Medical Policy

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Title: Amniotic Membrane and Amniotic Fluid

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

Professional / Institutional
Original Effective Date: March 20, 2017
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Populations	Interventions	Comparators	Outcomes
Individuals: • With nonhealing diabetic lower-extremity ulcers	Interventions of interest are: • Patch 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 formulation of human amniotic membrane	Comparators of interest are: • Compression therapy • Advanced wound therapies	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With knee osteoarthritis	Interventions of interest are: • Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid	Comparators of interest are: • Conservative therapy • Corticosteroid injections	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With plantar fasciitis	Interventions of interest are: • Injection of suspension or particulate formulation of human amniotic membrane or amniotic fluid	Comparators of interest are: • Conservative therapy • Corticosteroid injections	Relevant outcomes include: • Symptoms • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative treatment	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With corneal ulcers or melts that do not respond to initial medical therapy	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life
Individuals: • With corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment	Interventions of interest are: • Sutured or self-retained human amniotic membrane	Comparators of interest are: • Medical therapy • Bandage contact lens	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life

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

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

DESCRIPTION

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

OBJECTIVE

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

BACKGROUND

Human Amniotic Membrane

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

Fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist.[1,]There is evidence that the tissue has anti-inflammatory, antifibroblastic, and

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

Use of a HAM graft, which is fixated by sutures, is an established treatment for disorders of the corneal surface, including neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Amniotic membrane products that are inserted like a contact lens have more recently been investigated for the treatment of corneal and ocular surface disorders. Amniotic membrane patches are also being evaluated for the treatment of various other conditions, including skin wounds, burns, leg ulcers, and prevention of tissue adhesion in surgical procedures.[1,] Additional indications studied in preclinical models include tendonitis, tendon repair, and nerve repair. The availability of HAM opens the possibility of regenerative medicine for an array of conditions.

Amniotic Fluid

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

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

REGULATORY STATUS

In 2024, the U.S. Food and Drug Administration (FDA) issued a public safety notification on amniotic fluid eyedrops.[4,] The notice was to inform the public and health care practitioners "that manufacturers are marketing and distributing amniotic fluid eyedrops to treat, mitigate, or cure diseases or conditions such as dry eye disease without the required premarket review and approval, raising potential significant safety concerns." A list of related warning letters issued by the FDA can be found on the FDA website's Warning Letters page using the search term "amniotic fluid."[5,]

On December 19, 2024, the FDA issued a warning letter to Integra LifeSciences Corporation stating: "FDA investigators and a microbiologist determined that the above firms manufacture a variety of neurological and neurosurgical devices, including but not limited to, cranial perforators, disposable cottonoid patties and strips as well as collagen based medical devices, that are used for wound care, soft tissue repair and reconstruction surgery. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure,

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mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body."[6,]

The 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).[7,]

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

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

1. "The HCT/P is minimally manipulated;
2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4. Either:
    i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
        a. Is for autologous use;
        b. Is for allogeneic use in a first-degree or second-degree blood relative; or
        c. Is for reproductive use."

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

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

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

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In 2003, Prokera was cleared for marketing by the FDA through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104; product code: NQB). 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."[8,] The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

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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. Affinity® (Q4159)
   2. AmnioBand® Membrane (Q4151)
   3. Biovance® (Q4154)
   4. EpiCord® (Q4187)
   5. EpiFix® (Q4186)
   6. Grafix™ (Q4132, Q4133)
   7. NuShield® (Q4160)

B. Human amniotic membrane grafts (i.e., a human amniotic product commercially available specifically for ophthalmic use)with or without suture or glue, may be considered **medically necessary** for the treatment of any of the following ophthalmic indications:

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

C. Injection of micronized or particulated human amniotic membrane is considered **experimental / investigational** for all indications, including, but not limited to, treatment of osteoarthritis and plantar fasciitis.

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

E. The use of any human amniotic product (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly), including but not limited to those listed in Table PG2 (see Policy Guidelines), is considered **experimental / investigational** for all other indications, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency and repair following Mohs micrographic surgery.

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POLICY GUIDELINES

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

B. Non-healing of lower-extremity ulcers due to venous insufficiency is defined as less than a 30% decrease in wound area with standard wound care for at least 2 weeks, based on clinical trial entry criteria (Serena et al [2022]).

C. This review covers products that do not require FDA approval or clearance. The list of products named in this review is not a complete list of all commercially available products. Table PG1 lists products included in the Policy statements, and Table PG2 lists other amniotic products that have an HCPCS code.

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

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

Table PG1 Amniotic Products Listed in the Policy Statements

Trade Name	Supplier	HCPCS Code
Affinity®	Organogenesis (previously NuTech Medical)	Q4159
AmnioBand® Membrane	MTF Wound Care	Q4151
Biovance®	Celularity	Q4154
Epifix®	MiMedx	Q4186
Epicord®	MiMedx	Q4187
Grafix®	Osiris	Q4132, Q4133
NuShield®	Organogensis	Q4160

Table PG2 Other Amniotic Products with HCPCS Codes

Trade Name	Supplier	HCPCS Code
Abiomend membrane and abiomend hydromembrane	Abiomed	Q4356
Abiomend xplus membrane and abiomend xplus hydromembrane	Amnio Technology	Q4355
Acapatch	ExtremityCare	Q4325
Acesso	Dynamic Medical Services LLC	Q4311

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Trade Name	Supplier	HCPCS Code
Acesso ac	Dynamic Medical Services LLC	Q4312
AlloGen	Vivex Biomedical	Q4212
Alloply	ExtremityCare	Q4323
AlloWrap™	AlloSource	Q4150
Amchoplast	LifeCell International Pvt Ltd	Q4316
Amchoplast fd	LifeCell International Pvt Ltd	Q4360
Amnio burgeon dual-layer membrane	Amnio Technology	Q4365
Amnio burgeon membrane and hydromembrane	Amnio Technology	Q4363
Amnio burgeon xplus membrane and xplus hydromembrane	Amnio Technology	Q4364
AmnioAMP-MP	Stratus BioSystems	Q4250
Amnioarmor™	Tissue Transplant Technology	Q4188
Amniocore sl		Q4367
AmnioExcel®	Integra	Q4137
Amnio-maxx or Manio-maxx lite	Royal Biologics	Q4239
Amniotext	Regenerative Labs	Q4245
Amniowound	Alpha Tissue	Q4181
Amnion bio or Axomembrane	Axolotl Biologix	Q4211
Amnioplast 1	LifeCell International Pvt Ltd	Q4334
Amnioplast 2	LifeCell International Pvt Ltd	Q4335
Amniocore™	Stability Biologics	Q4227
Amniocyte	Predictive Biotech	Q4242
AmnioMatrix®	Integra Life Sciences	Q4139
Amniply	International Tissue	Q4249
Amniorepair or AltiPly	Zimmer Biomet	Q4235
Amniotext patch	Regenerative Labs	Q4247
Amniotx	RegenTX Partners LLC	Q4324
AmnioWrap2™	Direct Biologics	Q4221
Ardeograft	Surgenex	Q4333
Articent ac (flowable)	Tides Medical	Q4189
Artacent ac (patch)	Tides Medical	Q4190
Artacent c	Tides Medical	Q4336

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Trade Name	Supplier	HCPCS Code
Artacent trident	Tides Medical	Q4337
Artacent velos	Tides Medical	Q4338
Artacent vericlen	Tides Medical	Q4339
Artacent® Wound	Tides Medical	Q4169
Ascent	StimLabs	Q4213
Axolotl ambien or Axolotl Cryo	Axolotl Biology	Q4215
Axolotl dualgraft	Axolotl Biologix	Q4332
Axolotl graft	Axolotl Biologix	Q4331
BioDDryFlex®	BioD	Q4138
BioDfence™	Integra Life Science	Q4140
BioNextPATCH	BioNext Solutions	Q4228
BioWound, BioWound Plus™, BioWound XPlus™	HRT[a]	Q4217
Caregraft	ExtremityCare	Q4322
carePATCH	Extremity Care	Q4236
Cellesta/Cellesta duo	Ventris Medical	Q4184
Cellesta Cord	Ventris Medical	Q4214
Cellesta flowable	Ventris Medical	Q4185
Choriply		Q4359
Clarix®	Amniox Medical	Q4156
Clarix® Flo	Amniox Medical	Q4155
Cogenex flowable amnion	Ventris Medical	Q4230
Cogenex amniotic membrane	Ventris Medical	Q4229
Corecyte	Predictive Biotech	Q4240
Corplex	StimLabs	Q4232
Corplex P	StimLabs	Q4231
Corplex p or theracor p or allacor p	StimLabs	A2035
Coretext or Protext	Regenerative Labs	Q4246
Cryo-cord	Royal Biologics	Q4237
Cygnus	Vivex Biomedical	Q4170
Cygnus disk	VIVEX Biologics	Q4362
Dermabind fm	NovaMed Group LLC	Q4313
Dermacyte	Merakris Therapeutics	Q4248

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Trade Name	Supplier	HCPCS Code
Dermacyte ac matrix amniotic membrane allograft	Merakris Therapeutics	Q4343
Dermavest™ or Plurivest	AediCell[a]	Q4153
Derm-maxx	Royal Biologics	Q4238
Dual layer amnio burgeon x-membrane	Amnio Technology	Q4366
Duoamnion	Samaritan Biologics LLC	Q4327
E-graft	Skye Biologics	Q4318
Enclose tl matrix		Q4351
Epifix Injectable	MiMedx	Q4145
Epixpress	MIMEDX	Q4361
Floweramnioflo	Flower Orthopedics	Q4177
Floweramniopatch	Flower Orthopedics	Q4178
Fluid flow or Fluid GF	BioLab Sciences	Q4206
Genesis	Genesis Biologics	Q4198
Interfyl®	Celularity	Q4171
Mantle dl matrix		Q4349
Matrion	LifeNet Health	Q4201
Matrix hd allograft dermis	Enovis	Q4345
Most		Q4328
Neopatch or Therion	CryoLife	Q4176
Neox® Cord	Amniox Medical	Q4148
Neox® Flo	Amniox Medical	Q4155
Neox® Wound	Amniox Medical	Q4156
Restorigin	UMTB Biomedical	Q4191
Novafix®	Triad Life Sciences	Q4208
Novafix DL	Triad Life Sciences	Q4254
Overlay sl matrix		Q4352
Palingen dual-layer membrane	Amnio Technology	Q4354
PalinGen® Membrane	Amnio ReGen Solutions	Q4173
PalinGen® SportFlow	Amnio ReGen Solutions	Q4174
Palisade dm matrix		Q4350
Pellograft	Surgenex	Q4320
Plurivest™	AediCell	Q4153

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Trade Name	Supplier	HCPCS Code
Polycyte	Predictive Biotech	Q4241
Procenta	Lucina BioSciences	Q4244
Rampart dl matrix		Q4347
Reeva ft	BioXTek	Q4314
Regenelink amniotic membrane allograft	LifeLink Tissue Bank	Q4315
Reguard	New Life Medical	Q4255
Renograft		Q4321
Restorigin	UMTB Biomedical	Q4191
Restorigin Injectable	UMTB Biomedical	Q4192
Revita	StimLabs	Q4180
Revitalon™	Medline Industries	Q4157
Sanograft	Surgenex	Q4319
Sentry sl matrix		Q4348
Shelter dm matrix		Q4346
Simpligraft	Xtant Medical Holdings Inc	Q4340
Simplimax	Xtant Medical Holdings Inc	Q4341
Singlay		Q4329
Surgenex, Surfactor, and Nudyn	Surgenex	Q4233
Surgicord	Synergy Biologics	Q4218
SurgiGRAFT™	Synergy Biologics	Q4183
Theramend	LUX Therapeutics	Q4342
Total	TotalEnergies	Q4330
Tri-membrane wrap	Life Biologics	Q4344
Vitograft	Surgenex LLC	Q4317
WoundEx®	Skye Biologics[a]	Q4163
WoundEx® Flow	Skye Biologics[a]	Q4162
Woundfix, Woundfix Plus, Wounfix XPlus (see BioWound above)	HRT	Q4217
Woundplus	Skye Biologics	Q4326
Xceed tl matrix		Q4353
Xcellerate	Precise Bioscience	Q4234
Xwrap	Applied Biologics	Q4204
Xwrap dual	Applied Biologics	Q4358

