Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 7/1/25**
(See policy history boxes for previous effective dates)

Title: Amniotic Membrane and Amniotic Fluid (Human)

Description/Background

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

HUMAN AMNIOTIC MEMBRANE

Human amniotic membrane (HAM) consists of two conjoined layers, the amnion, and chorion, and forms the innermost lining of the amniotic sac. 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 dehydrated HAM products, resulting in a readily available tissue with regenerative potential. In support, one dehydrated HAM product has been shown to elute

growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.(2)

Use of a HAM graft, which is fixed 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 not addressed in this policy. ”

Regulatory Status

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. 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).(4)

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 Public Health Service Act and 21 Code of Federal Regulation 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 Food and Drug Administration through the 510(k) process for the ophthalmic conformer that incorporates amniotic membrane (K032104; product code: NQB). The Food and Drug Administration determined that this device was substantially equivalent to the Symblepharon Ring. The Prokera™ device is intended “for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred.”(5) The development of Prokera, a commercially available product, was supported in part by the National Institute of Health and the National Eye Institute.

Medical Policy Statement

The safety and effectiveness of select human amniotic membrane products have been established. They may be useful therapeutic options when indicated.

Injection of amniotic fluid is experimental/ investigational for all indications. The safety, effectiveness, and improvement in health outcomes have not been scientifically demonstrated or proven to be better than the standard of care.

Inclusionary and Exclusionary Guidelines

Inclusions

Treatment of nonhealing* diabetic lower-extremity venous stasis ulcers using the following human amniotic membrane products

- Affinity®
- AmnioBand® Membrane
- Biovance®
- Epicord®
- Epifix®
- Grafix™

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

Human amniotic membrane grafts with or without suture for the treatment of any of the following ophthalmic indications:

- Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy[a]
- Corneal ulcers and melts that do not respond to initial conservative therapy[a]
- 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 to conservative therapy[a]
- Severe dry eye (DEWS 3 or 4)[b] with ocular surface damage and inflammation that remains symptomatic after conservative therapy[a]
- Moderate or severe acute ocular chemical burn.

Human amniotic membrane grafts with suture or glue for the treatment of any of the following ophthalmic indications:

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

Treatment of wounds using the following human amniotic membrane grafts when criteria are met:

- Vendaje[b] when used as a protective covering during repair and reconstruction of one of the following:
  - Chronic or acute pressure sores/ulcers related to disease processes
  - Partial to full thickness burns
  - Draining wounds
  - Post-surgical wounds
  - Trauma wounds
- VIM™ Human Amniotic Membrane when used as a wound covering or barrier in one of the following wounds:
  - Surgical
  - Orthopedic
  - Ophthalmic

- Zenith amniotic membrane when used as a barrier or cover for one of the following that have not responded to conventional therapy:
  - Acute or chronic non-healing wounds, including but not limited to:
    - Noninfected partial or full-thickness diabetic foot ulcers
    - Venous leg ulcers
    - Pressure ulcers
    - Surgical wounds
  - Burn injuries

[a] *Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching.*

[b] *Does not include Vendaje AC*

Exclusions

All other human amniotic membrane products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) and indications not outlined under inclusions, including but not limited to:

- Grafts with or without suture for ophthalmic indications
- Injection of micronized or particulated human amniotic membrane for all indications, including but not limited to treatment of:
  - Osteoarthritis and plantar fasciitis
- Injection of human amniotic fluid for all indications
- Treatment of lower-extremity ulcers due to venous insufficiency
- Use of amniotic membrane products following Mohs micrographic surgery

Refer to PG tables - PG1 (EST) and PG2 (EI) below for clarification of individual products with assigned codes.

Policy Guidelines

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

Table PG1 Amniotic Products Listed in the Inclusion Criteria

Trade Name	Supplier	HCPCS Code
Affinity®	Organogenesis (previously NuTech Medical)	Q4159
AmbioDisk	Katena	65778
AmnioBand® Membrane	MTF Wound Care	Q4151
Biovance®	Celularity	Q4154
Epifix®	MiMedx	Q4186
Epicord®	MiMedx	Q4187
Grafix®	Osiris	Q4132, Q4133
Prokera	BioTissue	65778
Vendaje®	BioStem Technologies	Q4252
Vim®	Cook Biotech Inc.	Q4251
Zenith amniotic membrane	CyteMed	Q4253

Table PG2 Other Amniotic Products with HCPCS Codes – Investigational

Trade Name	Supplier	HCPCS Code

Acapatch	RegenTX Partners	Q4325
Acesso	Dynamic Medical Services LLC, Surgenex	Q4311
Acesso AC	Dynamic Medical Services LLC, Surgenex	Q4312
Acesso DL	Dynamic Medical Services LLC, Surgenex	Q4293
Acesso TL	Dynamic Medical Services LLC, Surgenex	Q4300
Activate matrix, per square centimeter		Q4301
Allogen	Vivex Biomedical	Q4212
Alloply	RegenTX Partners	Q4323
AlloWrap™	AlloSource	Q4150
Amchoplast	RMBB Health	Q4316
American amnion	BioStem Technologies	Q4307
American amnion AC	BioStem Technologies	Q4306
American amnion AC tri-layer,	BioStem Technologies	Q4305
AmnioAMP-MP	Stratus BioSystems	Q4250
Amnioarmor™	Tissue Transplant Technology	Q4188
AmnioBand® or Guardian	MTF Biologics	Q4168
Amniobind	Predictive Biotechnology	Q4225
Amniocore™	Stability Biologics	Q4227
Amnicore pro	Stability Biologics	Q4298
Amnicore pro+	Stability Biologics	Q4299
Amniocyte	Predictive Biotech	Q4242
AmnioExcel®	Integra	Q4137
Amnio quad-core	Stability Biologics	Q4294
AmnioMatrix®	Integra Life Sciences	Q4139
Amniorepair or AltiPly	Zimmer Biomet	Q4235
Amniotext	Regenerative Labs	Q4245
Amniotext patch	Regenerative Labs	Q4247
Amnio tri-core amniotic	Stability Biologics	Q4295
Amniotx	RegenTX Partners	Q4324
Amniowound	Alpha Tissue	Q4181
AmnioWrap2™	Direct Biologics	Q4221
Amniply	International Tissue	Q4249
Artacent ac (patch)	Tides Medical	Q4190
Artacent® Cord	Tides Medical	Q4216
Artacent® Wound	Tides Medical	Q4169
Articent ac (flowable)	Tides Medical	Q4189
Ascent	StimLabs	Q4213
Axoloti graft	Axolotl Biologix	Q4331
Axoloti dualgraft™	Axolotl Biologix	Q4332
Axolotl ambien or Axolotl Cryo	Axolotl Biology	Q4215
Barrera SL™ or Barrera DL™	RegenTx Partners	Q4281
BioDDryFlex®	BioD	Q4138
BioDfence™	Integra Life Science	Q4140
Biovance trilayer or Biovance 3L	Celularity Inc	Q4283
BioWound, BioWound Plus™, BioWound XPlus™	HRT[a]	Q4217
Caregraft	RegenTX Partners	Q4322
CarePatch™	ExtremityCare	Q4236
Celera	Nvision Biomedical Technologies, Inc	Q4259
Cellesta Cord	Ventris Medical	Q4214
Cellesta flowable	Ventris Medical	Q4185

