Policy Number	**SUR704.011**
Policy Effective Date	**12/15/2025**

Amniotic Membrane and Amniotic Fluid

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Related Policies (if applicable)
SUR703.051 Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow)
SUR704.012 Bioengineered Skin and Soft Tissue Substitutes

Disclaimer

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Coverage

Diabetic Lower-Extremity Ulcers
Treatment of nonhealing (see Policy Guidelines) diabetic lower-extremity ulcers using the following human amniotic membrane products (i.e., Affinity®, AmnioBand® Membrane, Biovance®, EpiCord®, Epifix®, Grafix®, NuShield®) **may be considered medically necessary**.

Ophthalmic Indications
Human amniotic membrane grafts with or without suture (e.g., Prokera®, AmbioDisk™) **may be considered medically necessary** for the treatment of the following ophthalmic indications:

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy;
- Corneal ulcers and melts that do not respond to initial conservative therapy;
- Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment;
- Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty);
- Partial limbal stem cell deficiency with extensive diseased tissue where selective removal

alone is not sufficient;
- Moderate or severe Stevens-Johnson syndrome;
- Persistent epithelial defects that do not respond within 2 days of conservative therapy;
- Severe dry eye (Dry Eye Workshop Score [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
- Moderate or severe acute ocular chemical burn.

Human amniotic membrane grafts with suture or glue **may be considered medically necessary** for the treatment of the following ophthalmic indications:
- Corneal perforation when corneal tissue is not immediately available; or
- Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft.

Human amniotic membrane grafts with or without suture **are considered experimental, investigational and/or unproven** for all other ophthalmic conditions not outlined above.

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

Injection of human amniotic fluid **is considered experimental, investigational and/or unproven** for all indications.

All other human amniotic membrane 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 and/or unproven** for indications reviewed herein, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency and repair following Mohs micrographic surgery.

Policy Guidelines

Non-healing 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]).

This policy covers products that do not require U.S. Food and Drug Administration (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 a Healthcare Common Procedure Coding System (HCPCS) code.

Table PG1. Amniotic Products Listed in the Policy Statements

Trade Name	HCPCS Code
Affinity®	Q4159
AmnioBand® Membrane	Q4151
Biovance®	Q4154, Q4283
Epicord®	Q4187
Epifix®	Q4186
Grafix®	Q4132, Q4133, Q4304, Q4392
NuShield®	Q4160

HCPCS: Healthcare Common Procedure Code System.

Table PG2. Other Amniotic Products with HCPCS Codes

Trade Name	HCPCS Code
Abiomend Membrane and Abiomend Hydromembrane	Q4356
Abiomend XPlus Membrane and Abiomend XPlus Hydromembrane	Q4355
Acapatch™	Q4325
Acelagraft™	Q4395
Acesso	Q4311
Acesso AC	Q4312
Acesso DL	Q4293
Acesso TL	Q4300
Acesso TrifACA	Q4386
Activate™ Membrane	Q4301
Advograft Dual	Q4382
Advograft One™	Q4380
AéroGuard™	Q4370
AlloGen™	Q4212
alloPLY™	Q4323
AlloWrap™	Q4150
American Amnion™	Q4307
American Amnion AC™	Q4306
American Amnion AC™ Tri-Layer	Q4305
Amchoplast™	Q4316
AmchoplastExcel®	Q4372
Amchoplast FD™	Q4360
AmchoThick™	Q4368
AmnioAMP-MP™	Q4250
AmnioArmor™	Q4188
AmnioBand® Particulate	Q4168
AmnioBind	Q4225
Amnio Burgeon Dual-Layer Membrane	Q4365

Amnio Burgeon Membrane and Hydromembrane	Q4363
Amnio Burgeon Xplus Membrane and Xplus Hydromembrane	Q4364
AmnioCore™	Q4227
AmnioCore Pro	Q4298
AmnioCore Pro+	Q4299
AmnioCore SL	Q4367
AmnioCyte Plus	Q4242
AmnioDefend™ FT Matrix	Q4379
AmnioExcel®	Q4137
AmnioMatrix®	Q4139
Amnio-Maxx® or Amnio-Maxx Lite	Q4239
Amnion Bio™ or AxoBioMembrane	Q4211
Amnioplast 1™	Q4334
Amnioplast 2™	Q4335
Amnioplast 3™	Q4369
AmnioPlast Double	Q4391
AmniPly™	Q4249
Amnio Quad-Core	Q4294
AmnioRepair® or AltiPly™	Q4235
AmnioText™	Q4245
AmnioText™ Patch	Q4247
Amnio Tri-Core Amniotic	Q4295
AmnioTX™	Q4324
Amnio Wound™	Q4181
AmnioWrap2™	Q4221
Apollo™ FT	Q4385
ArdeoGraft®	Q4333
Artacent® AC (flowable)	Q4189
Artacent® AC (patch)	Q4190
Artacent® C	Q4336
Artacent® Cord	Q4216
Artacent® Trident	Q4337
Artacent® Velos	Q4338
Artacent® Vericlen	Q4339
Artacent® Wound	Q4169
Ascendion™	Q4390
Ascent™	Q4213
Axolotl™ Ambient or Axolotl™ Cryo	Q4215
Axolotl™ Dualgraft	Q4332
Axolotl™ Graft	Q4331
Axolotl™ Graft Ultra	Q4383
Axolotl™ DualGraft Ultra	Q4384