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Trade Name	Supplier	HCPCS Code
Xwrap plus	Applied Biologics	Q4357

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

Tear Film and Ocular Surface Society staged management for dry eye disease (Jones et al, 2017)
Step 1:
- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)
- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if meibomian gland dysfunction is present, then consider lipid containing supplements)
- Lid hygiene and warm compresses of various types

Step 2:
If above options are inadequate consider:
- Non-preserved ocular lubricants to minimize preservative-induced toxicity
- Tea tree oil treatment for Demodex (if present)
- Tear conservation
- Punctal occlusion
- Moisture chamber spectacles/goggles
- Overnight treatments (such as ointment or moisture chamber devices)
- In-office, physical heating and expression of the meibomian glands
- In-office intense pulsed light therapy for meibomian gland dysfunction
- Prescription drugs to manage dry eye disease
- Topical antibiotic or antibiotic/steroid combination applied to the lid margins for anterior blepharitis (if present)
- Topical corticosteroid (limited-duration)
- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

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

Step 4:
If above options are inadequate consider:
- Topical corticosteroid for longer duration
- Amniotic membrane grafts

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- Surgical punctal occlusion
- Other surgical approaches (e.g. tarsorrhaphy, salivary gland transplantation)

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

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through March 10, 2026.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

DIABETIC LOWER-EXTREMITY ULCERS

AMNIOTIC MEMBRANE OR PLACENTAL MEMBRANE

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Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

REVIEW OF EVIDENCE

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Systematic Reviews

Zheng et al (2026) conducted a systematic review and meta-analysis of 14 RCTs encompassing 1,056 patients with chronic wounds, including 11 trials in patients with diabetic foot ulcers (DFUs; 803 patients) and 3 trials in patients with venous leg ulcers (253 patients).[9,] The review searched 9 electronic databases through August 2024 and assessed the risk of bias using the Cochrane Risk of Bias 2 tool and the certainty of evidence using the GRADE framework. For DFUs, pooled analysis showed that HAM therapy significantly increased the rate of complete wound healing compared with standard of care alone at both 6 weeks (RR = 3.02; 95% CI: 2.04 to 4.47; I^2 = 11%; 5 RCTs; moderate-quality evidence) and 12 weeks (RR = 1.74; 95% CI: 1.37 to 2.21; I^2 = 54%; 8 RCTs; low-quality evidence). HAM also reduced the mean time to complete healing by approximately 22 days (MD = −22.09 days; 95% CI: −39.13 to −5.05; low-quality evidence). No statistically significant difference was observed in wound-related infection rates between the HAM and standard of care groups (RD = −0.06; 95% CI: −0.13 to 0.01; I^2 = 0%; moderate-quality evidence). The included studies used various commercially available HAM products, including dehydrated amnion/chorion membrane, dehydrated amnion-only, cryopreserved, hypothermically stored, and acellular formulations. Limitations include possible publication bias indicated by funnel plot asymmetry (Egger's p = 0.031 for DFU), relatively small total sample sizes, and a maximum follow-up of 16 weeks across included trials.

Ruiz-Muñoz et al (2025) conducted a systematic review and meta-analysis of 12 RCTs comprising 833 patients with chronic DFUs, evaluating the effectiveness of placenta-derived biomaterial therapies compared with standard of care.[10,] The review searched PubMed, EMBASE, and Web of Science through September 2023 and assessed risk of bias using the Cochrane Collaboration tool and methodological quality using the CASPe critical appraisal instrument (all studies scored 10–11/11). Pooled analysis using a fixed-effects model showed a significantly higher rate of complete ulcer healing in the placenta-derived biomaterial groups compared with control groups (OR = 6.25; 95% CI: 4.43 to 8.82; $p < 0.01$; I^2 = 41%). Sensitivity analysis confirmed the robustness of findings, and trim-and-fill analysis estimated that 4 additional studies would be needed to account for potential publication bias, with the adjusted effect remaining statistically significant (OR = 5.20). The included trials evaluated products spanning dehydrated amnion/chorion membrane (AmnioBand, EpiFix), dehydrated umbilical cord (EpiCord), hypothermically stored amnion, dehydrated amniotic membrane allograft (AmnioExcel), cryopreserved amnion/chorion (Grafix), and acellular HAM formulations. Limitations include the use of odds ratios rather than risk ratios (which may overestimate relative effect sizes when event rates are high), no GRADE assessment of evidence certainty, blinding compromised in most included trials, and a search that predated more recent large RCTs.

Table SRx. Comparison of Trials Included in Systematic Reviews & Meta-Analyses

Study	Zheng (2026)[9,]	Ruiz-Muñoz (2025)[10,]
Zelen (2013)	●	●
Lavery (2014) [Grafix]	●	
Zelen (2015) [EpiFix]		●
DiDomenico (2016) [dHACA]		●
Mohajeri-Tehrani (2016) [aHAM]	●	●

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Study	Zheng (2026)[9,]	Ruiz-Muñoz (2025)[10,]
Snyder (2016) [DAMA/AmnioExcel]	●	●
Zelen (2016) [EpiFix]	●	●
DiDomenico (2018) [dHACA/AmnioBand]	●	●
Tettelbach (2018) [EpiCord]		●
Tettelbach (2019) [dHACM/EpiFix]	●	●
Thompson (2019) [AmnioExcel]	●	
Serena (2020) [HSAM]	●	●
Game (2021) [Omnigen]	●	
Mohammadi (2022) [HAM powder]		●
Rezaei-Nejad (2023) [aHAM gel]		●
Cazzell (2024) [NuShield/dACM]	●	

Table SR1. Systematic Review & Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Zheng (2026)[9,]	Inception–Aug 2024	14 (11 DFU, 3 VLU)	Adults with chronic wounds (DFU or VLU) persisting ≥4 wks; HAM (any preparation) vs SOC without HAM; reporting complete wound healing	1,056 (13–218)	RCTs only	6–16 wks
Ruiz-Muñoz (2025)[10,]	Inception–Sep 2023	12 (DFU only)	Adults aged 18–80 with chronic DFU; placenta-derived biomaterials (AM, chorion, UC) vs SOC; outcome: rate of complete ulcer healing	833 (22–161)	RCTs only	6–16 wks

Table SR2. Systematic Review & Meta-Analysis Results

	Complete Healing (DFU, Overall)	Complete Healing (DFU, 6 wks)	Complete Healing (DFU, 12 wks)	Time to Healing (DFU)	Wound-Related Infection (DFU)
Zheng (2026)[9,]					
Total N	1,056 (14 RCTs; DFU + VLU combined)	409 (5 RCTs)	692 (8 RCTs)	166 (4 RCTs)	408 (6 RCTs)
Pooled effect (95% CI)	RR = 1.82 (1.48 to 2.24)	RR = 3.02 (2.04 to 4.47)	RR = 1.74 (1.37 to 2.21)	MD = −22.09 days (−39.13 to −5.05)	RD = −0.06 (−0.13 to 0.01)
NNT (95% CI)	NR	NR	NR	NA (continuous)	NS

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	Complete Healing (DFU, Overall)	Complete Healing (DFU, 6 wks)	Complete Healing (DFU, 12 wks)	Time to Healing (DFU)	Wound-Related Infection (DFU)
I^2 (p)	48% (p=.02)	11% (p=.35)	54% (p=.03)	82% (p<.001)	0% (p=.42)
Ruiz-Muñoz (2025)[10,]					
Total N	833 (12 RCTs; DFU only)	NR (not separately pooled)	NR (not separately pooled)	NR	NR
Pooled effect (95% CI)	OR = 6.25 (4.43 to 8.82)	—	—	—	—
NNT (95% CI)	NR	—	—	—	—
I^2 (p)	41% (p=.066)	—	—	—	—

Randomized Controlled Trials

At least 7 RCTs have evaluated rates of healing with amniotic membrane grafts or placental membrane graft compared to SOC or an advanced wound therapy in patients with chronic diabetic foot ulcers (see Table 1). The number of patients in these studies ranged from 25 to 218. Human amniotic membrane (HAM) or placental membrane grafts improved healing compared to SOC by 22% (EpiCord vs. Alginate dressing) to 60% (EpiFix) in the intention-to-treat (ITT) analysis (see Table 2). In a 2018 trial, the cryopreserved placental membrane Grafix was found to be non-inferior to an advanced fibroblast-derived wound therapy (Dermagraft).

An additional large multicenter RCT (N=220) evaluated cryopreserved umbilical cord (NeoX 1K; see Table PG2) for complex DFUs with exposed bone, tendon, or joint capsule and controlled osteomyelitis.[11,] Complete wound healing rates did not differ significantly between the treatment and standard of care groups at 26 weeks (66.1% vs 59.8%; p=.40) or 50 weeks (77.1% vs 71.6%; p=.29).

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator
Cazzell et al (2024)[12,]	U.S.	15		218 patients with diabetic foot ulcers	n=109, NuShield	n=109, SOC
Serena et al (2020)[13,]	U.S.	14		76 patients with chronic (>4 weeks) non-healing diabetic foot ulcers unresponsive to SOC and extending into dermis, subcutaneous tissue, muscle, or tendon	n=38, Affinity	n=38, SOC
Ananian et al (2018)[14,]	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

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Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator
Tettelbach et al (2018)[15],	U.S.	11	2016-2018	155 patients with chronic (>4 weeks) non-healing diabetic foot ulcers	n=101 EpiCord plus SOC	n=54 SOC with alginate dressing
DiDomenico et al (2018)[16],				80 patients with non-healing (4 weeks) diabetic foot ulcers	AmnioBand Membrane plus SOC	SOC
Snyder et al (2016)[17],				29 patients with non-healing diabetic foot ulcers	AmnioExcel plus SOC	SOC
Zelen et al (2015, 2016)[18,19],		4		60 patients with less than 20% wound healing in a 2 week run-in period	EpiFix	Apligraf or SOC with collagen-alginate dressing
Tettelbach et al (2019)[20],	U.S.	14		110 patients with non-healing (4 weeks) lower extremity ulcers	EpiFix	SOC with alginate dressing
Lavery et al (2014)[21],				97 patients with chronic diabetic foot ulcers	Grafix Weekly	SOC

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

Table 2. Summary of Key RCT Results

Study	Wounds Healed	Wounds Healed	Time to Complete Healing	Adverse Events and Number of Treatments
Cazzell et al (2024)[12],	12 Weeks (ITT) (%)		Median	No adverse events or serious adverse events were reported
N	218		218	
NuShield	50%		84 days	
SOC	35%		not achieved by 12 weeks	
p-value	.04			
Serena et al (2020)[13],	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)		