Cellesta/Cellesta duo	Ventris Medical	Q4184
Clarix®	Amniox Medical	Q4156
Clarix® Flo	Amniox Medical	Q4155
Cocoon	Pinnacle Transplant Technologies	Q4264
Cogenex amniotic membrane	Ventris Medical	Q4229
Cogenex flowable amnion	Ventris Medical	Q4230
Amniocore™	Stability Biologics	Q4227
Amnicore pro	Stability Biologics	Q4298
Compete AA	Samaritan Biologics LLC	Q4303
Complete ACA	Samaritan Biologics LLC	Q4302
Complete FT	Samaritan Biologics	Q4271
Complete SL	Samaritan Biologics	Q4270
Corecyte	Predictive Biotech	Q4240
Coretext or Protext	Regenerative Labs	Q4246
Corplex	StimLabs	Q4232
Corplex P	StimLabs	Q4231
Cryo-cord	Royal Biologics	Q4237
Cygnus	Vivex Biomedical	Q4170
Cygnus dual	Vivex Biologics	Q4282
Dermabind CH	Health Tech Wound Care	Q4288
Dermabind DL	Health Tech Wound Care	Q4287
Dermabind FM	Health Tech Wound Care	Q4313
Dermabind SL	Health Tech Wound Care	Q4284
Dermacyte	Merakris Therapeutics	Q4248
Dermavest™ or Plurivest	AediCell[a]	Q4153
Duoamnion, per square centimeter	Samaritan Biologics	Q4327
E-graft	Skye Biologic	Q4318
Emerge matrix	Sequence LifeScience, Inc	Q4297
Enverse™	StimLabs, LLC	Q4258
Epieffect	MiMedx Group, Inc	Q4278
Epifix Injectable	MiMedx	Q4145
Esano A	Evolution Biologyx, LLC	Q4272
Esano AAA	Evolution Biologyx, LLC	Q4273
Esano AC	Evolution Biologyx, LLC	Q4274
Esano ACA	Evolution Biologyx, LLC	Q4275
Floweramnioflo	Flower Orthopedics	Q4177
Floweramniopatch	Flower Orthopedics	Q4178
Fluid flow or Fluid GF	BioLab Sciences	Q4206
Genesis	Genesis Biologics	Q4198
Grafix Plus	Smith+Nephew	Q4304
Guardian/AmnioBand®	MTF Wound Care	Q4151
Impax Membrane	Comprehensive Biological Solutions	Q4262
Interfyl®	Celularity	Q4171
Lamellas	Keyport Management	Q4292
Lamellas XT	Keyport Management	Q4291
Matrion	LifeNet Health	Q4201
Membrane graft/membrane wrap	Misc service	Q4205
Membrane wrap-hydor	BioLab Sciences	Q4290
MLG complete™	Samaritan Biologics LLC	Q4256
Most	Samaritan Biologics	Q4328
Neopatch or Therion	CryoLife	Q4176
NeoStim	NeoStim, LLC	Q4266
NeoStim DL	NeoStim, LLC	Q4267
NeoStim TL	NeoStim, LLC	Q4265
Neox® Cord	Amniox Medical	Q4148

Neox® Flo	Amniox Medical	Q4155
Neox® Wound	Amniox Medical	Q4156
Novachor	Organogenisis	Q4191
Novafix DL	Triad Life Sciences	Q4254
Novafix®	Triad Life Sciences	Q4208
NuShield	Organogenesis	Q4160
Orion	Legacy Medical Consultant, LLC	Q4276
PalinGen® Membrane	Amnio ReGen Solutions	Q4173
PalinGen® SportFlow	Amnio ReGen Solutions	Q4174
Pellograft, per square centimeter	Surgenex	Q4320
Plurivest™	AediCell	Q4153
Polycyte	Predictive Biotech	Q4241
Procenta	Lucina BioSciences	Q4310
Rebound matrix	Sequence LifeScience, Inc	Q4296
Reeva FT	Legacy Medical	Q4314
Regenelink amniotic membrane allograft	LifeLink Foundation	Q4315
Reguard	New Life Medical	Q4255
Relese™	StimLabs, LLC	Q4257
Renograft	Surgenex	Q4321
Restorigin	UMTB Biomedical	Q4191
Restorigin Injectable	UMTB Biomedical	Q4192
Revita	StimLabs	Q4180
Revitalon™	Medline Industries	Q4157
Revoshield + amniotic barrier	4Front Strategic Partners, Surgenex, LLC	Q4289
Sanograft, per square centimeter	Surgenex	Q4319
Sanopellis	ReNu LLC	Q4308
Signature apatch	Signature Biologics	Q4260
Singlay	Samaritan Biologics	Q4329
Stravix PL and Stravix	Osiris	Q4133
Surgenex, Surfactor, and Nudyn	Surgenex	Q4233
Surgicord	Synergy Biologics	Q4218
SurgiGRAFT Dual™	Synergy Biologics	Q4219
SurgiGRAFT™	Synergy Biologics	Q4183
SurGraft®	Surgenex	Q4209
SurGraft® FT	Surgenex	Q4268
SurGraft® TL	Surgenex	Q4262
SurGraft® XT	Surgenex	Q4269
Tag	Conventus Flower Orthopedics	Q4261
Vendaje AC	BopStem Technologies	Q4279
Via matrix	VIVEX Biologic	Q4309
Vitograft	Surgenex	Q4317
WoundEx®	Skye Biologics[a]	Q4163
WoundEx® Flow	Skye Biologics[a]	Q4162
Woundfix, Woundfix Plus, Wounfix XPlus (see BioWound above)	HRT	Q4217
Woundplus	Skye Biologics	Q4326
Xcell amnio matrix®	Precise Bioscience	Q4280
Xcellerate	Precise Bioscience	Q4234
Xwrap	Applied Biologics	Q4204

HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation

[a]Processed by HRT and marketed under different trade name

DEWS Definition and Classification

Table PG3 Dry Eye Severity Grading Scheme (45)

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival Injection	None to mild	None to mild	+/-	+/++
Conjunctival Staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, decreased meniscus	Filamentary keratitis, mucus clumping, increased tear debris	Filamentary keratitis, mucus clumping, increased tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤ 10	≤ 5	Immediate
Schirmer score (mm/5 min)	Variable	≤ 10	≤ 5	≤ 2

* Must have signs AND symptoms. TBUT: fluorescein tear break -up time. MGD: meibomian gland disease

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

Q4132	Q4133*	Q4151	Q4154	Q4159	Q4186
Q4187	Q4251	Q4252	Q4253	65778	65779

Other codes (investigational, not medically necessary, etc.):

Q4133 *	Q4137	Q4138	Q4139	Q4140	Q4145
Q4148	Q4150	Q4153	Q4155	Q4156	Q4157
Q4160	Q4162	Q4163	Q4168	Q4169	Q4170
Q4171	Q4173	Q4174	Q4176	Q4177	Q4178
Q4180	Q4181	Q4183	Q4184	Q4185	Q4188
Q4189	Q4190	Q4191	Q4192	Q4194	Q4198
Q4199	Q4201	Q4204	Q4205	Q4206	Q4208
Q4209	Q4211	Q4212	Q4213	Q4214	Q4215
Q4216	Q4217	Q4218	Q4219	Q4221	Q4224
Q4225	Q4227	Q4229	Q4230	Q4231	Q4232
Q4233	Q4234	Q4235	Q4236	Q4237	Q4239

Q4240	Q4241	Q4242	Q4245	Q4246	Q4247
Q4248	Q4249	Q4250	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	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				

**Q1333 is EST for Grafix and Grafix PL and EI for Stravix and Stravix PL*

If no specific HCPCS code exists for a product, unlisted code Q4100 would be used.

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length 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 to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 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 PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with diabetic lower extremity ulcers that have failed to heal with standard of care therapy.

Interventions
The therapy being considered is amniotic membrane or placental membrane applied every one to two weeks. It is applied in addition to the standard of care (SOC).

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

Outcomes
The primary end points of interest for trials of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration (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.

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

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

Review of Evidence

At least 7 RCTs have evaluated rates of healing with amniotic membrane grafts (AMG) or placental membrane graft compared to SOC or an advanced wound therapy in patients with chronic diabetic foot ulcers (see Table 1). The number of patients in these studies ranged from 25 to 155. HAM or placental membrane grafts improved healing compared to SOC by 22% (EpiCord vs Alginate dressing) to 60% (EpiFix) in intention-to-treat 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
Serena et al (2020)[6]	U.S.	14		76 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers unresponsive to SOC and extending into dermis, subcutaneous tissue, muscle, or tendon	N=38; Affinity	N=38; SOC
Ananian et al. (2018)[7]	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 wks
Tettelbach et al. (2018)[8]	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)[9]				80 patients with non-healing (4 weeks) diabetic foot ulcers	AmnioBand Membrane plus SOC	SOC
Snyder et al. (2016)[10]				29 patients with non-healing diabetic foot ulcers	AmnioExcel plus SOC	SOC
Zelen et al. (2015, 2016)[11,12]		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)[13]	U.S.	14		110 patients with non-healing (4 weeks) lower extremity ulcers	EpiFix	SOC with alginate dressing
Lavery et al. (2014)[14]				97 patients with chronic diabetic foot ulcers	Grafix Weekly	SOC

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

Table 2. Summary of Key RCT Results

Study	Wounds Healed	Wounds Healed	Time to Complete Healing	Adverse Events and Number of Treatments
Serena et al (2020)[6]	*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)[7]	*8 Weeks (PP) n (%)*			Patients with Index Ulcer Related Adverse Events n (%)
N	62			75
Grafix	15 (48.4%)			1 (5.9%)

Dermagraft	12 (38.7%)			4 (16.7%)
Diff (95% CI)	9.68% (−10.7 to 28.9)			
Lower bound for non-inferiority	-15%			
Tettlebach et al (2018)[8,]	*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)[9,]	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)[10,]	*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)[11,12,]	*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 (2019)[13,]		*Wounds Healed at 12 Weeks (ITT) n(%)*		
N		110		110
EpiFix		38 (81)		
SOC		28 (55)		
p-value				
Lavery et al (2014)[14,]		Wounds Healed at 12 Weeks		Patients With Adverse Events
N		97a	97	97
Grafix		62.0%	42.0	44.0%
SOC		21.3%	69.5	66.0%
p-value		<0.001	0.019	0.031

Difference in wounds healed between amniotic or placental membrane and SOC	Affinity 26% AmnioBand 55% AmnioExcel 33% EpiFix 60%	Affinity 28% EpiCord 22% Grafix 41%