Barrera™ SL or Barrera™ DL	Q4281
BellaCell HD® or SureDerm®	Q4220
BioDDryFlex®	Q4138
BioDfence™	Q4140
Bionext® Patch	Q4228 (deleted)
BioWound, BioWound Plus™, BioWound XPlus™	Q4217
CaregraFT™	Q4322
carePatch™	Q4236
Celera™ Dual Layer or Celera™ Dual Membrane	Q4259
Cellesta/Cellesta Duo	Q4184
Cellesta Cord	Q4214
Cellesta Flowable Amnion	Q4185
ChoriPly	Q4359
Clarix®	Q4156
Clarix® Flo	Q4155
Cocoon™ Membrane	Q4264
Cogenex Flowable Amnion	Q4230
Cogenex Amniotic Membrane	Q4229
Complete™ AA	Q4303
Complete ACA™	Q4302
Complete™ SL	Q4270
Complete™ FT	Q4271
CoreCyte™	Q4240
Corplex™	Q4232
Corplex™ P	Q4231
Corplex™ P or Theracor P™ or Allacor P™	A2035
CoreText™ or ProText™	Q4246
Cryo-Cord™	Q4237
Cygnus®	Q4170
Cygnus® Disk	Q4362
Cygnus® Dual	Q4282
Cygnus® Matrix	Q4199
Dermabind DL™	Q4287
Dermabind CH™	Q4288
Dermabind FM™	Q4313
Dermabind SL™	Q4284
Dermacyte®	Q4248
Dermacyte® AC Matrix	Q4343
Dermavest® or Plurivest®	Q4153
Derm-Maxx®	Q4238
Dual Layer Amnio Burgeon X-Membrane	Q4366
DuoAmnion™	Q4327

duoGRAFT AC™	Q4375
duoGRAFT AA™	Q4376
E-Graft™	Q4318
Emerge™ Matrix	Q4297
Enclose™ TL Matrix	Q4351
Enverse®	Q4258
Epieffect®	Q4278
Epifix® Injectable	Q4145
Epixpress®	Q4361
Esano™ A	Q4272
Esano™ AAA	Q4273
Esano™ AC	Q4274
Esano™ ACA	Q4275
FlowerAmnioFlow™	Q4177
FlowerAmnioPatch™	Q4178
Fluid Flow™ or Fluid GF™	Q4206
Genesis	Q4198
Human Health Factor 10 Amniotic Patch (HHF10-P™)	Q4224
Impax™ Dual Layer Membrane	Q4262
InnovaMatrix AC	A2001
Interfyl®	Q4171
Lamellas	Q4291
Lamellas XT	Q4292
Mantle™ DL Matrix	Q4349
Matrion®	Q4201
Matrix DS Allograft Dermis	Q4345
Membrane Graft™ or Membrane Wrap™	Q4205
Membrane Wrap-Hydro™	Q4290
Membrane Wrap-LITE™	Q4373
MLG-Complete™	Q4256
MOST™	Q4328
Natalin™	Q4396
Néoguard™	Q4371
NeoPatch™ or Therion	Q4176
NeoStim Membrane	Q4266
NeoStim DL	Q4267
NeoStim TL™	Q4265
NeoThelium™ FT	Q4387
NeoThelium™ 4L	Q4388
NeoThelium™ 4L Plus	Q4389
Neox® Cord	Q4148
Neox® Flo	Q4155

Neox® Wound	Q4156
Novachor®	Q4194
Novafix®	Q4208
Novafix DL	Q4254
NuDYN® DL or NuDYN® DL Mesh	Q4285
NuDYN® SL or NuDYN® SLW	Q4286
Orion™	Q4276
Overlay™ SL Matrix	Q4352
PalinGen® Dual-Layer Membrane	Q4354
PalinGen® Membrane	Q4173
PalinGen® SportFlow	Q4174
Palisade™ DM Matrix	Q4350
PelloGraft®	Q4320
Plurivest™	Q4153
PolyCyte™	Q4241
Procenta®	Q4244, Q4310
Rampart™ DL Matrix	Q4347
Rebound Matrix	Q4296
Reeva FT™	Q4314
Regenelink Amniotic Membrane Allograft	Q4315
ReGUaRD™	Q4255
Relese™	Q4257
Renew™ FT matrix	Q4378
RenoGraft®	Q4321
Restorigin™	Q4191
Restorigin™ Injectable	Q4192
Revita®	Q4180
Revitalon™	Q4157
Revoshield + Amniotic Barrier	Q4289
SanoGraft®	Q4319
Sanopellis™	Q4308
Sentry™ SL Matrix	Q4348
Shelter™ DM Matrix	Q4346
Signature APatch	Q4260
SimpliGraft™	Q4340
SimpliMax™	Q4341
Singlay™	Q4329
Summit AAA	Q4397
Surgenex®, SurFactor®, and NuDYN®	Q4233
SurgiCORD®	Q4218
SurgiGRAFT™	Q4183
SurgiGraft-DUAL	Q4219