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Study	Wounds Healed	Wounds Healed	Time to Complete Healing	Adverse Events and Number of Treatments
Ananian et al (2018)[14,]	8 Weeks (PP) n (%)			Patients with Index Ulcer Related Adverse Events n (%)
N	62			75
Grafix	15 (48.4%)			1 (5.9%)
Dermagraft	12 (38.7%)			4 (16.7%)
Diff (95% CI)	9.68% (−10.7 to 28.9)			
Lower bound for non-inferiority	-15%			
Tettlebach et al (2018)[15,]	12 Weeks (PP) n (%)	12 Weeks (ITT) n (%)		Patients with Adverse Events (% of total)
N	134	155		155
EpiCord	81 (81%)	71 (70%)		42 (42%)
SOC	29 (54%)	26 (48%)		33 (61%)
p-value	.001	.009		
DiDomenico et al (2018)[16,]	6 Weeks (ITT) n (%)	12 weeks ITT n (%)	Mean Days (95% CI)	
N	80	80	80	
AmnioBand	27 (68)	34 (85)	37.0 (29.5 to 44.4)	
SOC	8 (20)	13 (33)	67.3 (59.0 to 79.6)	
HR (95% CI)		4.25 (0.44 to 0.79)		
p-value	<.001	<.001	<.001	
Snyder et al (2016)[17,]	6 Weeks (PP) Mean (95% CI)			
N	21			
AmnioExcel	45.5% (32.9% to 58.0%)			
SOC	0%			
p-value	.014			

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Study	Wounds Healed	Wounds Healed	Time to Complete Healing	Adverse Events and Number of Treatments
Zelen et al (2015, 2016)[18,19,]	6 Weeks ITT n (%)	Wounds Healed at 12 Weeks		Weekly Treatments
N	60	100		
EpiFix	19 (95%)	NR		3.4
Apligraf	9 (45%)	NR		5.9
SOC	7 (35%)	NR		
HR (95% CI)		5.66; (3.03 to 10.57)		
p-value	.003	<.001 vs. SOC		.003
Tettelbach et al (2019)[20,]		Wounds Healed at 12 Weeks (ITT) n(%)		
N		110		110
EpiFix		38 (81)		
SOC		28 (55)		
p-value				
Lavery et al (2014)[21,]		Wounds Healed at 12 Weeks		Patients With Adverse Events
N		97a	97	97
Grafix		62.0%	42.0	44.0%
SOC		21.3%	69.5	66.0%
p-value		<.001	.019	.031
Difference in wounds healed between amniotic or placental membrane and SOC	Affinity 26% AmnioBand 55% AmnioExcel 33% EpiFix 60%	Affinity 28% EpiCord 22% Grafix 41%		

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

Limitations in study design and conduct are shown in Table 3. Studies without notable limitations reported power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and ITT analysis. Limitations from the RCT with AmnioExcel (Snyder et al 2016)[17,] preclude conclusions for this product.

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Table 3. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Cazzell et al (2024)[12,]		1, 2. No blinding of patients or investigators.				
Serena et al (2020)[13,]	3. The randomization process and allocation concealment were not described	1, 2. No blinding of patients or investigators. Assessors were blinded.		1. Although ITT analysis, there was substantial missing data for depth and volume with the digital analysis system.		
Ananian et al (2018)[14,]		2, 3. No blinding for outcomes assessment.				
Tettelbach et al (2018)[15,]		1, 2, 3. No blinding.				
DiDomenico et al (2018)[16,]						
Snyder et al (2016)[17,]				1. There was high loss to follow-up with discontinuation of 8 of 29 participants.	1. Power analysis was not reported.	
Zelen et al (2015, 2016)[18,19,]				1. Thirteen of 35 patients in the SOC group exited the study at 6 weeks due to less than 50% healing, which may have affected the 12-week results.		
Tettelbach et al (2019)[20,]		1, 2. No blinding of patients or investigators. Assessors were blinded.				
Lavery et al (2014)[21,]						

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

Prospective Single-arm or Registry Studies

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

Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about a third (n=47) were diabetic foot wounds.[22,] 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.

Frykberg et al (2016) 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.[23,]

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

Study	Study Design	Participants	Treatment Delivery
Smiell et al (2015)[22,]	Multicenter Registry	Various chronic wounds: 47 diabetic foot wounds, 20 pressure ulcers, and 89 venous ulcers; 28 had failed prior treatment with advanced biologic therapies (Apligraf, Dermagraft, or Regranex)	Biovance
Frykberg et al (2016)[23,]	Prospective multi-center single-arm study	31 patients with chronic complex diabetic foot wounds with exposed tendon or bone	Grafix weekly until closure or 16 weeks

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

Study	Treatment	Wounds Closed	Mean Time to Closure	Number of Applications
Smiell et al (2015)[22,]	Biovance	41.6%	8 weeks	2.4
Frykberg et al (2016)[23,]	Grafix	59.3%	9 weeks	9

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Section Summary: Diabetic Lower-Extremity Ulcers
For individuals who have non-healing diabetic lower-extremity ulcers who receive a formulation of HAM or placental membrane (ie, Affinity, AmnioBand Membrane, AmnioExcel, Biovance, EpiCord, EpiFix, Grafix, NuShield), the evidence includes RCTs. The RCTs evaluating amniotic and placental membrane products for the treatment of non-healing (<20% healing with ≥2 weeks of standard care) diabetic lower-extremity ulcers have compared HAM with standard care or with an established advanced wound care product. These trials used wound closure as the primary outcome measure, and some included power analysis, blinded assessment of wound healing, and ITT analysis. For the HAM products that have been sufficiently evaluated (ie, Affinity, AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix, NuShield), 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 individuals who have lower-extremity ulcers due to venous insufficiency is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

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

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

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

Outcomes
The primary endpoints of interest for trials of wound closure are as follows, consistent with guidance from the FDA for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds:
- Incidence of complete wound closure.
- Time to complete wound closure (reflecting accelerated wound closure).
- Incidence of complete wound closure following surgical wound closure.
- Pain control.

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

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

REVIEW OF EVIDENCE

Systematic Reviews
Zheng et al (2026) conducted a systematic review and meta-analysis that included a VLU subgroup of 3 RCTs involving 253 patients (Serena 2014, Bianchi 2018, Serena 2022).[9,] All three trials used dehydrated human amnion/chorion membrane (EpiFix or AmnioBand) with multilayer compression therapy. Pooled analysis showed that HAM therapy was associated with significantly higher rates of complete wound closure compared with standard care without HAM (RR 1.71; 95% CI: 1.26–2.32; I^2 = 19%; moderate-quality evidence). No statistically significant difference was observed between groups in the incidence of wound-related infections (RD = −0.05; 95% CI: −0.16 to 0.07; I^2 = 0%; low-quality evidence).

Randomized Controlled Trials
Three RCTs, 2 using EpiFix and 1 using AmnioBand, were identified on HAM for venous leg ulcers. Serena et al (2014) reported on an industry-sponsored multicenter open-label RCT that compared EpiFix d-HAM plus compression therapy with compression therapy alone for venous leg ulcers (see Tables 6 and 7).[24,] The primary outcome in this trial was the proportion of patients with 40% wound closure at 4 weeks, which was achieved by about twice as many patients in the combined EpiFix group compared with the control group (see Table 8). However, a similar percentage of patients in the combined EpiFix group and the control group achieved complete wound closure during the 4-week study. There was no significant difference in healing for wounds given 1 versus 2 applications of amniotic membrane (62% vs. 63%, respectively). Strengths of this trial included adequate power and ITT analysis with last observation carried forward. Limitations included the lack of blinding for wound evaluation and use of 40% closure rather than complete closure. A 2015 retrospective study of 44 patients from this RCT (31 treated with amniotic membrane) found that wounds with at least 40% closure at 4 weeks (n=20) had a closure rate of 80% by 24 weeks; however, this analysis did not take into account additional treatments after the 4-week randomized trial period.

A second industry-sponsored, multicenter, open-label RCT (Bianchi et al [2018; 2019]) evaluated the time to complete ulcer healing following weekly treatment with EpiFix d-HAM plus compression therapy or compression wound therapy alone (see Tables 6 and 7).[25,26,] Patients treated with EpiFix had a higher probability of complete healing by 12 weeks, as adjudicated by

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blinded outcome assessors (hazard ratio, 2.26; 95% confidence interval [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.

Serena et al (2022) reported an industry-sponsored, multicenter, open-label RCT comparing once- or twice-weekly applications of HAM (AmnioBand Membrane) plus compression bandaging with compression bandaging alone in patients with chronic venous leg ulcers (Tables 6 through 9).[27,] This HAM is a dehydrated aseptically processed product without terminal irradiation for sterilization. It is purported to retain the structural properties of the extracellular matrix that enhances wound healing. There were no significant differences in the proportion of wounds with percentage area reduction 40 percent at 4 weeks between all three study groups. A significantly greater proportion of patients assigned to weekly or twice-weekly HAM achieved the primary endpoint of blinded assessor-confirmed complete wound healing after 12 weeks of study treatment (75%) than those assigned to compression bandaging alone (30%; p=.001). Receiving HAM was independently associated with odds of complete healing at 12 weeks after adjusting for baseline wound area (odds ratio, 8.7; 95% CI, 2.2 to 33.6). Median reduction in wound area from baseline was also significantly greater in patients assigned to HAM therapy (100%; interquartile range, 5.3%) than those assigned to compression bandaging alone (75%; interquartile range, 68.7%; p=.012). Adverse events were reported in 55%, 60%, and 75% of the once-weekly HAM, twice-weekly HAM, and standard-of-care groups, respectively. The most commonly reported adverse events were wound-related infections (36.7%) and new ulcer (31.6%). No adverse events were attributed to study treatment.

Dhillon et al (2025) conducted a multicenter, prospective, randomized, open-label, controlled trial evaluating lyopreserved placental membrane (LPM; GrafixPL PRIME, Q4133) plus standard compression therapy versus standard compression therapy alone in 200 patients with chronic VLUs at 30 US sites (NCT03629236).[28,] Patients were enrolled between June 2018 and November 2020. Eligible wounds were located below the knee, measured 1–25 cm², and had been present for 4–52 weeks with at least 2 weeks of prior compression therapy. LPM was applied weekly for up to 12 weeks. The mean baseline wound size was 5.87 cm² (control) and 5.95 cm² (LPM). In the ITT population, complete wound closure at 12 weeks was 50.5% in the LPM group compared with 39.8% in the control group; this difference was not statistically significant (RR 1.27; 95% CI: 0.93–1.73). Subgroup analysis by initial wound size demonstrated that for wounds ≥3 cm² (n=130), LPM was associated with a statistically significant 72% higher probability of wound closure (RR 1.72; 95% CI: 1.03–2.86; p<0.05). Sensitivity analyses further supported this finding (wounds ≥4 cm²: RR 2.31; wounds ≥5 cm²: RR 2.74; both p<0.05). For wounds <3 cm², no

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significant difference was observed between groups (RR 1.11). LPM-treated wounds demonstrated significantly greater wound area reduction at all timepoints (73.6% vs 43.6% at 12 weeks, p<0.005) and 1.4–1.8-fold faster rates of wound progression. The LPM group showed a statistically significant fivefold improvement in quality of life physical symptom and daily living scores over baseline compared with the control group (p<0.05). Adverse event rates were comparable between groups (14% LPM vs 17% control). Limitations include the open-label design, failure of the primary endpoint in the overall ITT population, the post-hoc nature of the wound-size subgroup analysis, lack of wound-size stratification at randomization, and industry sponsorship (Osiris Therapeutics/Smith & Nephew). A high SOC closure rate in smaller wounds (>60% for wounds <3 cm²) likely diluted the overall treatment effect.