CI: confidence interval; DIFF: difference; HR: hazard ratio; ITT: intention-to-treat; NR: not reported; PP: per-protocol; RCT: randomized controlled trial; SOC: standard of care.
a. Power analysis indicated that 94 patients per arm would be needed. However, after a prespecified interim analysis at 50% enrollment, the blinded review committee recommended the trial is stopped due to the efficacy of the treatment.
Limitations in study design and conduct are shown in Table 3. Studies without notable limitations reported power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and ITT analysis. Limitations from the RCT with AmnioExcel (Snyder et al[2016]) [9] 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]
Serena et al (2020)[6]	3. The randomization process and allocation concealment were not described	1, 2. No blinding of patients or investigators. Assessors were blinded		1. Although ITT analysis, there was substantial missing data for depth and volume with the digital analysis system.		
Ananian et al (2018)[7]		2, 3. No blinding for outcomes assessment				
Tettelbach et al (2018)[8]		1, 2, 3. No blinding				
DiDomenico et al (2018)[9]						
Snyder et al (2016)[10]				1. There was high loss to follow-up with discontinuation of 8 of 29 participants	1. Power analysis was not reported	
Zelen et al (2015, 2016)[11,12]				1. Thirteen of 35 patients in the SOC group exited the study at 6 weeks due to less than 50% healing, which may have affected the 12-week results.		
Tettelbach et al (2019)[13]		1, 2. No blinding of patients or investigators. Assessors were blinded				
Lavery et al (2014)[14]						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
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.(15), 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 eight weeks and a mean of 2.4 amniotic membrane applications.

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

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

Study	Study Design	Participants	Treatment Delivery
Smiell et al. (2015)[15]	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)[16]	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)[15]	Biovance	41.6%	8 weeks	2.4
Frykberg et al. (2016)[16]	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), 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 used power analysis, blinded assessment of wound healing, and ITT analysis. For the HAM products that have been sufficiently evaluated (i.e., Affinity, AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix), results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries. No studies were identified that compared different amniotic

or placental products, and indirect comparison between products is limited by variations in the patient populations.

LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

Amniotic Membrane

Clinical Context and Therapy Purpose
The purpose of dehydrated 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 PICOs were used to select literature to inform this review.

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

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

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

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

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

Review of Evidence
Three RCTs, 2 using EpiFix and 1 using AmnioBand, were identified on amniotic membrane grafts for venous leg ulcers. Serena et al (2014) reported on an industry sponsored multicenter open-label RCT that compared EpiFix d-HAM plus compression therapy with compression therapy alone for venous leg ulcers (see Tables 6 and 7).(17) The primary outcome in this trial was the proportion of patients with 40% wound closure at four weeks, which was achieved by about twice as many patients in the combined EpiFix group compared with the control group (see Table 8). However, a similar percentage of patients in the combined EpiFix group and the control group achieved complete wound closure during the four week study. There was no

significant difference in healing for wounds given one vs two 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 four weeks (n=20) had a closure rate of 80% by 24 weeks; however, this analysis did not take into account additional treatments after the four-week randomized trial period.

A second industry-sponsored multicenter open-label RCT, (Bianchi et al [2017]), evaluated the time to complete ulcer healing following weekly treatment with EpiFix d-HAM and compression therapy or compression therapy with standard dressing (see Tables 6 and 7).(18,19) Patients treated with EpiFix had a higher probability of complete healing by 12 weeks, as adjudicated by blinded outcome assessors (hazard ratio, 2.26; 95% CI, 1.25 to 4.10; p=0.01), and improved time to complete healing, as assessed by Kaplan-Meier analysis. 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 (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=0.0473). There were several limitations of this trial (see Tables 8 and 9). In the per-protocol analysis nineteen (15%) patients were excluded from the analysis, and the proportion of patients excluded differed between groups (19% from the EpiFix group vs 11% from the control group). There was also a difference between the groups in how treatment failures at eight weeks were handled. Patients in the control group who did not have a 40% decrease in wound area at eight weeks were considered study failures and treated with advanced wound therapies. 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).(20) 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

					Interventions	
Study	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Serena et al. (2014)[17]	U.S.	8	2012-2014	84 patients with a full-thickness chronic VLU between 2 and 20 cm2 treated for at least 14 d	1 (n=26) or 2 (n=27) applications of EpiFix plus standard wound therapy (n=53)	Standard wound therapy (debridement with alginate dressing and compression) (n=31)
Bianchi et al. (2018, 2019)[18.19]	U.S.	15	2015-2017	128 patients with a full-thickness VLU of at least 30-d duration	Weekly EpiFix plus moist wound therapy plus compression (n=64 ITT; 52 PP)	Moist wound therapy plus compression (n=64 ITT; 57 PP)
Serena et al (2022)[20]	U.S.	8	2015-2019	101 patients with full-thickness VLU (≥2 to <20cm2) 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; PP: per-protocol; RCT: randomized controlled trial; SOC: standard of care; 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**	**Complete Wound Closure at 16 Weeks n (%)**		
			PP		**ITT**	**PP**	**ITT**
Serena et al (2014)[17]				ITT			
EpiFix	62	11.3					
Control	32	12.9					
p-Value	0.005						
Bianchi et al (2018, 2019)[18,19]							
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)[20]							
Amnioband	75		30 (75)	100 (5.3)			
Control	85		6 (30)	75 (68.7)			
p-value			.001	.012			

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

Table 8. Relevance Limitations

Study	**Population[a]**	**Intervention[b]**	**Comparator[c]**	**Outcomes[d]**	**Follow-Up[e]**
Serena et al. (2014)[17]					

Bianchi et al. (2018, 2019)[18,19]	1. Advanced wound therapy was allowed in the control group before the primary endpoint was reached.
Serena et al (2022)[20]	

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

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)[17]						
Bianchi et al. (2018, 2019)[18,19]		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)[20]		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 limitations 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.(15) Of the 179 treated, 28 (16%) ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of 8 weeks and a mean of 2.4 amniotic membrane applications. However, without a control group, the percentage of wounds that would have healed with SOC is unknown.

Section Summary: Lower-Extremity Ulcers due to Venous Insufficiency
The evidence on HAM for the treatment of venous leg ulcers includes two multicenter RCTs with EpiFix and 1 multicenter RCT with AmnioBand Membrane. One RCT reported a larger percent wound closure at four weeks, but the percentage of patients with complete wound closure at four weeks did not differ between EpiFix and the SOC. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression. Although a significant difference in complete healing was reported, data interpretation is limited by the differential loss to follow-up and exclusions between groups. 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) of cryopreserved human amniotic membrane (c-HAM) suspension with amniotic fluid–derived cells for the treatment of knee osteoarthritis.(21) 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.