SurGraft®	Q4209
SurGraft AC	Q4393
SurGraft ACA	Q4394
SurGraft FT®	Q4268
SurGraft TL®	Q4263
SurGraft XT®	Q4269
TAG™	Q4261
Theramend™	Q4342
TOTAL™	Q4330
triGRAFT FT™	Q4377
Tri-Membrane Wrap™	Q4344
Vendaje®	Q4252
Vendaje® AC	Q4279
Via Matrix™	Q4309
VIM™	Q4251
VitoGraft®	Q4317
WoundEx®	Q4163
WoundEx® Flow	Q4162
WoundFIX™, WoundFIX™ Plus, WoundFIX™ XPlus (see BioWound above)	Q4217
WoundPlus™	Q4326
XCell Amnio Matrix™	Q4280
Xceed TL™ matrix	Q4353
Xcellerate®	Q4234
XWrap®	Q4204
XWrap Dual®	Q4358
XWrap Plus®	Q4357
Zenith™	Q4253

HCPCS: Healthcare Common Procedure Code System.

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 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 (e.g., tarsorrhaphy, salivary gland transplantation).

Dry eye severity level Dry Eye Workshop Score 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

Description

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

Human Amniotic Membrane

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

Fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist. (1) There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause 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. The use of stem cells in orthopedic applications is addressed in medical policy SUR703.051.

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, 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.

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.

Rationale

Medical policies 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

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 policy.

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.

At least 7 RCTs have evaluated rates of healing with amniotic membrane grafts or placental membrane grafts 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).

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator
Cazzell et al. (2024) (9)	U.S.	15		218 patients with diabetic foot ulcers	n=109, NuShield	n=109, SOC
Serena et al. (2020) (10)	U.S.	14		76 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers unresponsive to SOC and	n=38, Affinity	n=38, SOC

				extending into dermis, subcutaneous tissue, muscle, or tendon		
Ananian et al. (2018) (11)	U.S.	7	2016-2017	75 patients with chronic (>4 weeks) non-healing diabetic foot ulcers between 1 cm^2 and 15 cm^2	n=38, Grafix weekly for up to 8 weeks	n=37, Dermagraft (fibroblast-derived) weekly for up to 8 weeks
Tettelbach et al. (2018) (12)	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) (13)				80 patients with non-healing (4 weeks) diabetic foot ulcers	AmnioBand Membrane plus SOC	SOC
Snyder et al. (2016) (14)				29 patients with non-healing diabetic foot ulcers	AmnioExcel plus SOC	SOC
Zelen et al. (2015, 2016) (15, 16)		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) (17)	U.S.	14		110 patients with non-healing (4 weeks) lower extremity ulcers	EpiFix	SOC with alginate dressing
Lavery et al. (2014) (18)				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; U.S.: United States.

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) (9)	**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) (10)	**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)		
Ananian et al. (2018) (11)	**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%			
Tettelbach et al. (2018) (12)	**12 Weeks (PP) n (%)**	**12 Weeks (ITT) n (%)**		**Patients with Adverse Events (% of total)**
N	134	155		155
EpiCord	81 (81%)	71 (70%)		42 (42%)
SOC	29 (54%)	26 (48%)		33 (61%)
p-value	0.001	0.009		
DiDomenico et al. (2018) (13)	**6 Weeks (ITT) n (%)**	**12 Weeks (ITT) n (%)**	**Mean Days (95% CI)**	
N	80	80	80	
AmnioBand	27 (68)	34 (85)	37.0 (29.5 to 44.4)	

SOC	8 (20)	13 (33)	67.3 (59.0 to 79.6)	
HR (95% CI)		4.25 (0.44 to 0.79)		
p-value	<0.001	<0.001	<0.001	
Snyder et al. (2016) (14)	**6 Weeks (PP) Mean (95% CI)**			
N	21			
AmnioExcel	45.5% (32.9% to 58.0%)			
SOC	0%			
p-value	0.014			
Zelen et al. (2015, 2016) (15, 16)	**6 Weeks (ITT) n (%)**	**Wounds Healed at 12 Weeks**		**Weekly Treatments**
N	60	100		
EpiFix	19 (95%)	NR		3.4
Apligraf	9 (45%)	NR		5.9
SOC	7 (35%)	NR		
HR (95% CI)		5.66; (3.03 to 10.57)		
p-value	0.003	<0.001 vs. SOC		0.003
Tettelbach et al. (2019) (17)		**Wounds Healed at 12 Weeks (ITT) n (%)**		
N		110		110
EpiFix		38 (81)		
SOC		28 (55)		
p-value				
Lavery et al. (2014) (18)		**Wounds Healed at 12 Weeks**		**Patients With Adverse Events**
N		97[a]	97	97
Grafix		62.0%	42.0	44.0%
SOC		21.3%	69.5	66.0%
p-value		<0.001	0.019	0.031
Difference in wounds healed between amniotic or placental	Affinity 26% AmnioBand 55% AmnioExcel 33%	Affinity 28% EpiCord 22% Grafix 41%		

membrane and SOC	EpiFix 60%			

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 intention-to-treat (ITT) analysis. Limitations from the RCT with AmnioExcel (Snyder et al., 2016) (14) preclude conclusions for this product.

