1 eye at a time) for a mean of 4.9 days (range, 2-8 days), after which the c-HAM was either dissolved or cloudy. Treatment resulted in symptomatic relief for a mean of 4.2 months (range, 0.3 to 6.8 months) after a single treatment. Symptomatic improvement was accompanied by statistically significant reductions of Ocular Surface Disease Index scores, use of topical medications, conjunctival hyperemia, corneal staining (all p<0.001), and a trend toward improved visual acuity (p=0.06).

Other

Use of Prokera has also been reported for refractory ulcerative keratitis, neurotrophic keratitis, recurrent epithelial erosion, high-risk corneal grafts, acute chemical and thermal burns, acute Stevens-Johnson syndrome, necrotizing scleritis, and limbal stem cell deficiency (referenced in Cheng et al, 2016).[23]

Section Summary: Ophthalmic Conditions

Traditionally, amniotic membrane has been sutured onto the eye for a variety of ocular surface disorders. Results from 2 recent RCTs have suggested benefit, but the studies are at high or uncertain risk of bias due to unequal baseline scores and the lack of masking (blinding). Additional study in a larger number of subjects is needed to demonstrate consistent effects. The Prokera device is novel by having a ring around the c-HAM allograft that allows it to be inserted under topical anesthesia similar to insertion of a contact lens, allowing for more widespread use. Current evidence on use of the Prokera device includes case reports and case series. Results are generally positive, but controlled studies are needed.

SUMMARY OF EVIDENCE

Diabetic Lower-Extremity Ulcers

For individuals who have nonhealing diabetic lower-extremity ulcers who receive patch or flowable formulation of human amniotic membrane (HAM; AmnioBand Membrane, Biovance, Epifix, Grafix), the evidence includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on amniotic and placental membrane products for the treatment of nonhealing (<20% healing with ≥2 weeks of standard care) diabetic lower-extremity ulcers includes several RCTs that compared HAM to standard care or to an established advanced wound care product. These industry-sponsored studies used wound closure as the primary outcome measure, and some used power analysis, blinded assessment of wound healing, and intention-to-treat analysis. For the HAM products that have been sufficiently evaluated (AmnioBand Membrane, Biovance, Epifix, Grafix), results have shown improved outcomes compared to standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are

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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 patch or flowable formulation of HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. In a randomized comparison of a cryopreserved HAM (c-HAM) product to standard of care, there was no difference between the experimental and controls groups in complete wound closure at 4 weeks. Because HAM has not been shown to improve healing of venous ulcers in controlled studies, comparative studies on other HAM products 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 injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid, the evidence includes a feasibility study. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The pilot study was in preparation for a larger RCT of HAM injection. Additional trials, which will have a larger sample sizes 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 injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid, the evidence includes 2 small RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Literature on HAM injections is at a very early stage. 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 this treatment on plantar fasciitis pain. Also needed are RCTs in humans to evaluate the efficacy of amniotic membrane and amniotic fluid injections for the treatment of other conditions, including but not limited to tendonitis. The evidence is insufficient to determine the effects of the technology on health outcomes.

Ophthalmic Conditions
For individuals who have ophthalmic conditions who receive patch formulation of HAM, the evidence includes RCTs and case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Traditionally, amniotic membrane has been sutured onto the eye for a variety of severe ocular surface disorders. Results from 2 recent RCTs have suggested benefit, but additional study in a larger number of subjects is needed to demonstrate consistent effects. The Prokera device is novel by having a ring around the c-HAM allograft that allows it to be inserted under topical anesthesia, similar to insertion of a contact lens, allowing for more widespread use. Current evidence on use of the Prokera device includes case reports and case series. Results are generally positive, but controlled studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