Table 6. Summary of Key RCT Characteristics

					Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Serena et al (2014)[24,]	U.S.	8	2012-2014	84 patients with a full-thickness chronic VLU between 2 and 20 cm^2 treated for at least 14 d	1 (n=26) or 2 (n=27) applications of EpiFix plus standard wound therapy (n=53)	Standard wound therapy (debridement with alginate dressing and compression) (n=31)
Bianchi et al (2018, 2019)[25,26,]	U.S.	15	2015-2017	128 patients with a full-thickness VLU of at least 30-d duration	Weekly EpiFix plus moist wound therapy plus compression (n=64 ITT; 52 PP)	Moist wound therapy plus compression (n=64 ITT; 57 PP)
Serena et al (2022)[27,]	U.S.	8	2015-2019	101 patients with full-thickness VLU (≥2 to <20 cm^2) of >1-mo duration and failing >1 mo of SOC treatment	Once-weekly (n=20) or twice-weekly (n=20) applications of Amnioband plus SOC compression bandaging	SOC compression bandaging alone (n=20)
Dhillon et al (2025)[28,]	U.S.	30	2018–2020	200 patients with chronic VLU (1–25 cm²), 4–52 wk duration, below the knee, with ≥2 wk prior compression	Weekly LPM (GrafixPL PRIME) plus standard compression therapy (n=100; 99 ITT)	Standard compression therapy alone (n=100; 98 ITT)

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

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Table 7. Summary of Key RCT Results

Study	Percent With 40% Wound Closure at 4 Weeks	Percent With Complete Wound Closure at 4 Weeks	Complete Wound Closure at 12 Weeks, n (%)		Median (IQR) Percentage Area Reduction at 12 Weeks	Complete Wound Closure at 16 Weeks, n (%)		
			PP	ITT	ITT	PP	ITT	
Serena et al (2014)[24,]								
EpiFix	62	11.3						
Control	32	12.9						
p-Value	.005							
Bianchi et al (2018, 2019)[25,26,]								
EpiFix			31 (60)	32 (50)		37 (71)	38 (59)	
Control			20 (35)	20 (31)		25 (44)	25 (39)	
p-Value			.013	.047		.007	.034	
Serena et al (2022)[27,]								
Amnioband	75			30 (75)	100 (5.3)			
Control	65			6 (30)	75 (68.7)			
p-Value				.001	.012			
Dhillon et al (2025)[28,]								
GrafixPL PRIME (LPM)	NR	NR	—	50/99 (50.5%)	NR	—	—	24/55 (43.6%)
Control	NR	NR	—	39/98 (39.8%)	NR	—	—	16/63 (25.4%)
RR (95% CI); p-Value	—	—	—	1.27 (0.93–1.73); NS	—	—	—	1.72 (1.03–2.86); p<.05

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

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Table 8. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Serena et al (2014)[24,]					
Bianchi et al (2018, 2019)[25,26,]					1. Advanced wound therapy was allowed in the control group before the primary endpoint was reached.
Serena et al (2022)[27,]					
Dhillon et al (2025)[28,]				5. Primary endpoint (complete closure, all wounds) did not reach significance; clinically significant subgroup difference (≥3 cm²) was not pre-specified.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

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

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

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

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Table 9. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Serena et al (2014)[24,]						
Bianchi et al (2018, 2019)[25,26,]		1. Open-label with blinded assessors.		1. Unequal exclusion of patients in the 2 groups in the per-protocol analysis. 3. Advanced wound therapy was allowed in the control group before the primary endpoint was reached.		
Serena et al (2022)[27,]		1. Open-label with blinded assessors.				4. Incomplete reporting of regression including wound duration.
Dhillon et al (2025)[28,]		1. Open-label; wound closure confirmed by blinded evaluators at Wound Core Lab.			3. Power calculation assumed 45% vs 25% closure; SOC arm achieved ~40%, exceeding assumptions. Study may have been underpowered for the observed effect size in the overall population.	4. Primary ITT analysis was not significant; reported significant result derives from post-hoc subgroup analysis by wound size without pre-specified stratification at randomization. Outlier trimming applied (99.9th percentile).

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

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

Biovance

As described above, Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about half (n=89) were venous ulcers.[22,] Of the 179 treated, 28 (16%) ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of 8 weeks and a mean of 2.4 amniotic membrane applications. However, without a control group, the percentage of wounds that would have healed with SOC is unknown.

Section Summary: Lower-Extremity Ulcers Due to Venous Insufficiency

The evidence on HAM for the treatment of venous leg ulcers includes 2 multicenter RCTs with EpiFix and 1 multicenter RCT with AmnioBand Membrane. 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. An additional RCT evaluated outcomes using AmnioBand Membrane, a dehydrated aseptically processed product without terminal irradiation for sterilization that s purported to retain the structural properties of the extracellular matrix that enhances wound healing. The application of HAM plus SOC resulted in significantly higher rates of complete wound closure at 12 weeks compared with SOC alone. This endpoint was confirmed by a blinded assessor panel in the ITT population. All 60 subjects received the allocated intervention, and none were lost to follow-up or exited because of protocol deviation. Adverse event rates were numerically greater in the biweekly HAM group but no adverse events were attributed to appeared to be similar between groups.

OSTEOARTHRITIS

Systematic Reviews

Hou et al (2025) conducted a systematic review and meta-analysis evaluating the effectiveness of amnion allograft injections in patients with degenerative musculoskeletal diseases, including 3 studies in knee OA (Farr 2019, Gomoll 2021, Olufade 2022; products: ReNu amniotic suspension allograft and an amniotic dehydrated cell concentrate) and 4 studies in plantar fasciitis.[29,] Pooled analysis across all 7 studies (590 participants) showed significant improvements in pain, physical

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function, and quality of life compared with control groups; however, OA and plantar fasciitis were pooled together for all outcomes except overall pain. In the disease-specific subgroup analysis for knee OA, the pain effect was marginally significant (SMD: −0.483; p=.049) based on 3 small studies. Only 3 of 7 included studies had a low overall risk of bias, heterogeneity was high for several outcomes, and all studies originated from the United States.

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.[30,] A single intra-articular injection of the suspension was used, with follow-up at 1 and 2 weeks and at 3, 6, and 12 months posttreatment. Outcomes included the Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee scale, and a numeric pain scale. Statistical analyses were not performed for this small sample. No adverse events, aside from a transient increase in pain, were noted. RCTs are in progress.

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

BioDRestore in Patients with Knee Osteoarthritis
Pill et al (2025) conducted a double-blind, randomized, prospective study comparing the effectiveness of amniotic tissue injections versus corticosteroid injections for pain relief and function in patients with severe knee osteoarthritis (N=81).[31,] Patients were randomized to receive either a single injection of BioDRestore (amniotic tissue) or triamcinolone acetonide (corticosteroid). Outcome measures included the Knee Injury and Osteoarthritis Outcome Score (KOOS), Single Alpha Numeric Evaluation (SANE), visual analog scale (VAS) pain, Lysholm Rating, and Veterans-Rand-12 scales collected at baseline, 6 weeks, and 3, 6, and 12 months postinjection. The study found no overall difference in function or pain relief between amniotic tissue and corticosteroid injections for patients with knee osteoarthritis. Integra LifeSciences, the maker of the product used in this study, was issued an FDA warning letter in 2024. Details are described in the Regulatory Section.

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 individuals who have plantar fasciitis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

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

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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: VAS for pain and function measured by the Foot Functional Index.

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

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

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

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

Systematic Review
A 2016 network meta-analysis of 22 RCTs (total N=1216 patients) compared injection therapies for plantar fasciitis.[32,] In addition to c-HAM and micronized d-HAM/chorionic membrane, treatments included corticosteroids, botulinum toxin type A, autologous whole blood, platelet-rich plasma, nonsteroidal anti-inflammatory drugs, dry needling, dextrose prolotherapy, and polydeoxyribonucleotide. Placebo arms included normal saline, local anesthetic, sham dry needling, and tibial nerve block. Analysis indicated d-HAM had the highest probability for improvement in pain and composite outcomes in the short-term ; however, this finding was based only on a single RCT. Outcomes at 2 to 6 months (7 RCTs) favored botulinum toxin for pain and patient recovery plan for composite outcomes.

Hou et al (2025) conducted a systematic review and meta-analysis that included 4 studies evaluating amnion allograft injections for plantar fasciitis (Zelen 2013, Hanselman 2014, Cazzell 2018, Matthews 2023; products included micronized dHACM [AmnioFix] and cryopreserved amniotic membrane).[29,] In the disease-specific subgroup analysis for overall pain, the plantar

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fasciitis subgroup showed a significant effect favoring amnion injection over control (SMD: −1.313; p=.002). However, all other outcomes (physical function, quality of life, and pain at individual timepoints) were reported only as pooled estimates combining plantar fasciitis and knee OA studies and cannot be attributed to plantar fasciitis alone. Approximately half of the included studies had an uncertain risk of bias, and sample sizes were small.

Randomized Controlled Trials

Zelen et al (2013) reported a preliminary study with 15 patients per group (placebo, 0.5 mL, and 1.25 mL) and 8-week follow-up.[33,] A subsequent RCT by Cazell et al (2018) enrolled 145 patients and reported 3-month follow-up (see Table 10).[34,] In Cazzell et al (2018) amniotic membrane injection led to greater improvements in the VAS for pain and the Foot Functional Index between baseline and 3 months (see Table 11) compared to controls. VAS at 3 months had decreased to 17.1 in the AmnioFix group compared to 38.8 in the placebo control group, which would be considered a clinically significant difference.

Table 10. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator Intervention
Cazzell et al (2018)[34,];AIPF004 (NCT02427191)	U.S.	14	2015-2018	Adult patients with plantar fasciitis with VAS for pain >45	n=73; Single injection of AmnioFix 40 mg/mL	n = 72; Single injection of saline

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

Table 11. Summary of Key RCT Results

Study	Change in VAS-Pain Between Baseline and 3 mo (95% CI)	Change in FFI-R Between Baseline and 3 mo (95% CI)	Patients with Adverse Events up to 3 mo n(%)	Patients with Serious Adverse Events up to 3 mo n(%)
Cazzell et al (2018)[34,]; AIPF004	N=145	N=145	N=145	N=145
AmnioFix	54.1 (48.3 to 59.9)	35.7 (30.5 to 41.0)	30 (41.1%)	1 (0.6%)
Placebo	31.9 (24.8 to 39.1)	22.2 (17.1 to 27.4)	39 (54.2%)	3 (1.8%)
Diff (95% CI)	22.2 (13.1 to 31.3)	13.5 (6.2 to 20.8)		
p-Value	<.001	<.001		

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

Limitations in relevance and design and conduct of this publication are described in Tables 12 and 13. The major limitation of the study is the short-term follow-up, which the authors note is continuing to 12 months. The authors stated that extended follow-up would be reported in a subsequent publication; no subsequent publications have been identified for this trial.

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Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Cazzell et al (2018)[34]; AIPF004			3. Placebo injections were used. A control delivered at a similar intensity as the investigational treatment would be corticosteroid injections.		1, 2. Follow-up to 12 mo to be reported in a subsequent publication.

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

Table 13. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Cazzell et al (2018)[34]; AIPF004		1. Single blinded trial, although outcomes were self-reported by blinded patients.		1. Only the first 3 months of 12-month follow-up were reported.		

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

Section Summary: Plantar Fasciitis

The evidence on injection of amniotic membrane for the treatment of plantar fasciitis includes preliminary studies and a larger (N =145) patient-blinded comparison of micronized injectable-HAM and placebo control. Injection of micronized amniotic membrane resulted in greater

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improvements in VAS for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is this is an interim report of 3 months' results. The authors noted that 12-month follow-up will be reported in a subsequent publication. No additional publications have been identified as of the latest update.

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

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

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

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

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

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

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

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

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

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

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

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

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

Suri et al (2013) reported on 11 eyes of 11 patients with neurotrophic keratopathy that had not responded to conventional treatment.[35,] The mean duration of treatment prior to ProKera insertion was 51 days. Five of the 11 patients (45.5%) were considered to have had a successful outcome.

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

CORNEAL ULCERS AND MELTS THAT DO NOT RESPOND TO INITIAL MEDICAL THERAPY

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

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

Populations
The relevant population of interest is individuals 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.