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) (9)		1, 2. No blinding of patients or investigators				
Serena et al. (2020) (10)	3. The randomiza-tion 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) (11)		2, 3. No blinding for outcomes assessment				
Tettelbach et al. (2018) (12)		1, 2, 3. No blinding				
DiDomenico et al. (2018) (13)						
Snyder et al. (2016) (14)				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,				1. Thirteen of 35 patients in the SOC group		

2016) (15, 16)				exited the study at 6 weeks due to less than 50% healing, which may have affected the 12-week results		
Tettelbach et al. (2019) (17)		1, 2. No blinding of patients or investigators. Assessors were blinded				
Lavery et al. (2014) (18)						

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. (19) 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. (20)

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

Study	Study Design	Participants	Treatment Delivery
Smiell et al. (2015) (19)	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) (20)	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) (19)	Biovance	41.6%	8 weeks	2.4
Frykberg et al. (2016) (20)	Grafix	59.3%	9 weeks	9

Section Summary: Diabetic Lower-Extremity Ulcers

For individuals who have non-healing diabetic lower-extremity ulcers who receive a formulation of HAM or placental membrane (i.e., 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 (i.e., 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 policy.

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.
- 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.

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). (21) 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). (22, 23) Patients treated with EpiFix had a higher probability of complete healing by 12 weeks, as adjudicated by blinded outcome assessors (hazard ratio, 2.26; 95% 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). (24) 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.

Table 6. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Serena et al. (2014) (21)	U.S.	8	2012-2014	84 patients with a full-thickness chronic VLU between 2 and 20 cm^2 treated for at least 14 days	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) (22, 23)	U.S.	15	2015-2017	128 patients with a full-thickness VLU of at least 30-day 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) (24)	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)

ITT: intent-to-treat; mo: month; PP: per-protocol; RCT: randomized controlled trial; SOC: standard of care; U.S.: United States; VLU: venous leg ulcer.

Table 7. Summary of Key RCT Results

Study	Percent With 40% Wound Closure at 4 Weeks	Percent With Complete Wound Closure at 4 Weeks	Complete Wound Closure at 12 Weeks, n (%)		Median (IQR) Percentage Area Reduction at 12 Weeks	Percent With Complete Wound Closure at 16 Weeks, n (%)	
			PP	**ITT**	**ITT**	**PP**	**ITT**
Serena et al. (2014) (21)							
EpiFix	62	11.3					

Control	32	12.9					
p Value	0.005						
Bianchi et al. (2018, 2019) (22, 23)							
EpiFix			31 (60)	32 (50)		37 (71)	38 (59)
Control			20 (35)	20 (31)		25 (44)	25 (39)
p Value			0.013	0.047		0.007	0.034
Serena et al. (2022) (24)							
AmnioBand	75			30 (75)	100 (5.3)		
Control	65			6 (30)	75 (68.7)		
p Value				0.001	0.012		

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

Table 8. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Serena et al. (2014) (21)					
Bianchi et al. (2018, 2019) (22, 23)					1. Advanced wound therapy was allowed in the control group before the primary endpoint was reached
Serena et al. (2022) (24)					

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. 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 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) (21)						
Bianchi et al. (2018, 2019) (22, 23)		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) (24)		1. Open-label with blinded assessors.				4. Incomplete reporting of regression including wound duration.

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.

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. (19) 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

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. (25) 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). (26) 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 policy.

Populations

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

Interventions

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

Comparators

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

Outcomes

The primary endpoints of interest for trials of plantar fasciitis are as follows: 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.

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. (27) In addition to c-HAM and micronized d-HAM/chorionic membrane, treatments included corticosteroids, botulinum toxin type A, autologous whole blood, platelet-rich plasma, nonsteroidal anti-inflammatory drugs, dry needling, dextrose prolotherapy, and polydeoxyribonucleotide. Placebo arms included normal saline, local anesthetic, sham dry needling, and tibial nerve block. Analysis indicated d-HAM had the highest probability for improvement in pain and composite outcomes in the short-term; however, this finding was based only on a single RCT. Outcomes at 2 to 6 months (7 RCTs) favored botulinum toxin for pain and patient recovery plan for composite outcomes.