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PRACTICE GUIDELINES AND POSITION STATEMENTS

No guidelines or statements were identified.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01693133[a]	A Multicenter, Prospective, Randomized, Controlled, Comparative Parallel Study of Dehydrated Human Amnion/Chorion Membrane (dHACM) Wound Graft in the Management of Diabetic Foot Ulcers	84	Dec 2016
NCT02011503[a]	A Randomized Controlled Clinical Trial Evaluating The Application Of Dehydrated Human Amnion/ Chorion Membrane (dHACM) Plus Standard Of Care Vs. Standard Of Care Alone In The Treatment Of Venous Leg Ulcers	120	Dec 2016
NCT02609594[a]	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 2016
NCT02318511[a]	An Investigation of ReNu™ Knee Injection: Monitoring the Response of Knee Function and Pain in Patients With Osteoarthritis	150	Mar 2017
NCT02427191[a]	A Prospective, Single-Blinded, Randomized Controlled Trial of the Micronized dHACM Injection as Compared to the Saline Placebo Injection in the Treatment of Plantar Fasciitis (AmnioFix Injectable)	146	Dec 2017
NCT02765737[a]	Randomized Multicenter Trial - Dehydrated Human Amnion Chorion Membrane (dHACM) vs. Control in the Treatment of Partial Thickness Burns	60	Dec 2017
NCT02322554	The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers	50,000	Jan 2020
Unpublished			
NCT02399826[a]	A Prospective, Randomized, Comparative Parallel Study of Amniotic Membrane Graft in the Management of Diabetic Foot Ulcers	40	Jan 2016

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

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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

Q4100	Skin substitute, not otherwise specified
Q4131	EpiFix or Epicord, per sq cm
Q4132	Grafix Core, per sq cm
Q4133	Grafix Prime, per sq cm
Q4137	AmnioExcel 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 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, per sq cm
Q4157	Revitalon, per sq cm
Q4159	Affinity, per sq cm
Q4160	Nushield, per sq cm
Q4162	AmnioPro Flow, BioSkin Flow, BioRenew Flow, WoundEx Flow, Amniogen-A, Amniogen-C, 0.5 cc
Q4163	AmnioPro, BioSkin, BioRenew, WoundEx, Amniogen-45, Amniogen-200, 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

- 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 is possible that 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).

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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.)
L97212	Non-pressure chronic ulcer of right calf with fat layer exposed
L97213	Non-pressure chronic ulcer of right calf with necrosis of muscle
L97214	Non-pressure chronic ulcer of right calf with necrosis of bone
L97222	Non-pressure chronic ulcer of left calf with fat layer exposed
L97223	Non-pressure chronic ulcer of left calf with necrosis of muscle
L97224	Non-pressure chronic ulcer of left calf with necrosis of bone
L97312	Non-pressure chronic ulcer of right ankle with fat layer exposed
L97313	Non-pressure chronic ulcer of right ankle with necrosis of muscle
L97314	Non-pressure chronic ulcer of right ankle with necrosis of bone
L97322	Non-pressure chronic ulcer of left ankle with fat layer exposed
L97323	Non-pressure chronic ulcer of left ankle with necrosis of muscle
L97324	Non-pressure chronic ulcer of left ankle with necrosis of bone
L97412	Non-pressure chronic ulcer of right heel and midfoot with fat layer exposed
L97413	Non-pressure chronic ulcer of right heel and midfoot with necrosis of muscle
L97414	Non-pressure chronic ulcer of right heel and midfoot with necrosis of bone
L97422	Non-pressure chronic ulcer of left heel and midfoot with fat layer exposed
L97423	Non-pressure chronic ulcer of left heel and midfoot with necrosis of muscle
L97424	Non-pressure chronic ulcer of left heel and midfoot with necrosis of bone
L97512	Non-pressure chronic ulcer of other part of right foot with fat layer exposed
L97513	Non-pressure chronic ulcer of other part of right foot with necrosis of muscle
L97514	Non-pressure chronic ulcer of other part of right foot with necrosis of bone
L97522	Non-pressure chronic ulcer of other part of left foot with fat layer exposed
L97523	Non-pressure chronic ulcer of other part of left foot with necrosis of muscle
L97524	Non-pressure chronic ulcer of other part of left foot with necrosis of bone
L97812	Non-pressure chronic ulcer of other part of right lower leg with fat layer exposed
L97813	Non-pressure chronic ulcer of other part of right lower leg with necrosis of muscle
L97814	Non-pressure chronic ulcer of other part of right lower leg with necrosis of bone
L97822	Non-pressure chronic ulcer of other part of left lower leg with fat layer exposed
L97823	Non-pressure chronic ulcer of other part of left lower leg with necrosis of muscle