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

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

Review of Evidence
Liu et al (2019) conducted a systematic review of 17 studies (390 eyes) of amniotic membrane for corneal ulcers.[36,] All but one of the studies was conducted outside of the U.S. There was one RCT with 30 patients, the remainder of the studies were prospective or retrospective case series. Corneal healing was obtained in 97% (95% CI , 0.94 to 0.99 ; p=.089) of patients evaluated. In the 12 studies (222 eyes) that reported on vision, the vision improvement rate was improved in 113 eyes (53% ; 95% CI , 0.42 to 0.65 ; p<.001).

Yin et al (2020) compared epithelialization and visual outcomes of 24 patients with corneal infectious ulcers and visual acuity of less than 20/200 who were treated with (n=11) or without (n=13) self-retained amniotic membrane.[37,] Utilization of amniotic membrane was initiated in their institution in 2018, allowing a retrospective comparison of the 2 treatment groups. Complete epithelialization occurred more rapidly (3.56 ± 1.78 weeks vs. 5.87 ± 2.20 weeks ; p=.01) and was reached in significantly more patients (72.7% vs. 23.1% ; p=.04). The group treated with amniotic membrane plus the standard therapy had more patients with clinically significant (>3 lines) improvement in visual acuity (81.8% vs. 38.4% ; p=.047) and greater total improvement in visual acuity (log MAR, 0.7 ± 0.6 vs. 1.6 ± 0.9 ; p=.016).

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

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

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

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Clinical Context and Therapy Purpose
The purpose of HAM in individuals who have active inflammation after a corneal transplant is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

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

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

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

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

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

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

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

Review of Evidence
No evidence was identified for this indication.

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

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

Clinical Context and Therapy Purpose
The purpose of HAM in individuals 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.

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

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

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

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

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

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

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

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

Review of Evidence
Dos Santos Paris et al (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy.[38,] Forty patients with pain from bullous keratopathy who were either waiting for a corneal transplant or had no potential for sight in the affected eye were randomized to the 2 treatments. Symptoms had been present for approximately 2 years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with use of HAM only if the pain did not resolve.

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

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

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

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

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

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

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

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

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

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

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

Review of Evidence
No RCTs were identified on HAM for limbal stem cell deficiency.

Keirkhah et al (2008) reported on the use of HAM in 11 eyes of 9 patients who had limbal stem cell deficiency.[39,] 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.[40,] Following treatment with ProKera, 3 of the 6 patients had a smooth corneal surface and

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improved vision to 20/40.[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 RCTs were identified on HAM for partial limbal stem cell deficiency. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus.

MODERATE OR SEVERE STEVENS-JOHNSON SYNDROME

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

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

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

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

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

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

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

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

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

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Review of Evidence
One RCT from India by Sharma et al (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or medical therapy alone.[41,] 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=.042), better tear breakup time (p=.015), improved Schirmer test results (p<.001), and less conjunctival congestion (p=.03). In the c-HAM group at 180 days, there were no cases of corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. These outcomes are dramatically better than those in the medical therapy alone group, which had 11 (44%) cases with corneal haze (p=.001), 6 (24%) cases of corneal vascularization and conjunctivalization (p=.03), and 6 (24%) cases of trichiasis and metaplastic lashes.

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

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

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

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

Populations
The relevant population of interest is individuals 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.

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

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

Review of Evidence
Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease.[42,] They noted that c-HAM has been available since 1995, and has become an established treatment for persistent epithelial defects and ulceration refractory to conventional therapy. However, there was a lack of controlled studies due to the rarity of the diseases and the absence of standard therapy. They identified 661 reported cases in the peer-reviewed literature. Most cases reported assessed the conjunctival indications of pterygium, scars and symblepharon, and corneal indications of acute chemical injury and postinfectious keratitis.

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

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

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

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

Populations
The relevant population of interest is individuals 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.

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

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

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

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

Review of Evidence
John et al (2017) reported on an RCT with 20 patients with moderate-to-severe dry eye disease who were treated with Prokera c-HAM or maximal conventional treatment.[43,] The c-HAM was applied for an average of 3.4 days (range, 3 to 5 days), while the control group continued treatment with artificial tears, cyclosporine A, serum tears, antibiotics, steroids, and nonsteroidal anti-inflammatory medications. The primary outcome was an increase in corneal nerve density. Signs and symptoms of dry eye disease improved at both 1-month and 3-month follow-ups in the c-HAM group but not in the conventional treatment group. For example, pain scores decreased from 7.1 at baseline to 2.2 at 1 month and 1.0 at 3 months in the c-HAM group. In vivo confocal microscopy, reviewed by masked readers, showed a significant increase in corneal nerve density in the study group at 3 months, with no change in nerve density in the controls. Corneal sensitivity was similarly increased in the c-HAM group but not in controls.

The treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study (McDonald et al [2018]) was a retrospective series of 84 patients (97 eyes) with severe dry eye despite maximal medical therapy who were treated with Prokera self-retained c-HAM.[44,] 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.

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

MODERATE OR SEVERE ACUTE OCULAR CHEMICAL BURNS

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

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

Populations
The relevant population of interest is individuals 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.

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

Review of Evidence
An RCT of 100 patients with chemical or thermal ocular burns was published by Tandon et al (2011).[45,] Half of the patients (n=50) had moderate ocular burns and the remainder (n=50) had

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severe ocular burns. All but 8 of the patients had alkali or acid burns. Patients were randomized to HAM transplantation plus medical therapy or medical therapy alone. Epithelial healing, which was the primary outcome, was improved in the group treated with HAM, but there was no significant difference between the 2 groups for final visual outcome, symblepharon formation, corneal clarity or vascularization.

A second RCT that compared amniotic membrane plus medical therapy (30 eyes) to medical therapy alone (30 eyes) for grade IV ocular burn was reported by Eslani et al (2018).[46,] Medical therapy at this tertiary referral hospital included topical preservative-free lubricating gel and drops, chloramphenicol, betamethasone, homatropine, oral vitamin C, and doxycycline. There was no significant difference in the time to epithelial healing (amniotic membrane: 75.8 vs. 72.6 days) or in visual acuity between the 2 groups (2.06 logMAR for both groups). There was a trend for a decrease in corneal neovascularization (p=.108); the study was not powered for this outcome.

A third RCT by Tamhane et al (2005) found no difference between amniotic membrane and medical therapy groups in an RCT of 37 patients with severe ocular burns.[47,]

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

CORNEAL PERFORATION WHEN CORNEAL TISSUE IS NOT IMMEDIATELY AVAILABLE

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

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

Populations
The relevant population of interest is individuals 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.

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

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

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

Review of Evidence
No RCTs were identified on corneal perforation.

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

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

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

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

Populations
The relevant population of interest is individuals 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.

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

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

Review of Evidence
RCTs have been reported on the use of amniotic membrane following pterygium repair. In 2013, the American Academy of Ophthalmology published a technology assessment on options and adjuvants for pterygium surgery.[48,] Reviewers identified 4 RCTs comparing conjunctival or limbal autograft procedure with amniotic membrane graft, finding that conjunctival or limbal autograft was more effective than HAM graft in reducing the rate of pterygium recurrence. A 2016 Cochrane review of 20 RCTs (total N=1866 patients) arrived at the same conclusion.[49,]

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

REPAIR FOLLOWING MOHS MICROSCOPIC SURGERY

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

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

Populations
The relevant population of interest is individuals 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 (ie, the wound is left open to heal by granulation, contraction, and epithelialization) is a nonsurgical option for certain defects.

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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.

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

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

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

Review of Evidence
No RCTs were identified for this indication.

Nonrandomized Studies
Toman et al (2022) conducted an observational study that compared repair using a dehydrated human amnion/chorion membrane product (Epifix) with surgical repair using autologous tissue in patients who underwent same-day repair following Mohs microsurgery for removal of skin cancer on the face, head, or neck (Table 14).[50,] Propensity-score matching using retrospective data from medical records was used to identify 143 matched pairs. The primary endpoint was the incidence of postoperative morbidity, including the rate of infection, bleeding/hematoma, dehiscence, surgical reintervention, or development of a nonhealing wound. Postoperative cosmetic outcomes were assessed at 9 months or later and included documentation of suboptimal scarring, scar revision treatment, and patient satisfaction.

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

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potential for bias due to missing data. Additionally, the study's relevance is limited due to a lack of diversity in the study population and no comparison to non-surgical treatment options.

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

Study	Study Type	Country	Dates	Participants	Repair using dHACM	Repair using autologous tissue	Follow-Up
Toman et al (2022)[50,]	Retrospective, observational Propensity-score matching used to identify matched pairs	US	2014-2018	Patients who underwent Mohs microsurgery for removal of a basal or squamous cell carcinoma and required same day repair for moderate- to high-risk defects on the face, head, and neck. Mean age 78.0 years; 76.9% male 100% white	n=143	n=143	Unclear; 9 months or later for postoperative cosmetic outcomes.

dHACM: dehydrated human amnionic/chorionic membrane.

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

Study	dHACM repair n=143	Autogolous tissue Repair n=143	P
Toman et al (2022)[50,]			
Experienced no complications, n (%)	140 (97.9)	102 (71.3)	<.0001
Infection, n (%)	3 (2.0)	15 (10.0)	.004
Bleeding or hematoma, n (%)	0 (0.0)	7 (5.0)	.015
Wound dehiscence, n (%)	0 (0.0)	4 (3.0)	.122
Surgical reintervention, n (%)	0 (0.0)	11 (8.0)	.0007
Nonhealing wound, n (%)	0 (0.0)	5 (3.5)	.060
Poor scar cosmesis, n (%)	0 (0.0)	21 (15.0)	<.0001

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

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

Table 16. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Toman et al (2022)[50,]	4. Study participants were 100% White, over two-thirds male.		2. No comparison to non-surgical options (eg, second intention healing).	1. Not all outcomes mentioned in methods had results reported (eg, patient satisfaction with scar appearance).	

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

Table 17. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Toman et al (2022)[50,]	1. Not randomized.	1, 2. Not blinded.		7. Data extracted from medical records could be incomplete/ inaccurate; 10 of 153 patients excluded because no match identified.		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

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

Section Summary: Repair Following Mohs Microscopic Surgery

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

SUPPLEMENTAL INFORMATION

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

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2019 Input

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

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

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.
- Corneal ulcers and melts that do not respond to initial medical therapy. Non-sutured HAM in an office setting would be preferred to avoid a delay in treatment associated with scheduling a surgical treatment.
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment.

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- 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.

Further details from clinical input are included in the Appendix.

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

Society for Vascular Surgery et al.
In 2016, the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine made the following recommendation: "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amnionic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."[51,]

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.[34,] 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.

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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 lymphocyte function-associated antigen-1 (LFA-1) antagonist drugs (such as lifitegrast).
- Oral macrolide or tetracycline antibiotics.

Step 3:
If above options are inadequate consider:

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

Step 4:
If above options are inadequate consider:

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

Wound Healing Society

In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.[52,] The Society concluded that there was level 1 evidence that cellular and acellular skin equivalents improve diabetic foot ulcer healing, noting that, "healthy living skin cells assist in healing DFUs [diabetic foot ulcers] by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed." References from 2 randomized controlled trials on amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

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Some currently unpublished trials that might influence this review are listed in Table 18.