Randomized Controlled Trials

Zelen et al. (2013) reported a preliminary study with 15 patients per group (placebo, 0.5 mL, and 1.25 mL) and 8-week follow-up. (28) A subsequent RCT by Cazell et al. (2018) enrolled 145 patients and reported 3-month follow-up (see Table 10). (29) 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) (29); 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; U.S.: United States; 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) (29); AIPF004	N=145	N=145	N=145	N=145
AmnioFix	54.1 (48.3 to 59.9)	35.7 (30.5 to 41.0)	30 (41.1%)	1 (0.6%)
Placebo	31.9 (24.8 to 39.1)	22.2 (17.1 to 27.4)	39 (54.2%)	3 (1.8%)
Diff (95% CI)	22.2 (13.1 to 31.3)	13.5 (6.2 to 20.8)		
p Value	<0.001	<0.001		

CI: confidence interval; FFI-R: Foot Function Index; mo: month(s); 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 separate publication; no subsequent publications have been identified for this trial.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Cazzell et al. (2018) (29); AIPF004			3. Placebo injections were used. A control delivered at a similar intensity as the investigational treatment would be corticosteroid injections.		1, 2. Follow-up to 12 months will be reported in a subsequent publication.

The 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) (29); AIPF004		1. Single blinded trial, although outcomes were self-reported by blinded patients		1. Only the first 3 months of 12-month follow-up were reported		

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

Section Summary: Plantar Fasciitis

The evidence on injection of amniotic membrane for the treatment of plantar fasciitis includes preliminary studies and a larger (N=145) patient-blinded comparison of micronized injectable-HAM and placebo control. Injection of micronized amniotic membrane resulted in greater improvements in VAS for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is this is an interim report of 3 months' results. The authors noted that 12-month follow-up will be reported in a subsequent publication. No additional publications have been identified as of the latest update.

HUMAN AMNIOTIC MEMBRANE FOR OPHTHALMOLOGIC CONDITIONS

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

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

Clinical Context and Therapy Purpose

The purpose of HAM in 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 policy.

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.
- 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.

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. (48) 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. (30) 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 policy.

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.

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.

Liu et al. (2019) conducted a systematic review of 17 studies (390 eyes) of amniotic membrane for corneal ulcers. (31) 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. (32) 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. (30) Nine of the eyes had non-healing corneal ulcers. Complete or partial success was seen in 2 of 9 (22%) patients with this indication.

Section Summary: Corneal Ulcers and Melts That Do Not Respond to Initial Medical Therapy

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

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

Clinical Context and Therapy Purpose

The purpose of HAM in 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 policy.

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.

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 (e.g., 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.

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

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.

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

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

An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy.

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

Clinical Context and Therapy Purpose

The purpose of HAM in 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 policy.

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.

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. (34) 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. (35) Following treatment with ProKera, 3 of the 6 patients had a smooth corneal surface and improved vision to 20/40. (35) 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 policy.

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.

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. (36) 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 policy.

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 (e.g., topical lubricants, topical antibiotics, therapeutic contact lens, or patching).

Outcomes
The general outcomes of interest are epithelial closure.

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

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.

Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease. (37) 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 policy.

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.

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.

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. (38) 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. (39) 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.

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 policy.

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 (e.g., topical antibiotics, lubricants, steroids and cycloplegics, oral vitamin C, doxycycline).

Outcomes

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

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

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.

An RCT of 100 patients with chemical or thermal ocular burns was published by Tandon et al. (2011). (40) Half of the patients (n=50) had moderate ocular burns and the remainder (n=50) had severe ocular burns. All but 8 of the patients had alkali or acid burns. Patients were randomized to HAM transplantation plus medical therapy or medical therapy alone. Epithelial healing, which was the primary outcome, was improved in the group treated with HAM, but there was no significant difference between the 2 groups for final visual outcome, symblepharon formation, corneal clarity or vascularization.

A second RCT that compared amniotic membrane plus medical therapy (30 eyes) to medical therapy alone (30 eyes) for grade IV ocular burn was reported by Eslani et al. (2018). (41) 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. (42)

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 policy.

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.

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.

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 policy.

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.

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.

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. (43) 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. (44)

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 policy.

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 (e.g., local flaps and full-thickness skin grafts) and healing without surgery. Second intention healing (i.e., the wound is left open to heal by granulation, contraction, and epithelialization) is a nonsurgical option for certain defects.

Outcomes
The primary endpoints of interest for trials of wound closure are as follows, consistent with guidance from the 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.

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). (45) 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 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) (45)	Retrospective, observational Propensity-score matching used to identify matched pairs	U.S.	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.	n=143	n=143	Unclear; 9 months or later for postoperative cosmetic outcomes.

				Mean age 78.0 years; 76.9% male 100% White			

dHACM: dehydrated human amnionic/chorionic membrane; U.S.: United States.

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

Study	dHACM Repair n=143	Autologous Tissue Repair n=143	P
Toman et al. (2022) (45)			
Experienced no complications, n (%)	140 (97.9)	102 (71.3)	<0.0001
Infection, n (%)	3 (2.0)	15 (10.0)	0.004
Bleeding or hematoma, n (%)	0 (0.0)	7 (5.0)	0.015
Wound dehiscence, n (%)	0 (0.0)	4 (3.0)	0.122
Surgical reintervention, n (%)	0 (0.0)	11 (8.0)	0.0007
Nonhealing wound, n (%)	0 (0.0)	5 (3.5)	0.060
Poor scar cosmesis, n (%)	0 (0.0)	21 (15.0)	<0.0001
Scar revision, n (%)	0 (0.0)	14 (9.8)	<0.0001
Follow-up visits, mean (SD)	3.4 (1.6)	2.5 (1.1)	<0.0001
Days to discharge, mean (SD)	30.7 (16.9)	30.3 (22.9)	0.840

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

Table 16. Study Relevance Limitations

Study	Population[a]	Intevention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Toman et al. (2022) (45)	4. Study participants were 100% White, over two-thirds male		2. No comparison to non-surgical options (e.g., second intention healing)	1. Not all outcomes mentioned in methods had results reported (e.g., 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 (e.g., 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) (45)	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.
[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.