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L97824 Non-pressure chronic ulcer of other part of left lower leg with necrosis of bone

REVISIONS

03-20-2017	Policy added to the bcbsks.com web site.

REFERENCES

1. 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):275-291. PMID 19317646
2. 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
3. Shimberg M, Wadsworth K. The use of amniotic-fluid concentrate in orthopaedic conditions. J Bone Joint Surg. 1938;20(I):167-177.
4. U.S. Food and Drug Administration. Guidance for industry: Chronic cutaneous ulcer and burn wounds. 2006; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071324.pdf. Accessed December 22, 2016.
5. Gottrup F, Apelqvist J, Price P, et al. Outcomes in controlled and comparative studies on non-healing wounds: recommendations to improve the quality of evidence in wound management. J Wound Care. Jun 2010;19(6):237-268. PMID 20551864
6. Sheehan P, Jones P, Caselli A, et al. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care. Jun 2003;26(6):1879-1882. PMID 12766127
7. DiDomenico LA, Orgill DP, Galiano RD, et al. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. Plast Reconstr Surg Glob Open. Oct 2016;4(10):e1095. PMID 27826487
8. 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):70-77. PMID 26978860
9. Smiell JM, Treadwell T, Hahn HD, et al. Real-world experience with a decellularized dehydrated human amniotic membrane allograft. Wounds. Jun 2015;27(6):158-169. PMID 26061491
10. Zelen CM, Serena TE, Denoziere G, et al. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. Int Wound J. Oct 2013;10(5):502-507. PMID 23742102
11. Zelen CM, Serena TE, Fetterolf DE. Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: a long term follow-up study. Wound Med. 2014;4:1-4.
12. 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):724-732. PMID 25424146

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13. Kirsner RS, Sabolinski ML, Parsons NB, et al. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. Wound Repair Regen. Sep 2015;23(5):737-744. PMID 26100572
14. 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):554-560. PMID 25048468
15. 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 and Regeneration. Nov-Dec 2014;22(6):688-693. PMID 25224019
16. Serena TE, Yaakov R, DiMarco D, et al. Dehydrated human amnion/chorion membrane treatment of venous leg ulcers: correlation between 4-week and 24-week outcomes. J Wound Care. Nov 2015;24(11):530-534. PMID 26551645
17. Vines JB, Aliprantis AO, Gomoll AH, et al. Cryopreserved amniotic suspension for the treatment of knee osteoarthritis. J Knee Surg. Aug 2016;29(6):443-450. PMID 26683979
18. 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
19. Hanselman AE, Tidwell JE, Santrock RD. Cryopreserved human amniotic membrane injection for plantar fasciitis: a randomized, controlled, double-blind pilot study. Foot Ankle Int. Feb 2015;36(2):151-158. PMID 25249320
20. 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):1332-1339. PMID 23945520
21. Clare G, Suleman H, Bunce C, et al. Amniotic membrane transplantation for acute ocular burns. Cochrane Database Syst Rev. 2012;9:CD009379. PMID 22972141
22. 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):484-491. PMID 26686968
23. Cheng AM, Zhao D, Chen R, et al. Accelerated restoration of ocular surface health in dry eye disease by self-retained cryopreserved amniotic membrane. Ocul Surf. Jan 2016;14(1):56-63. PMID 26387870

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