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT07159282	A Multicenter, Prospective, Controlled Clinical Trial Evaluating the Efficacy of a Single Layer Placental-based Allograft and Standard of Care in the Management of Nonhealing Diabetic Foot Ulcers	60	Aug 2027
NCT06704893	The Efficacy of Amniotic Suspension Allograft Injection in the Treatment of Knee Osteoarthritis: a Randomized Double-blind Controlled Trial	160	Dec 2027
NCT06600724[a]	A Multicenter, Prospective, Randomized Controlled Modified Platform Trial Evaluating PURION Processed Lyophilized Human Amnion/Chorion Membrane (ppLHACM) and Standard of Care Versus Standard of Care Alone in the Treatment of Nonhealing Diabetic Foot Ulcers	170	Aug 2026
NCT04457752[a]	A Randomised Controlled Multicentre Clinical Trial, Evaluating the Efficacy of Dual Layer Amniotic Membrane (Artacent®) and Standard of Care Versus Standard of Care Alone in the Healing of Chronic Diabetic Foot Ulcers	124	Mar 2023
NCT03390920[a]	Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions	200	Jan 2030
NCT04553432[a]	Dry Eye OmniLenz Application of Omnigen Research Study	79 (actual)	Jul 2023
NCT05842057[a]	Phase 2 Randomized Trial: Human Amnion Membrane Allograft and Early Return of Erectile Function After Radical Prostatectomy (HAMMER)	118 (actual)	Aug 2028
NCT06150209[a]	A Controlled Data Collection and Prospective Treatment Study to Evaluate the Efficacy of Vendaje in the Management of Foot Ulcers in Diabetic Patients	100	Jun 2025
NCT05796765[a]	A Phase 2B, Prospective, Double-Blind, Randomized Controlled Trial of the Micronized DHACM Injectable Product Compared to Saline Placebo Injection for the Treatment of Osteoarthritis of the Knee	43 (terminated)	Dec 2023
Unpublished			
NCT03855514[a]	A Prospective, Multicenter, Randomized, Controlled Clinical Study Of NuShield® and Standard of Care (SOC) Compared to SOC Alone For The Management Of Diabetic Foot Ulcers	200	Dec 2021
NCT04612023	A Prospective, Double-Blinded, Randomized Controlled Trial of an Amniotic Membrane Allograft Injection Comparing Two Doses (1 mL and 2 mL Injection) and a Placebo (Sterile Saline) in the Treatment of Osteoarthritis of the Knee	90	Jul 2022

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04599673	Prospective Analysis of Intraoperative AMNIOGEN® Injection in Patients With Rotator Cuff Tear	100	Sep 2022
NCT04636229[a]	A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients With Osteoarthritis of the Knee	516 (actual)	Aug 2025
NCT06000410[a]	A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients With Osteoarthritis of the Knee	594 (actual)	Nov 2025

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

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

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

CPT/HCPCS	
65778	Placement of amniotic membrane on the ocular surface; without sutures
65779	Placement of amniotic membrane on the ocular surface; single layer, sutured
A2001	Innovamatrix ac, per square centimeter
A2049	Theracor, per square centimeter (add-on, list separately in addition to primary procedure)
A2035	Corplex p or theracor p or allacor p, per milligram
Q4132	Grafix Core and GrafixPL Core, per sq cm
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq cm
Q4137	AmnioExcel, AmnioExcel Plus or BioDExcel, per sq cm
Q4138	BioDFence DryFlex, per sq cm
Q4139	AmnioMatrix or BioDMatrix, injectable, 1 cc
Q4140	BioDFence, per sq cm
Q4145	EpiFix, injectable, 1 mg
Q4148	Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per sq cm
Q4150	AlloWrap DS or dry, per sq cm
Q4151	AmnioBand or Guardian, per sq cm
Q4153	Dermavest and Plurivest, per sq cm
Q4154	Biovance, per sq cm
Q4155	Neox Flo or Clarix Flo 1 mg
Q4156	Neox 100 or Clarix 100, per sq cm
Q4157	Revitalon, per sq cm
Q4159	Affinity, per sq cm
Q4160	Nushield, per sq cm
Q4162	WoundEx Flow, BioSkin Flow, 0.5 cc
Q4163	WoundEx, BioSkin, per sq cm
Q4168	AmnioBand, 1 mg
Q4169	Artacent wound, per sq cm
Q4170	Cygnus, per sq cm
Q4171	Interfyl, 1 mg
Q4173	PalinGen or PalinGen XPlus, per sq cm
Q4174	PalinGen or ProMatrX, 0.36 mg per 0.25 cc
Q4176	NeoPatch or Therion per sq. cm

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CPT/HCPCS	
Q4177	FlowerAmnioFlo, 0.1 cc
Q4178	FlowerAmnioPatch, per sq cm
Q4180	Revita, per square centimeter
Q4181	Amnio Wound, per sq cm
Q4183	Surgigraft, per sq cm
Q4184	Cellesta, per sq cm
Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4186	Epifix, per sq cm
Q4187	Epicord, per sq cm
Q4188	AmnioArmor, per sq cm
Q4189	Artacent AC, 1 mg
Q4190	Artacent AC, per sq cm
Q4191	Restorigin, per sq cm
Q4192	Restorigin, 1 cc
Q4194	Novachor, per sq cm
Q4198	Genesis Amniotic Membrane, per sq cm
Q4199	Cygnus matrix, per square centimeter
Q4201	Matrion, per sq cm
Q4204	XWRAP, per sq cm
Q4205	Membrane graft or membrane wrap, per square centimeter
Q4206	Fluid flow or fluid GF, 1 cc
Q4207	Carbon life, per square centimeter
Q4208	Novafix, per square centimeter
Q4209	Surgraft, per square centimeter
Q4211	Amnion bio or Axobiomembrane, per square centimeter
Q4212	Allogen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta cord, per square centimeter
Q4215	Axolotl ambient or axolotl cryo, 0.1 mg
Q4216	Artacent cord, per square centimeter
Q4217	Woundfix, BioWound, Woundfix Plus, BioWound Plus, Woundfix Xplus or BioWound Xplus, per square centimeter
Q4218	Surgicord, per square centimeter
Q4219	Surgigraft-dual, per square centimeter
Q4220	BellaCell HD or Surederm, per square centimeter
Q4221	Amniowrap2, per square centimeter
Q4223	Dermabind sl optic, per square centimeter
Q4224	Human health factor 10 amniotic patch (hhf10-p), per square centimeter
Q4225	Amniobind or dermabind tl, per square centimeter
Q4227	Corplex, per square centimeter
Q4229	Cogenex Amniotic Membrane
Q4230	Cogenex Flowable Amnion, per 0.5 cc
Q4232	Corplex, per square centimeter
Q4233	SurFactor or NuDyn, per 0.5 cc
Q4234	XCellerate, per square centimeter

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CPT/HCPCS	
Q4235	Amniorepair, altiply, per square centimeter
Q4236	Carepatch, per square centimeter (reactivated 01-01-2023)
Q4237	Cryo-Cord, per square centimeter
Q4238	Derm-maxx, per square centimeter
Q4239	Amnio-Maxx, Amnio-Maxx Lite, per square centimeter
Q4240	Amniotext patch, per square centimeter
Q4241	PolyCyte, per 0.5 mL
Q4242	AmnioCyte Plus, per 0.5 mL
Q4243	Amchomatrix, per square centimeter
Q4245	AmnioText, per square centimeter
Q4246	CoreText, ProText, per cc
Q4247	Amniotext patch, per square centimeter
Q4248	Dermacyte Matrix, per sq cm
Q4249	Amniply, for topical use only, per square centimeter
Q4250	Amnioamp-mp, per square centimeter
Q4251	Vim, per square centimeter
Q4252	Vendaje, per square centimeter
Q4253	Zenith amniotic membrane, per square centimeter.
Q4254	Novafix dl, per square centimeter
Q4255	Reguard, for topical use only, per square centimeter
Q4256	Mlg-complete, per square centimeter
Q4257	Relese, per square centimeter
Q4258	Enverse, per square centimeter
Q4259	Celera dual layer or celera dual membrane, per square centimeter
Q4260	Signature apatch, per square centimeter
Q4261	Tag, per square centimeter
Q4262	Dual layer impax membrane, per square centimeter
Q4263	Surgraft tl, per square centimeter
Q4264	Cocoon membrane, per square centimeter
Q4265	Neostim tl, per square centimeter
Q4266	Neostim membrane, per square centimeter
Q4267	Neostim dl, per square centimeter
Q4268	Surgraft ft, per square centimeter
Q4269	Surgraft xt, per square centimeter
Q4270	Complete sl, per square centimeter
Q4271	Complete ft, per square centimeter
Q4272	Esano a, per square centimeter
Q4273	Esano aaa, per square centimeter
Q4274	Esano ac, per square centimeter
Q4275	Esano aca, per square centimeter
Q4276	Orion, per square centimeter
Q4278	Epieffect, per square centimeter
Q4279	Vendaje ac, per square centimeter
Q4280	Xcell amnio matrix, per square centimeter
Q4281	Barrera sl or barrera dl, per square centimeter

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CPT/HCPCS	
Q4282	Cygnus dual, per square centimeter
Q4283	Biovance tri-layer or biovance 3l, per square centimeter
Q4284	Dermabind sl, per square centimeter
Q4285	Nudyn dl or nudyn dl mesh, per square centimeter
Q4286	Nudyn sl or nudyn slw, per square centimeter
Q4287	Dermabind dl, per square centimeter
Q4288	Dermabind ch, per square centimeter
Q4289	Revoshield + amniotic barrier, per square centimeter
Q4290	Membrane wrap-hydro, per square centimeter
Q4291	Lamellas xt, per square centimeter
Q4292	Lamellas, per square centimeter
Q4293	Acesso dl, per square centimeter
Q4294	Amnio quad-core, per square centimeter
Q4295	Amnio tri-core amniotic, per square centimeter
Q4296	Rebound matrix, per square centimeter
Q4297	Emerge matrix, per square centimeter
Q4298	Amniocore pro, per square centimeter
Q4299	Amnicore pro+, per square centimeter
Q4300	Acesso tl, per square centimeter
Q4301	Activate matrix, per square centimeter
Q4302	Complete aca, per square centimeter
Q4303	Complete aa, per square centimeter
Q4304	Grafix plus, per square centimeter
Q4305	American amnion ac tri-layer, per square centimeter
Q4306	American amnion ac, per square centimeter
Q4307	American amnion, per square centimeter
Q4308	Sanopellis, per square centimeter
Q4309	Via matrix, per square centimeter
Q4310	Procenta, per 100 mg
Q4311	Acesso, per square centimeter
Q4312	Acesso ac, per square centimeter
Q4313	Dermabind fm, per square centimeter
Q4314	Reeva ft, per square cenitmeter
Q4315	Regenelink amniotic membrane allograft, per square centimeter
Q4316	Amchoplast, per square centimeter
Q4317	Vitograft, per square centimeter
Q4318	E-graft, per square centimeter
Q4319	Sanograft, per square centimeter
Q4320	Pellograft, per square centimeter
Q4321	Renograft, per square centimeter
Q4322	Caregraft, per square centimeter
Q4323	Alloply, per square centimeter
Q4324	Amniotx, per square centimeter
Q4325	Acapatch, per square centimeter
Q4326	Woundplus, per square centimeter