Summary of Evidence

Diabetic Lower-Extremity Ulcers

For individuals who have non-healing diabetic lower-extremity ulcers who receive a formulation of human amniotic membrane (HAM) or placental membrane (i.e., Affinity, AmnioBand

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

Lower-Extremity Ulcers due to Venous Insufficiency

For individuals who have lower-extremity ulcers due to venous insufficiency who receive a formulation of HAM, the evidence includes 3 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The published evidence on HAM for the treatment of venous leg ulcers includes 2 multicenter RCTs with EpiFix and 1 multicenter RCT with Amnioband. One RCT reported a larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure at 4 weeks did not differ between EpiFix and the standard of care. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression, but interpretation is limited by methodologic concerns. The third RCT demonstrated significantly greater blinded assessor-confirmed rates of complete wound closure at 12 weeks after weekly or twice-weekly application of AmnioBand Membrane with compression bandaging compared with compression bandaging alone. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Osteoarthritis

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

Plantar Fasciitis

For individuals who have plantar fasciitis who receive an injection of amniotic membrane, the evidence includes preliminary studies and a larger (N=145) patient-blinded comparison of micronized injectable-HAM and placebo control. Injection of micronized amniotic membrane resulted in greater improvements in the visual analog score for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is that this is an

interim report with 12-month results pending. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ophthalmic Conditions

Sutured HAM transplant has been used for many years for the treatment of ophthalmic conditions. Many of these conditions are rare, leading to difficulty in conducting RCTs. The rarity, severity, and variability of the ophthalmic condition was taken into consideration in evaluating the evidence.

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

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

Corneal Ulcers and Melts That Do Not Respond to Initial Medical Therapy

For individuals who have corneal ulcers and melts, that do not respond to initial medical therapy who receive HAM, the evidence includes a systematic review of primarily case series and a non-randomized comparative study. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Corneal ulcers and melts are uncommon and variable and additional RCTs are not expected. The systematic review showed healing in 97% of patients with an improvement of vision in 53% of eyes. One retrospective comparative study with 22 patients found more rapid and complete epithelialization and more patients with a clinically significant improvement in visual acuity following early treatment with self-retained amniotic membrane when compared to historical controls. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

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

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

For individuals who have bullous keratopathy and who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty) who receive HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT found no advantage of sutured HAM over the simpler stromal puncture

procedure for the treatment of pain from bullous keratopathy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Partial Limbal Stem Cell Deficiency with Extensive Diseased Tissue Where Selective Removal Alone is Not Sufficient
For individuals who have partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient who receive HAM, the evidence is limited. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. No comparative trials were identified on HAM for limbal stem cell deficiency. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

Severe Dry Eye with Ocular Surface Damage and Inflammation That Does Not Respond to Conservative Therapy
For individuals who have severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy, who receive HAM, the evidence includes an RCT and a large case series. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Moderate or Severe Acute Ocular Chemical Burns
For individuals who have moderate or severe acute ocular chemical burn who receive HAM, the evidence includes 3 RCTs. Relevant outcomes are symptoms, morbid events, functional

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

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

Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft
For individuals who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft who receive HAM, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Repair Following Mohs Micrographic Surgery
For individuals who have undergone Mohs micrographic surgery for skin cancer on the face, head, neck, or dorsal hand who receive human amniotic/chorionic membrane, the evidence includes a nonrandomized, comparative study and no RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A retrospective analysis using data from medical records compared a dehydrated human amnionic/chorionic membrane product (dHACM, Epifix) to repair using autologous surgery in 143 propensity-score matched pairs of patients requiring same-day reconstruction after Mohs microsurgery for skin cancer on the head, face, or neck. 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). This study is limited by its retrospective observational design. Well-designed and conducted prospective studies are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

2019 Input
Clinical input supports the use of amniotic membrane in individuals with the following indications:

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

Practice Guidelines and Position Statements

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." (46)

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. (49) The report evaluated the evidence on treatments for dry eye and provided the following treatment algorithm for dry eye disease management:

Step 1:
- Education regarding the condition, its management, treatment, and prognosis.
- Modification of local environment.
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation).
- Identification and potential modification/elimination of offending systemic and topical medications.

- Ocular lubricants of various types (if meibomian gland dysfunction is present, then consider lipid containing supplements).
- Lid hygiene and warm compresses of various types.

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

<u>Wound Healing Society</u>
In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment. (47) 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.