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 PICOs were used to select literature to inform this review.

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

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

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

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

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

Study Selection Criteria
Methodologically credible studies were selected using the same principles described above.

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

Systematic Review
A 2016 network meta-analysis of 22 RCTs (total n=1216 patients) compared injection therapies for plantar fasciitis.(22) 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 cc, and 1.25 cc) and 8-week follow-up.(23) A subsequent RCT by Cazzell et al (2018) enrolled 145 patients and reported 3-month follow-up (see Table 11).(24) In the Cazzell et al (2018) RCT, amniotic membrane injection led to greater improvements in the VAS for pain and the Foot Functional Index between baseline and 3 months (see Table 10) compared to controls. VAS at

3 months had decreased to 17.1 in the AmnioFix group compared to 38.8 in the placebo control group, which would be considered a clinically significant difference.

Table 10. Summary of Key RCT Characteristics

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

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

Table 11. Summary of Key RCT Results

Study	Change in VAS-Pain Between Baseline and 3 mo (95% CI)	Change in FFI-R Between Baseline and 3 mo (95% CI)	Patients with Adverse Events up to 3 mo n (%)	Patients with Serious Adverse Events up to 3 mo n (%)
Cazzell et al. (2018); AIPF004	n=145	n=145	n=145	n=145
AmnioFix	54.1 (48.3 to 59.9)	35.7 (30.5 to 41.0)	30 (41.1%)	1 (0.6%)
Placebo	31.9 (24.8 to 39.1)	22.2 (17.1 to 27.4)	39 (54.2%)	3 (1.8%)
Diff (95% CI)	22.2 (13.1 to 31.3)	13.5 (6.2 to 20.8)		
p-Value	<0.001	<0.001		

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

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

Table 12. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Cazzell et al. (2018) AIPF004			3. Placebo injections were used. A control delivered at a similar intensity as the investigational treatment would be corticosteroid injections.		1, 2. Follow-up to 12 mo 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 limitations 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)		1. Single blinded trial, although outcomes		1. Only the first 3 months of 12-		

AIPF004	were self-reported by blinded patients	month follow-up were reported.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations 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 note 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 PICOs were used to select literature to inform this review.

Populations

The relevant population of interest are 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 same principles described above.

Review of Evidence
Khokhar et al (2005) reported on an RCT of 30 patients (30 eyes) with refractory neurotrophic corneal ulcers who were randomized to HAM transplantation (n=15) or conventional treatment with tarsorrhaphy or bandage contact lens.(23) 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.(25) 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 PICOs were used to select literature to inform this review.

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

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

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

Outcomes

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

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

Study Selection Criteria
Methodologically credible studies were selected using the same principles described above.

Review of Evidence
Liu et al (2019) conducted a systematic review of 17 studies (390 eyes) of amniotic membrane for corneal ulcers.(26) 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=0.089) 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<0.001).

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.(27) 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 = 0.01) and was reached in significantly more patients (72.7% vs 23.1%, p = 0.04). 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 = 0.047) and greater total improvement in visual acuity (log MAR 0.7 ± 0.6 vs 1.6± 0.9, p = 0.016).

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.(25) 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 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 PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are 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 one to three months**.**

Study Selection Criteria
Methodologically credible studies were selected using the same principles described above.

Review of Evidence
No evidence was identified for this indication.

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

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

Clinical Context and Therapy Purpose
The purpose of HAM in individuals who have bullous keratopathy is to provide a treatment option that is an alternative to or an improvement on existing therapies. Bullous keratopathy is characterized by stromal edema and epithelial and subepithelial bulla formation.

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

Populations
The relevant population of interest are 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 same principles described above.

Review of Evidence
Dos Santos Paris et al (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy.(28) 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 two years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with the use of HAM only if the pain did not resolve.

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 limbal stem cell deficiency (LSCD) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

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

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

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

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

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 same principles described above.

Review of Evidence
No RCTs were identified on HAM for LSCD.

Keirkhah et al (2008) reported on the use of HAM in 11 eyes of 9 patients who had LSCD.(29) Patients underwent superficial keratectomy to remove the conjunctivalized pannus followed by HAM transplantation using fibrin glue. An additional Prokera patch was used in seven patients. An improvement in visual acuity was observed in all but two patients. Pachigolla et al (2009) reported a series of 20 patients who received a Prokera implant for ocular surface disorders; six of the patients had limbal stem cell deficiency with a history of chemical burn.(30) Following treatment with Prokera, three of the six patients had a smooth corneal surface and improved vision to 20/40.(30) The other three patients had final visual acuity of 20/400, counting fingers, or light perception.

Section Summary: Partial LSCD with Extensive Diseased Tissue Where Selective Removal Alone is not Sufficient
No RCTs were identified on HAM for LSCD. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus.

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 PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are 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 same principles described above.

Review of Evidence

One RCT from India by Sharma et al (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or medical therapy alone.(31) The c-HAM was prepared locally and applied with fibrin glue rather than sutures. Application of c-HAM in the early stages of Stevens-Johnson syndrome resulted in improved visual acuity (p=0.042), better tear breakup time (p=0.015), improved Schirmer test results (p<0.001), and less conjunctival congestion (p=0.03). In the c-HAM group at 180 days, there were no cases of corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. These outcomes are dramatically better than those in the medical therapy alone group, which had 11 (44%) cases with corneal haze (p=0.001), 6 (24%) cases of corneal vascularization and conjunctivalization (p=0.03), and 6 (24%) cases of trichiasis and metaplastic lashes.

Section Summary: Moderate or Severe Stevens-Johnson Syndrome
The evidence on HAM for the treatment of Stevens-Johnson syndrome includes one 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 DOES 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 PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are 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 one to three months.

Study Selection Criteria
Methodologically credible studies were selected using the same principles described above.

Review of Evidence

Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease.(32) 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 does 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 PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are 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 nine domains with a score of one 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 same principles described above.