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CPT/HCPCS	
Q4327	Duoamnion, per square centimeter
Q4328	Most, per square centimeter
Q4329	Singlay, per square centimeter
Q4330	Total, per square centimeter
Q4331	Axolotl graft, per square centimeter
Q4332	Axolotl dualgraft, per square centimeter
Q4333	Ardeograft, per square centimeter
Q4334	Amnioplast 1, per square centimeter
Q4335	Amnioplast 2, per square centimeter
Q4336	Artacent c, per square centimeter
Q4337	Artacent trident, per square centimeter
Q4338	Artacent velos, per square centimeter
Q4339	Artacent vericlen, per square centimeter
Q4340	Simpligraft, per square centimeter
Q4341	Simplimax, per square centimeter
Q4342	Theramend, per square centimeter
Q4343	Dermacyte ac matrix amniotic membrane allograft, per square centimeter
Q4344	Tri-membrane wrap, per square centimeter
Q4345	Matrix hd allograft dermis, per square centimeter
Q4346	Shelter dm matrix, per square centimeter
Q4347	Rampart dl matrix, per square centimeter
Q4348	Sentry sl matrix, per square centimeter
Q4349	Mantle dl matrix, per square centimeter
Q4350	Palisade dm matrix, per square centimeter
Q4351	Enclose tl matrix, per square centimeter
Q4352	Overlay sl matrix, per square centimeter
Q4353	Xceed tl matrix, per square centimeter
Q4354	Palingen dual-layer membrane and dual-layer palingen x membrane, per square centimeter
Q4355	Abiomend xplus membrane and abiomend xplus hydromembrane, per square centimeter
Q4356	Abiomend membrane and abiomend hydromembrane, per square centimeter
Q4357	Xwrap plus, per square centimeter
Q4358	Xwrap dual, per square centimeter
Q4359	Choriply, per square centimeter
Q4360	Amchoplast fd, per square centimeter
Q4361	Epixpress, per square centimeter
Q4362	Cygnus disk, per square centimeter
Q4363	Amnio burgeon membrane and hydromembrane, per square centimeter
Q4364	Amnio burgeon xplus membrane and xplus hydromembrane, per square centimeter
Q4365	Amnio burgeon dual-layer membrane, per square centimeter
Q4366	Dual layer amnio burgeon x-membrane, per square centimeter
Q4367	Amniocore sl, per square centimeter
Q4368	Amchothick, per square centimeter
Q4369	Amnioplast 3, per square centimeter

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CPT/HCPCS	
Q4370	Aeroguard, per square centimeter
Q4371	Neoguard, per square centimeter
Q4372	Amchoplast excel, per square centimeter
Q4373	Membrane wrap-lite, per square centimeter
Q4375	Duograft ac, per square centimeter
Q4376	Duograft aa, per square centimeter
Q4377	Trigraft ft, per square centimeter
Q4378	Renew ft matrix, per square centimeter
Q4379	Amniodefend ft matrix, per square centimeter
Q4380	Advograft one, per square centimeter
Q4382	Advograft dual, per square centimeter
Q4368	Amchothick, per square centimeter
Q4369	Amnioplast 3, per square centimeter
Q4370	Aeroguard, per square centimeter
Q4371	Neoguard, per square centimeter
Q4372	Amchoplast excel, per square centimeter
Q4373	Membrane wrap-lite, per square centimeter
Q4375	Duograft ac, per square centimeter
Q4376	Duograft aa, per square centimeter
Q4377	Trigraft ft, per square centimeter
Q4378	Renew ft matrix, per square centimeter
Q4379	Amniodefend ft matrix, per square centimeter
Q4380	Advograft one, per square centimeter
Q4382	Advograft dual, per square centimeter
Q4383	Axolotl graft ultra, per square centimeter
Q4384	Axolotl dualgraft ultra, per square centimeter
Q4385	Apollo ft, per square centimeter
Q4386	Acesso trifaca, per square centimeter
Q4387	Neothelium ft, per square centimeter
Q4388	Neothelium 4l, per square centimeter
Q4389	Neothelium 4l+, per square centimeter
Q4390	Ascendion, per square centimeter
Q4391	Amnioplast double, per square centimeter
Q4392	Grafix duo, per square centimeter
Q4393	Surgraft ac, per square centimeter
Q4394	Surgraft aca, per square centimeter
Q4395	Acelagraft, per square centimeter
Q4396	Natalin, per square centimeter
Q4397	Summit aaa, per square centimeter
Q4398	Summit ac, per square centimeter
Q4399	Summit fx, per square centimeter
Q4400	Polygon3 membrane, per square centimeter
Q4401	Absolv3 membrane, per square centimeter
Q4402	Xwrap 2.0, per square centimeter
Q4403	Xwrap dual plus, per square centimeter

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CPT/HCPCS	
Q4404	Xwrap hydro plus, per square centimeter
Q4405	Xwrap fenestra plus, per square centimeter
Q4406	Xwrap fenestra, per square centimeter
Q4407	Xwrap tribus, per square centimeter
Q4408	Xwrap hydro, per square centimeter
Q4409	Amniomatrixf3x, per square centimeter
Q4410	Amchomatrixdl, per square centimeter
Q4411	Amniomatrixf4x, per square centimeter
Q4412	Choriofix, per square centimeter
Q4413	Cygnus solo, per square centimeter
Q4414	Simplichor, per square centimeter
Q4415	Alexiguard sl-t, per square centimeter
Q4416	Alexiguard tl-t, per square centimeter
Q4417	Alexiguard dl-t, per square centimeter
Q4418	Biolab membrane wrap flow, per square centimeter (add-on, list separately in addition to primary procedure)
Q4419	Biolab membrane wrap lite flow, per square centimeter (add-on, list separately in addition to primary procedure)
Q4420	Nuform, per square centimeter
Q4421	Biolab membrane wrap solo, per square centimeter (add-on, list separately in addition to primary procedure)
Q4422	A/c wrap, per square centimeter (add-on, list separately in addition to primary procedure)
Q4423	Biolab tri-membrane wrap flow, per square centimeter (add-on, list separately in addition to primary procedure)
Q4424	Revive ft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4425	Revive tl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4426	DermaBind TL + or dermabind tl X, per square centimeter (add-on, list separately in addition to primary procedure)
Q4427	Dermabind dl n or dermabind dl + or dermabind dl x, per square centimeter (add-on, list separately in addition to primary procedure)
Q4428	Dermabind sl n or dermabind sl + or dermabind sl x, per square centimeter (add-on, list separately in addition to primary procedure)
Q4429	Dermabind ch n or dermabind ch x, per square centimeter (add-on, list separately in addition to primary procedure)
Q4435	Ranati membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4436	Ranati ac membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4437	Revival ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4438	Pretect, per square centimeter (add-on, list separately in addition to primary procedure)

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CPT/HCPCS	
Q4439	Instagraft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4440	Curamatrix, per square centimeter (add-on, list separately in addition to primary procedure)

REVISIONS	
03-20-2017	Policy added to the bcbsks.com web site.
01-01-2019	Updated Description section.
	In Policy section: ▪ In Item A 1, added "Q4168". ▪ In Item A 3, removed "Q4131" and added "Q4145, Q4186". ▪ Added new Item B, "FDA-approved sutured and non-sutured human amniotic membrane grafts may be considered medically necessary for the treatment of the following ophthalmic indications: 1. Neurotrophic keratitis 2. Corneal ulcers and melts 3. Pterygium repair 4. Stevens-Johnson syndrome 5. Persistent epithelial defects (with documented pain for ≥5 days) 6. Acid or alkaline burn. ▪ Added new Item C, "FDA-approved sutured and non-sutured human amniotic membrane grafts are considered experimental / investigational for the treatment of all other ophthalmic conditions including but not limited to dry eye syndrome, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy." ▪ In Item D (previous Item B), added "including but not limited to treatment of osteoarthritis and plantar fasciitis" to read "Injection of micronized or particulated human amniotic membrane is considered experimental / investigational for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis." ▪ In Item F (previous Item D), removed "human amniotic membrane products and" and added "including but not limited to treatment of lower-extremity ulcers due to venous insufficiency" to read "All other human amniotic membrane products and indications not listed above are considered experimental / investigational, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency." ▪ Updated Policy Guidelines.
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes: 65778, 65779. ▪ Added new HCPCS codes: Q4183, Q4184, Q4185, Q4186, Q4187, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4201, Q4204. ▪ Removed deleted HCPCS code: Q4131. ▪ Revised nomenclature to HCPCS codes: Q4132, Q4133, Q4137, Q4148, Q4156, Q4162, Q4163. ▪ Added ICD-10 codes: H11.001, H11.002, H11.003, H11.011, H11.012, H11.013, H11.021, H11.022, H11.023, H11.031, H11.032, H11.033, H11.041, H11.042, H11.043, H11.051, H11.052, H11.053, H11.061, H11.062, H11.063, H16.011, H16.012, H16.013, H16.021, H16.022, H16.023, H16.031, H16.032, H16.033, H16.041, H16.042, H16.043, H16.051, H16.052, H16.053, H16.061, H16.062, H16.063, H16.121, H16.122, H16.123, H16.231, H16.232, H16.233, H18.831, H18.832, H18.833, T26.11XA, T26.11XD, T26.11XS, T26.12XA, T26.12XD, T26.12XS, T26.31XA, T26.31XD, T26.31XS, T26.32XA, T26.32XD, T26.32XS, T26.51XA, T26.51XD, T26.51XS, T26.52XA, T26.52XD, T26.52XS, T26.61XA, T26.61XD, T26.61XS, T26.62XA, T26.62XD, T26.62XS, T26.81XA, T26.81XD, T26.81XS, T26.82XA, T26.82XD, T26.82XS.
	Updated References section.

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REVISIONS	
02-18-2019	In Policy section: ▪ In Item A 3, removed "Q4145".
03-27-2019	Updated Description section.
	In Policy section: ▪ In Item A, added new Item A 3, "Epicord (Q4187)".
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-10 codes: T26.51XA, T26.51XD, T26.51XS, T26.52XA, T26,52XD, T26.52XS.
	Updated References section.
05-21-2019	In Policy section: ▪ In Item A 1, removed HCPCS code Q4168.
09-27-2019	Policy published to the bcbsks.com website on 08-28-2019 with an effective date of 09-27-2019.
	In Coding section: ▪ Added ICD-10 codes: H18.891, H18.892, H18.893.
	Updated References section.
10-01-2019	In Coding section: ▪ Added HCPCS Codes: Q4205, Q4206, Q4208, Q4209, Q4210, Q4211, Q4212, Q4213, Q4214, Q4215, Q4216, Q4217, Q4218, Q4219, Q4221
07-01-2020	In Coding section: ▪ Added HCPCS Codes: Q4176, Q4177, Q4178, Q4181, Q4227, Q4228, Q4229, Q4230, Q4231, Q4232, Q4233, Q4234, Q4235, Q4236, Q4237, Q4239, Q4240, Q4241, Q4242, Q4244, Q4245, Q4246, Q4247, Q4248
07-16-2021	Updated Description section
	In Policy section <u>Added item A.1</u> <u>In Item B</u> • Removed: "FDA-approved sutured and non-sutured human amniotic membrane grafts may be considered medically necessary for the treatment of the following ophthalmic indications: 1. Neurotrophic keratitis 2. Corneal ulcers and melts 3. Pterygium repair 4. Stevens-Johnson syndrome 5. Persistent epithelial defects (with documented pain for ≥5 days) 6. Acid or alkaline burn" • Added: "Human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) or glue may be considered medically necessary for the treatment of the following ophthalmic indications: 1. Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy; 2. Corneal ulcers and melts that do not respond to initial conservative therapy; 3. Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment; 4. Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty); 5. Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient; 6. Moderate or severe Stevens-Johnson syndrome; 7. Persistent epithelial defects that do not respond as stated in policy guideline #2;