Ongoing and Unpublished Clinical Trials

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

Table 18. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
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
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	474	Dec 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	474	Mar 2026
NCT05842057[a]	Phase 2 Randomized Trial: Human Amnion Membrane Allograft and Early Return of Erectile Function After Radical Prostatectomy (HAMMER)	240	Aug 2028
NCT06150209[a]	A Controlled Data Collection and Prospective Treatment Study to Evaluate the Efficacy of	100	Jun 2025

	Vendaje in the Management of Foot Ulcers in Diabetic Patients		
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
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 2mL Injection) and a Placebo (Sterile Saline) in the Treatment of Osteoarthritis of the Knee	90	Jul 2022
NCT04599673	Prospective Analysis of Intraoperative AMNIOGEN® Injection in Patients with Rotator Cuff Tear	100	Sep 2022

NCT: national clinical trial

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	65778, 65779, 65780
HCPCS Codes	A2001, A2035, Q4132, Q4133, Q4137, Q4138, Q4139, Q4140, Q4145, Q4148, Q4150, Q4151, Q4153, Q4154, Q4155, Q4156, Q4157, Q4159, Q4160, Q4162, Q4163, Q4168, Q4169, Q4170, Q4171, Q4173, Q4174, Q4176, Q4177, Q4178, Q4180, Q4181, Q4183, Q4184, Q4185, Q4186, Q4187, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4199, Q4201, Q4204, Q4205, Q4206, Q4208, Q4209, Q4211, Q4212, Q4213, Q4214, Q4215, Q4216, Q4217, Q4218, Q4219, Q4220, Q4221, Q4224, Q4225, Q4227, Q4229, Q4230, Q4231, Q4232, Q4233, Q4234, Q4235, Q4236, Q4237, Q4238, Q4239, Q4240, Q4241, Q4242, Q4244, Q4245,

	Q4246, Q4247, Q4248, Q4249, Q4250, Q4251, Q4252, Q4253, Q4254, Q4255, Q4256, Q4257, Q4258, Q4259, Q4260, Q4261, Q4262, Q4263, Q4264, Q4265, Q4266, Q4267, Q4268, Q4269, Q4270, Q4271, Q4272, Q4273, Q4274, Q4275, Q4276, Q4278, Q4279, Q4280, Q4281, Q4282, Q4283, Q4284, Q4285, Q4286, Q4287, Q4288, Q4289, Q4290, Q4291, Q4292, Q4293, Q4294, Q4295, Q4296, Q4297, Q4298, Q4299, Q4300, Q4301, Q4302, Q4303, Q4304, Q4305, Q4306, Q4307, Q4308, Q4309, Q4310, Q4311, Q4312, Q4313, Q4314, Q4315, Q4316, Q4317, Q4318, Q4319, Q4320, Q4321, Q4322, Q4323, Q4324, Q4325, Q4326, Q4327, Q4328, Q4329, Q4330, Q4331, Q4332, Q4333, Q4334, Q4335, Q4336, Q4337, Q4338, Q4339, Q4340, Q4341, Q4342, Q4343, Q4344, Q4345, Q4346, Q4347, Q4348, Q4349, Q4350, Q4351, Q4352, Q4353, Q4354, Q4355, Q4356, Q4357, Q4358, Q4359, Q4360, Q4361, Q4362, Q4363, Q4364, Q4365, Q4366, Q4367, Q4368, Q4369, Q4370, Q4371, Q4372, Q4373, Q4375, Q4376, Q4377, Q4378, Q4379, Q4380, Q4382, Q4383, Q4384, Q4385, Q4386, Q4387, Q4388, Q4389, Q4390, Q4391, Q4392, Q4393, Q4394, Q4395, Q4396, Q4397, V2790, [Deleted 7/2024: Q4210, Q4277]

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
12/15/2025	Document updated. The following changes were made to Coverage: 1) Added NuShield® to list of medically necessary products for treatment of nonhealing diabetic lower-extremity ulcers; 2) Removed "not medical necessary" statements under Diabetic Lower-Extremity Ulcers section; 3) Added "e.g." to list of medically necessary products for treatment of specified ophthalmic indications; 4) Modified conditional criteria for multiple indications under "Ophthalmic Indications" section; 5) Removed NOTE 1; 6) Modified comprehensive experimental, investigational and/or unproven statement on "all other human amniotic membrane products" without change to intent; and 7) Moved list, with additions, of experimental, investigational and/or unproven products to a Table in Policy Guidelines section. Added reference 4-6, 9, and 26.
04/01/2025	Coverage revised to add PalinGen Dual-Layer Membrane, Abiomend Xplus Membrane/Abiomend Xplus Hydromembrane, Abiomend Membrane/Abiomend Hydromembrane, XWRAP Plus, XWRAP Dual, ChoriPly, AmchoPlast FD, EPIEXPRESS, CYGNUS Disk, Amnio Burgeon Membrane and Hydromembrane, Amnio Burgeon XPlus membrane and XPlus Hydromembrane, Amnio Burgeon Dual-Layer Membrane, Dual Layer Amnio Burgeon X-Membrane, and AmnioCore SL to the list of experimental, investigational and/or unproven products.
03/15/2025	Coverage revised to add Shelter™ DM Matrix, Rampart™ DL Matrix, Sentry™ SL Matrix, Mantle™ DL Matrix, Palisade™ DM Matrix, Enclose™ TL Matrix, Overlay™ SL Matrix, and Xceed™ TL Matrix to the list of experimental, investigational and/or unproven products.
07/01/2024	Document updated with literature review. Added AmnioExcel® to the list of medically necessary products for the treatment of nonhealing diabetic lower extremity ulcers. Added ACApatch, Acesso, Acesso ac, alloPLY, AmchoPlast, AmnioTX, ArdeoGraft, CaregraFT, DermaBind FM, DuoAmnio, E-Graft, MOST, PelloGraft, Reeva FT, RegeneLink Amniotic Membrane Allograft, RenoGraft,