Review of Evidence
John et al (2017) reported on an RCT with 20 patients with moderate-to-severe dry eye disease who were treated with Prokera c-HAM or maximal conventional treatment.(33) The c-HAM was applied for an average of 3.4 days (range, 3-5 days), while the control group continued treatment with artificial tears, cyclosporine A, serum tears, antibiotics, steroids, and nonsteroidal anti-inflammatory medications. The primary outcome was an increase in corneal nerve density. Signs and symptoms of dry eye disease improved at both 1-month and 3-month follow-ups in the c-HAM group but not in the conventional treatment group. For example, pain scores decreased from 7.1 at baseline to 2.2 at 1 month and 1.0 at 3 months in the c-HAM group. In vivo confocal microscopy, reviewed by masked readers, showed a significant increase in corneal nerve density in the study group at 3 months, with no change in nerve density in the controls. Corneal sensitivity was similarly increased in the c-HAM group but not in controls.

The treatment outcomes in the DRy Eye Amniotic Membrane study (McDonald et al [2018]) was a retrospective series of 84 patients (97 eyes) with severe dry eye despite maximal medical therapy who were treated with Prokera self-retained c-HAM.(34) A majority of patients (86%) had superficial punctate keratitis. Other patients had filamentary keratitis (13%), exposure keratitis (19%), neurotrophic keratitis (2%), and corneal epithelial defect (7%). Treatment with Prokera for a mean of 5.4 days (range, 2 to 11) resulted in an improved ocular surface and reduction in the DEWS score from 3.25 at baseline to 1.44 at 1 week, 1.45 at 1 month and 1.47 at 3 months (p=0.001). Ten percent of eyes required repeated treatment. There was no significant difference in the number of topical medications following c-HAM treatment.

Section Summary: Severe Dry Eye with Ocular Surface Damage and Inflammation that does not Respond to Conservative Therapy
The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months.

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 PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are 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 same principles described above.

Review of Evidence
An RCT of 100 patients with chemical or thermal ocular burns was published by Tandon et al.(35) Half of the patients (n=50) had moderate ocular burns and the remainder (n=50) had severe ocular burns. All but eight of the patients had alkali or acid burns. Patients were randomized to HAM transplantation plus medical therapy or medical therapy alone. Epithelial healing, which was the primary outcome, was improved in the group treated with HAM, but there was no significant difference between the two groups for the final visual outcome, symblepharon formation, corneal clarity or vascularization.

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).(36) 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 two groups (2.06 logMAR for both groups). There was a trend for a decrease in corneal neovascularization (p=0.108); 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.(37)

Section Summary: Moderate or Severe Acute Ocular Chemical Burns
Evidence includes 3 RCT 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 PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are 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 same principles described above.

Review of Evidence
No RCTs were identified on corneal perforation.

Section Summary: Corneal Perforation When Corneal Tissue is not Immediately Available
The standard treatment for corneal perforation is corneal transplantation. Based on clinical input, sutured HAM may be used as a temporary measure when corneal tissue is not immediately available.

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

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

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

Populations
The relevant population of interest are 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 same principles described above.

Review of Evidence
RCTs have been reported on the use of amniotic membrane following pterygium repair. The American Academy of Ophthalmology (2013) published a technology assessment on options and adjuvants for pterygium surgery.(37) Reviewers identified four RCTs comparing conjunctival or limbal autograft procedure with amniotic membrane graft, finding that conjunctival or limbal autograft was more effective than HAM graft in reducing the rate of pterygium recurrence. A 2016 Cochrane review of 20 RCTs (total n=1866 patients) arrived at the same conclusion.(38)

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

Repair Following Mohs Microscopic Surgery

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

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

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

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

Comparators
Comparators of interest include surgical repair using autologous tissue (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 U.S. Food and Drug Administration (FDA) for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds:

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

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

Study Selection Criteria
Methodologically credible studies were selected using the same principles listed above.

Review of Evidence
No RCTs were identified for this indication.

Nonrandomized Studies
Toman et al (2022) conducted an observational study that compared repair using a dehydrated human amnion/chorion membrane product (Epifix) with surgical repair using autologous tissue in patients who underwent same-day repair following Mohs microsurgery for removal of skin cancer on the face, head, or neck (Table 14).(40) 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)	Retrospective, observational Propensity-score matching used to identify matched pairs	US	2014-2018	Patients who underwent Mohs microsurgery for removal of a basal or squamous cell carcinoma and required same day	n = 143	n = 143	Unclear; 9 months or later for postoperative cosmetic outcomes.

	repair for moderate- to high-risk defects on the face, head, and neck. Mean age 78.0 years; 76.9% male 100% white	

dHACM: dehydrated human amniotic/chorionic membrane.

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

Study	dHACM repair	Autologous tissue Repair	P
Toman et al (2022)	n = 143	n = 143	
• Experienced no complications, n (%)	140 (97.9)	102 (71.3)	<.0001
• Infection, n (%)	3 (2.0)	15 (10.0)	.004
• Bleeding or hematoma, n (%)	0 (0.0)	7 (5.0)	.015
• Wound dehiscence, n (%)	0 (0.0)	4 (3.0)	.122
• Surgical reintervention, n (%)	0 (0.0)	11 (8.0)	.0007
• Nonhealing wound, n (%)	0 (0.0)	5 (3.5)	.060
• Poor scar cosmesis, n (%)	0 (0.0)	21 (15.0)	<.0001
• Scar revision, n (%)	0 (0.0)	14 (9.8)	<.0001
• Follow-up visits, mean (SD)	3.4 (1.6)	2.5 (1.1)	<.0001
• Days to discharge, mean (SD)	30.7 (16.9)	30.3 (22.9)	.840

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

Table 16. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Toman et al (2022)	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)	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.