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	8. Severe dry eye (DEWS 3 or 4) with ocular surface damage and inflammation that remains symptomatic after Steps 1, 2, and 3 of the dry eye disease management algorithm (see Policy Guidelines); or 9. Moderate or severe acute ocular chemical burn." 10. Corneal perforation when corneal tissue is not immediately available; or 11. Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft In Item C • Removed: "FDA approved sutured and non-sutured human amniotic membrane grafts are considered experimental / investigational for the treatment of all other ophthalmic conditions including, but not limited to, dry eye syndrome, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy." • Added: "Human amniotic membrane grafts with or without suture are considered experimental / investigational for all ophthalmic indications not outlined above." Added • Item F • Policy Guidelines
	Updated Rationale section
	In Coding section: • Added HCPCS Codes: Q4180, Q4220, Q4238, Q4249, Q4250, Q4254, Q4255 • Added ICD 10 Diagnosis codes: H18.11, H18.12, H18.13, H18.30, H18.52, I87.2, L51.1, T26.50XA, T26.50XD, T26.50XS, T26.51XA, T26.51XD, T26.51XS, T26.52XA, T26.52XD, T26.52XS • Removed ICD 10 Diagnosis codes: H16.121, H16.122, H16.123, L97.212, L97.213, L97.214, L97.222, L97.223, L97.224, L97.312, L97.313, L97.314, L97.322, L97.323, L97.324, L97.412, L97.413, L97.414, L97.422, L97.423, L97.424, L97.512, L97.513, L97.514, L97.522, L97.523, L97.524, L97.812, L97.813, L97.814, L97.822, L97.823, L97.824, T26.31XA, T26.31XD, T26.31XS, T26.32XA, T26.32XD, T26.32XS, T26.61XA, T26.61XD, T26.61XS, T26.62XA, T26.62XD, T26.62XS, T26.81XA, T26.81XD, T26.81XS, T26.82XA, T26.82XD, T26.82XS
	Updated Reference section
	Added Appendix
10-08-2021	In Coding section: Effective 10-01-2021 Added HCPCS codes: Q4251, Q4252, Q4253 Deleted HCPCS codes: Q4228, Q4236 (no longer being manufactured)
01-03-2022	In Coding Section Added HCPCS code A2001, Q4199 (effective 01-01-2022)
04-01-2022	In Coding Section Added: Q4224, Q4225, Q4256, Q4257, Q4258 (new codes 04-01-2022)
04-08-2022	Updated Description Section
	Updated Policy Section ▪ Section G "All other indications not listed above are considered experimental / investigational, including, but not limited to, treatment of lower-extremity ulcers due to venous insufficiency." added "and repair following Mohs micrographic surgery" to the end of the statement.
	Updated Rationale Section
	Updated Coding Section ▪ Removed coding bullets

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	• There are specific HCPCS codes for some of these products. If no specific HCPCS code exists for the product, an unlisted code such as Q4100 would be used. • There are no specific codes for AmnioFix or OrthoFlo. It might be reported using the code for another MiMedx product such as Q4145 or the not otherwise specified code Q4100. • There is no specific code for this type of injection. It might be reported with one of the musculoskeletal system injection codes (e.g., 20550), the unlisted general musculoskeletal system code (20999), or if subcutaneous or intramuscular, the therapeutic injection code (96372). • There are codes for the placement of amniotic membrane on the ocular surface: 65778, 65779 ▪ Removed Code: Q4100 ▪ Added ICD-10 Codes: H04.121-H04.129, M17.10-M17.9 and M72.2 ▪ Converted ICD-10 codes to ranges
	Updated References Section
01-03-2023	Updated Coding Section ▪ Added codes Q4259, Q4260, Q4261 (eff. 07-01-2022) and Q4262, Q4263, Q4264 (eff. 01-01-2023)
03-28-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Added Q4236 (reactivated 01-01-2023), Q4265, Q4266, Q4267, Q4268, Q4269, Q4270, Q4271 (eff. 04-01-2023) ▪ Removed ICD-10 Codes
	Updated References Section
	Removed Appendix Section
07-03-2023	Updated Coding Section ▪ Added: Q4272, Q4273, Q4274, Q4275, Q4276, Q4277, Q4278, Q4280, Q4281, Q4282, Q4283 and Q4284 (eff. 7-1-2023)
10-02-2023	Updated Coding Section ▪ Added: Q4285 and Q4286 (eff. 10-1-2023)
01-01-2024	Updated Coding Section ▪ Updated nomenclature for Q4225 ▪ Added Q4279, Q4287, Q4288, Q4289, Q4290, Q4291, Q4292, Q4293, Q4294, Q4295, Q4296, Q4297, Q4298, Q4299, Q4300, Q4301, Q4302, Q4303 and Q4304 (eff. 01-01-2024)
Posted 04-23-2024 Effective 05-23-2024	Updated Description Section
	Update Policy Section ▪ Added A3: AmnioExcel® to statement A: "Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered medically necessary." ▪ Removed "(Prokera®, AmbioDisk™)" from statement B: "Human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) or glue, may be considered medically necessary for the treatment of the following ophthalmic indications:" ▪ Added to statement G "other human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) including but not limited to those in Table PG2 (see Policy Guidelines) for indications not listed above are considered experimental / investigational for indications reviewed herein,"

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	Updated Policy Guidelines ▪ Added "Non-healing of lower-extremity ulcers due to venous insufficiency is defined as less than a 30% decrease in wound area with standard wound care for at least 2 weeks, based on clinical trial entry criteria (Serena et al [2022])." And "This review covers products that do not require FDA approval or clearance. The list of products named in this review is not a complete list of all commercially available products. Table PG1 lists products included in the Policy statements, and Table PG2 lists other amniotic products that have an HCPCS code." ▪ Added: AmnioExcel® Integra Q4137 to PG1 Table ▪ Removed: AmnioBand® Particulate, MTF Wound Care, Q4168 and AmnioExcel®, Derma Sciences, Q4137
	Updated Rationale Section
	Updated Coding Section ▪ Deleted Q4244 (eff. 04-01-2024) ▪ Added Q4305, Q4306, Q4307, Q4308, Q4309, Q4310 (eff. 04-01-2024)
	Updated Rationale Section
07-01-2024	Updated Coding Section ▪ Added: Q4311, Q4312 Q4313, Q4314, Q4315, Q4316, Q4317, Q4318, Q4319, Q4320, Q4321, Q4322, Q4323, Q4324, Q4325, Q4326, Q4327, Q4328, Q4329, Q4330, Q4331, Q4332, Q4333 (eff. 07-01-2024) ▪ Removed Deleted Codes: Q4210 and Q4277 (eff. 07-01-2024)
10-01-2024	Updated Coding Section ▪ Added: Q4334, Q4335, Q4336, Q4337, Q4338, Q4339, Q4340, Q4341, Q4342,Q4343, Q4344, and Q4345 (eff. 10-01-2024)
01-01-2025	Updated Coding Section ▪ Added: Q4346, Q4347, Q4348, Q4349, Q4350, Q4351, Q4352, and Q4353 (eff. 01-01-2025)
04-01-2025	Updated Coding Section ▪ Added: A2035, Q4354, Q4355, Q4356, Q4357, Q4358, Q4359, Q4360, Q4361, Q4362, Q4363, Q4364, Q4365, Q4366 and Q4367 (eff. 04-01-2025) ▪ Removed: Deleted code Q4231
Posted 05-28-2025; Effective 06-27-2025	Updated Description Section
	Updated Policy Section ▪ Section A: " Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered medically necessary." Added: NuShield®(Q4160)
	Updated Policy Guideline Section ▪ Added the following products to Table PG1 Amniotic Products Listed in the Policy Statements: NuShield® Organogensis Q4160 ▪ Added the following products to Table PG2 Other Amniotic Products with HCPCS Codes: Abiomend membrane and abiomend hydromembrane Q4356, Abiomend xplus membrane and abiomend xplus hydromembrane Q4355, Acapatch Q4325, Acesso Q431, Acesso Q4312, Alloply Q4323, Amchoplast Q4316, Amchoplast fd Q4360, Amnio burgeon dual-layer membrane Q4365, Amnio burgeon membrane and hydromembrane Q4363, Amnio burgeon xplus membrane and xplus hydromembrane Q4364, Amniocore sl Q4367, Amnioplast 1 Q4334,Amnioplast 2 Q4335, Amniotx Q4324, Ardeograft Q4333, Artacent c Q4336, Artacent trident Q4337, Artacent velos Q4338, Artacent vericlen Q4339, Axolotl dualgraft Q4332, Axolotl graft Q4331, Caregraft Q4322, Choriply Q4359, Corplex p or theracor p

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	or allacor p A2035, Cygnus disk Q4362, Dermabind fm Q4313, Dermacyte ac matrix amniotic membrane allograft Q4343, Dual layer amnio burgeon x-membrane Q4366, Duoamnion Q4327, E-graft Skye Biologics Q4318, Enclose tl matrix Q4351, Epixpress Q4361, Mantle dl matrix Q4349, Matrix hd allograft dermis Q4345, Most Q4328 Overlay sl matrix Q4352, Palingen dual-layer membrane Q4354, Palisade dm matrix Q4350, Pellograft Q4320, Rampart dl matrix Q4347, Reeva ft 4314, Regenelink amniotic membrane allograft Q4315, Renograft Q4321, Sanograft Q4319, Sentry sl matrix Q4348, Shelter dm matrix Q4346, Simpligraft Q4340, Simplimax Q4341, Singlay Q4329, Theramend Q4342, Total Q4330, Tri-membrane wrap Q4344, Vitograft Q4317, Woundplus Q4326, Xceed tl matrix Q4353, Xwrap dual Q4358, Xwrap plus Q4357 ▪ Removed the following product from Table PG2 Other Amniotic Products with HCPCS Codes: NuShield®(Q4160)
	Updated Rationale Section
	Updated Coding Section ▪ Added New Codes Q4368, Q4369, Q4370, Q4371, Q4372, Q4373, Q4375, Q4376, Q4377, Q4378, Q4379, Q4380, Q4382, Q4368, Q4369, Q4370, Q4371, Q4372, Q4373, Q4375, Q4376, Q4377, Q4379, Q4380, and Q4382 (eff. 07-01-2025)
	Updated Reference Section
10-01-2025	Updated Coding Section ▪ Added Q4383, Q4384, Q4385, Q4386, Q4387, Q4388, Q4389, Q4390, Q4391, Q4392, Q4393, Q4394, Q4395, Q4396 and Q4397 (eff. 10-01-2025)
01-01-2026	Updated Coding Section ▪ Added New Codes Q4398, Q4399, Q4400, Q4401, Q4402, Q4403, Q4404, Q4405, Q4406, Q4407, Q4408, Q4409, Q4410, Q4411, Q4412, Q4413, Q4414, Q4415, Q4416, Q4417, and Q4420 (eff. 01-01-2026) ▪ Updated nomenclature for Q4354 (eff. 01-01-2026)
04-01-2026	Updated Coding Section ▪ Added New Codes Q4418, Q4419, Q4421, Q4422, Q4423, Q4424, Q4425, Q4426, Q4427, Q4428, Q4429, Q4435, Q4436, Q4437, Q4438, Q4439, and Q4440 (Eff. 04-01-2026)
Posted 07-14-2026 Effective 08-13-2026	Updated Description Section
	Updated Policy Section ▪ Section A: Removed A.3. AmnioExcel ▪ Section B: Added "(i.e., a human amniotic product commercially available specifically for ophthalmic use)" and "any of" ▪ Section B7: Removed "as stated in policy guidelines" and added "within 2 days to conservative therapy;" ▪ Removed Statement C: Human amniotic membrane grafts with or without suture are considered experimental / investigational for all ophthalmic indications not outlined above. ▪ Removed Statement F: All other uses reviewed herein of the human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) not listed above are considered experimental / investigational (see policy guidelines). ▪ Removed Statement G: All other human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) including but not limited to those in Table PG2 (see Policy Guidelines) for indications not listed above are considered experimental / investigational for indications reviewed

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	herein, including but not limited to, treatment of lower-extremity ulcers due to venous insufficiency and repair following Mohs micrographic surgery. ▪ Added Statement: "The use of any human amniotic product (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly), including but not limited to those listed in Table PG2 (see Policy Guidelines), is considered experimental / investigational for all other indications, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency and repair following Mohs micrographic surgery."
	Updated Policy Guidelines Section ▪ Removed Statement D: A persistent epithelial defect is one that failed to close completely after 5 days of conservative treatment or has failed to demonstrate a decrease in size after 2 days of conservative treatment.
	Updated Rationale Section
	Updated Reference Section
10-01-2026	Updated Coding Section ▪ Added new codes A2049, Q4207, Q4223 and Q4243 (eff. 10-01-2026)

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