	SanoGraft, Singlay, TOTAL, VitoGraft to the experimental, investigational and/or unproven product listing. Added reference 20.
09/15/2023	Reviewed. No changes.
01/15/2023	Coverage revised to add Dual Layer Impax Membrane, SurGraft TL and Cocoon Membrane to the list of experimental, investigational, and/or unproven products.
12/01/2022	Document updated with literature review. The following changes were made to Coverage: 1) Added: Treatment of nonhealing diabetic lower-extremity ulcers using one of the above listed products may be considered medically necessary for a maximum of 12 weeks when there is evidence of wound healing (e.g., signs of epithelization and reduction in ulcer size). Additional applications of any product beyond 12 weeks are considered not medically necessary regardless of wound status; 2) Revised the experimental, investigational and/or unproven statement to include (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly); and repair following Mohs micrographic surgery; 3) Edits made to the experimental, investigational and/or unproven example list on human amniotic products. Added the following reference: 40; renumbered others.
02/01/2022	Document updated with literature review. The following changes were made to Coverage: 1) Affinity added to medically necessary statement for the treatment of diabetic foot ulcers; 2) Edits made to experimental, investigational and/or unproven example list on human amniotic products. Added the following references: 6, 27, 40 and 41.
12/15/2020	Coverage revised to add GrafixPL®, GrafixPL Prime™, Grafix® Prime to list of covered products for treatment of non-healing lower extremity diabetic ulcers. Those products removed from the experimental, investigational and/or unproven listing. No other changes made.
11/15/2020	Document updated with literature review. Coverage revised to include list of products considered experimental, investigational and/or unproven. Rationale and references revised; references 4, 8, 12, 25, 34 and 35 added.
05/01/2020	Document updated with literature review. The following changes were made: EpiCord® added as a medically necessary product for treatment of nonhealing diabetic lower-extremity ulcers when there is medical documentation of less than 20% decrease in wound area with standard wound care for at least 2 weeks. Human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) may be considered medically necessary for the treatment of the following ophthalmic indications: Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy which may include 5 days of pressure patching, therapeutic contact lens, topical lubricants and topical antibiotics; OR Corneal ulcers and melts that do not respond to initial conservative therapy which may include 2 days of patching, therapeutic contact lens, and topical antimicrobial agents; OR Corneal perforation when

	there is active inflammation after corneal transplant requiring adjunctive treatment; OR Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty); OR Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient; OR Moderate or severe Stevens-Johnson syndrome; OR Persistent epithelial defects that do not respond to conservative therapy (See NOTE 1); OR, 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; OR Moderate or severe acute ocular chemical burn. Note 2 added identifying the Tear Film and Ocular Surface Society staged management for dry eye disease. Human amniotic membrane grafts with suture or glue may be considered medically necessary for the treatment of corneal perforation when corneal tissue is not immediately available; or pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft. References revised and renumbered; added references 5, 6, 13, 19, 21, 23, 24, 28, 29, 30, 33.
08/01/2018	New medical document. Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products (AmnioBand® Membrane, Biovance®, Epifix®, Grafix™) may be considered medically necessary when there is medical record documentation of less than a 20% decrease in wound area with standard wound care for at least 2 weeks. Sutured human amniotic membrane grafts may be considered medically necessary for the treatment of the following ophthalmic indications: Neurotrophic keratitis, Corneal ulcers and melts, Pterygium repair, Stevens-Johnson syndrome, and Persistent epithelial defects (See NOTE 1). NOTE 1: 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. Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. Sutured human amniotic membrane grafts are considered experimental, investigational and/or unproven for the treatment of all other ophthalmic conditions including but not limited to dry eye syndrome, burns, corneal perforation, bullous keratopathy, limbus stem-cell deficiency, and after photorefractive keratectomy. Human amniotic membrane without suture (e.g., Prokera®, AmbioDisk™) for ophthalmic indications is considered experimental, investigational and/or unproven. Injection of micronized or particulated human amniotic membrane is considered experimental, investigational and/or unproven for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis. Injection of human amniotic fluid is considered experimental, investigational and/or unproven for all indications. All other human amniotic membrane products and indications not listed above are considered experimental, investigational and/or unproven,

	including but not limited to treatment of lower-extremity ulcers due to venous insufficiency.