Trigger Point Therapy

Trigger points are discrete, focal, hyperirritable spots within a taut band of skeletal muscle fibers that produce local and/or referred pain when stimulated. Tender points also produce local pain when stimulated but lack the taut band of tissue and hyperirritability when palpated. The usual treatment consists of injections of an anesthetic, botulinum toxin, or corticosteroid into trigger points or tender points. It has recently been suggested that dehydrated amniotic/chorionic membrane allograft may offer a minimally invasive alternative to steroids and/or surgical repair.(44-45)

SUMMARY OF EVIDENCE

Diabetic Lower-Extremity Ulcers

For individuals who have nonhealing diabetic lower-extremity ulcers who receive a patch formulation of HAM (i.e., Affinity, AmnioBand Membrane, Biovance, EpiFix, Grafix), the evidence includes 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 nonhealing (<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, EpiFix, Grafix), results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Lower-Extremity Ulcers due to Venous Insufficiency

For individuals who have lower-extremity ulcers due to venous insufficiency who receive a patch formulation of HAM, the evidence includes 3 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of lower-extremity venous ulcers includes 2 multicenter RCTs with EpiFix and 1 multicenter RCT with Amnioband. One RCT reported 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 standard of care. A second multicenter RCT reported a significant difference in complete healing at 12 weeks, but the interpretation is limited by methodologic concerns. A 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 insufficient to determine the effects of the technology on health outcomes.

Osteoarthritis
For individuals who have knee osteoarthritis who receive an injection of suspension or particulate formulation of HAM or amniotic fluid, the evidence includes a feasibility study. 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 the effects of the technology on health outcomes.

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. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens. 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, which does 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 QOL. Corneal ulcers and melts are uncommon and variable and 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. Corneal ulcers and melts are uncommon and variable and RCTs are not expected. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Corneal Perforation when there is Active Inflammation after Corneal Transplant Requiring Adjunctive Treatment

For individuals who have corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No comparative evidence was identified for this indication. 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. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. 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 LSCD with extensive diseased tissue where selective removal alone is not sufficient who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No RCTs were identified on HAM for LSCD. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus. 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. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for the treatment of Stevens-Johnson includes 1 RCT with 25 patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Persistent Epithelial Defects and Ulceration That do not Respond to Conservative Therapy

For individuals who have persistent epithelial defects that does not respond to conservative therapy who receive HAM, the evidence is limited. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. No RCTs were identified on persistent epithelial

defects and ulceration. 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. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months. The evidence is sufficient to determine that the technology results in a meaningful 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 an RCT. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. 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. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. 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. The relevant outcomes are symptoms, morbid events, functional outcomes, and QOL. Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence. 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 amnionic/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 scarcosmesis (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.

Trigger Point Therapy
For individuals who have myofascial pain syndrome who receive trigger point injections, the evidence includes several randomized controlled trials (RCTs) and a systematic review of RCTs. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The results suggest a strong placebo effect of the treatment. There have been no long-term, double-blinded study of the use of amniotic fluid injections for trigger points or facet injections. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

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

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

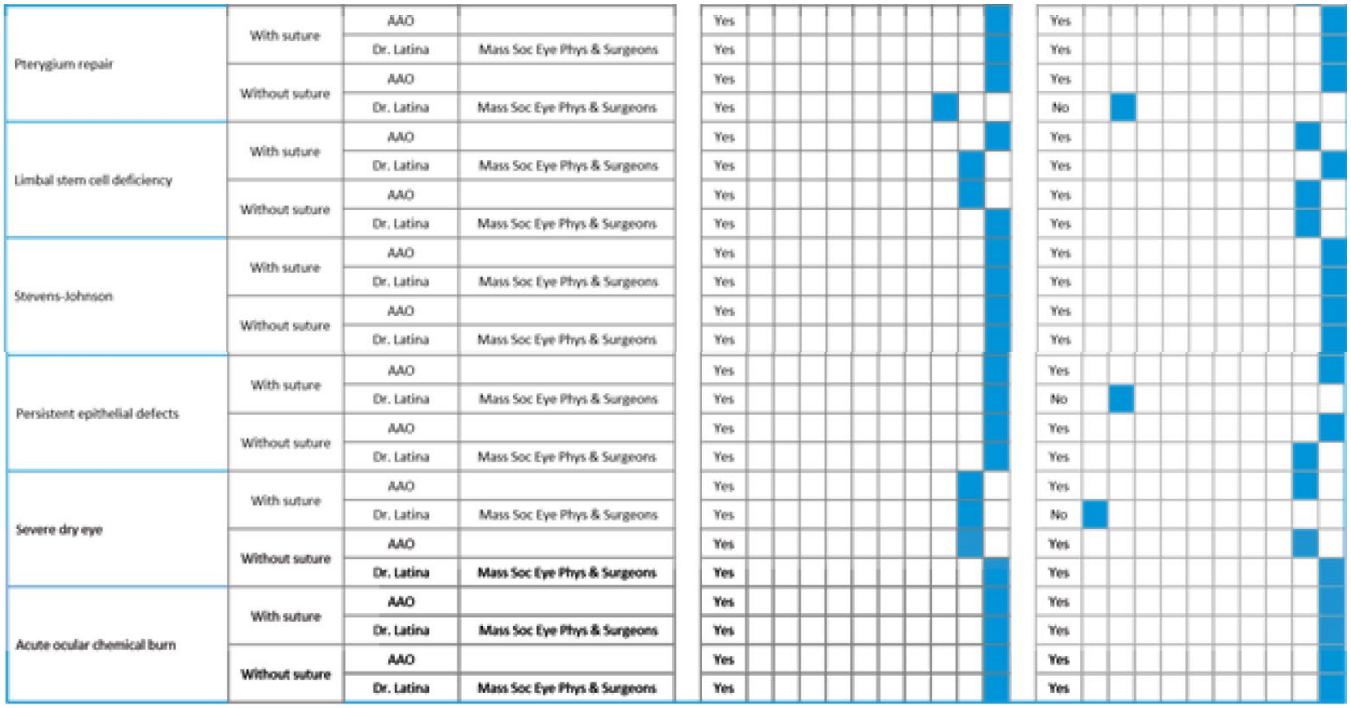
Clinical input was provided by the following specialty societies and physician members identified by a specialty society or clinical health system:

- American Academy of Ophthalmology (AAO)
- Mark Latina, MD, Ophthalmology. Tufts University School of Medicine, identified by Massachusetts Society of Eye Physicians and Surgeons

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by the specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide a review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a special society and/or physician member designated by the specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

Clinical Input Responses

Use of human amniotic membrane for following indications	Type of HAM	Respondent	Identified by	Confidence Level That Clinical Use Expected to Provide Clinically Meaningful Improvement in Net Health Outcome										Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice									
					NO					YES						NO					YES				
				Yes or No	5	4	3	2	1	1	2	3	4	5	Yes or No	5	4	3	2	1	1	2	3	4	5
Neurotrophic keratitis	With suture	AAO		Yes										■	Yes										■
		Dr. Latina	Mass Soc Eye Phys & Surgeons	Yes									■		Yes									■	
	Without suture	AAO		Yes										■	Yes										■
		Dr. Latina	Mass Soc Eye Phys & Surgeons	Yes										■	Yes									■	
Corneal ulcers and melts	With suture	AAO		Yes										■	Yes										■
		Dr. Latina	Mass Soc Eye Phys & Surgeons	Yes										■	No		■								
	Without suture	AAO		Yes										■	Yes										■
		Dr. Latina	Mass Soc Eye Phys & Surgeons	Yes										■	Yes										■
Corneal perforation	With suture	AAO		Yes										■	Yes										■
		Dr. Latina	Mass Soc Eye Phys & Surgeons	Yes										■	Yes										■
	Without suture	AAO		No	■										No	■									
		Dr. Latina	Mass Soc Eye Phys & Surgeons	No		■									No		■								
Bullous keratopathy	With suture	AAO		Yes										■	Yes										■
		Dr. Latina	Mass Soc Eye Phys & Surgeons	Yes									■		No		■								
	Without suture	AAO		Yes										■	Yes										■
		Dr. Latina	Mass Soc Eye Phys & Surgeons	Yes										■	Yes									■	



AAO: American Academy of Ophthalmology: Mass Soc Eye Phys & Surgeons: Massachusetts Society of Eye Physicians and Surgeons

Additional Comments

Neuropathic keratitis

- “Sutured and non-sutured human amniotic membrane HAM are both accepted and effective treatments for neurotrophic keratopathy that does not respond to conservative therapy in patients with corneal staining or an epithelial defect that (1) has failed to completely close after five days of conservative treatment, or (2) has failed to demonstrate a decrease in size after two 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. Failure of multiple modalities should not be required prior to moving to HAM. HAM requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in that regard over treatments that require multiple drops per day. Non-sutured HAM is the preferred initial treatment because it can be performed rapidly in an office setting, bypassing the delay associated with scheduling a procedure in an outpatient facility. It also avoids the facility fees associated with the sutured HAM procedure. Patients that are responding to non-sutured HAM may need a second or third application if healing is not yet complete. Those who show a poor response or poorly tolerate a non-sutured HAM device are candidates for sutured HAM.” (AAO)
- “In my opinion and based on the literature, the use of AM (with or without sutures) for treating neurotrophic keratoconjunctivitis is medically necessary when the standard therapy fails. It interrupts the disease process by controlling inflammation, preventing further damage and restoring ocular surface integrity. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

Corneal ulcers and melts

- “Corneal ulcers and melts comprise a wide range of disorders with varying etiologies. Common to many of these are an underlying inflammatory component. HAM has been shown to reduce inflammation and promote epithelial healing. These properties make HAM an effective adjunct in treating these conditions while the primary etiology is addressed with targeted therapy (e.g., corticosteroids, antibiotics, biologic immunomodulators). HAM is typically employed when there is a lack of response to initial medical treatment or where HAM can offer some degree of tectonic support in cases where there is significant stromal tissue loss. The varied and uncommon nature of the etiology of ulcers and melts makes it unlikely that there will ever be significantly-sized RCTs comparing HAM to conventional therapy or sutured vs. non-sutured HAM. There are numerous small series and case reports without controls showing improvement after HAM placement in cases that were not responding to conventional therapy.” (AAO)
- “Based on my experience, the use of AM at an early stage of the disease would prevent any unexpected complications such as infection, scarring, melt and perforation. Particularly, using AM without suture for this indication provides the advantage of in-office treatment without any delay. Furthermore, it avoids potential sight-threatening complications and achieves a clinically meaningful improvement in net visual outcome.” (Dr. Latina)

Corneal perforation

- “Multilayered sutured HAM has been performed in some cases of corneal perforation. While it offers some tectonic support, corneal tissue is the preferred graft material in these cases. HAM alone may be a reasonable temporizing alternative when corneal tissue is not immediately available. Non-sutured HAM would not offer significant tectonic support in these cases. Both sutured and non-sutured HAM reduces inflammation and promotes epithelial healing. It is therefore a useful adjunct in addition to corneal transplantation in those patients with active inflammation and perforation.” (AAO)
- “Depending on the size and location of the corneal perforation, treatment options include gluing, amniotic membrane transplantation, and corneal transplantation. The success rate of using AM to repair corneal perforation is reported to be as high as 93%. [1-7] Kim et al used multiple layers of AM with tissue glue in ten patients with large corneal perforations up to five mm and noted 90% success in complete closure of perforation.(10) AM offers the advantage of avoiding potential corneal graft rejection and postoperative astigmatism of tectonic corneal grafts.” (Dr. Latina)

Bullous Keratopathy

- “HAM is one of several modalities for treatment of bullous keratopathy due to corneal endothelial dysfunction. HAM does not address the underlying endothelial disease, so it is considered palliative rather than curative therapy. It is a reasonable alternative for patients who are not candidates for curative endothelial or penetrating keratoplasty. Sutured HAM has been shown to be as effective for bullous keratopathy as anterior stromal puncture (Paris F. Br J Ophthalmol 2013;97:980. PMID 23723410) and phototherapeutic keratectomy (Chawla B. Cornea 2010;29:976. PMID 20517149). Non-sutured HAM is a reasonable alternative to anterior stromal puncture as it is faster and simpler to perform. Sutured HAM in an operating room setting and non-sutured HAM in the office are of particular value in patients who have difficulty holding still for office procedures such as anterior stromal puncture in which there is a risk of increased corneal scarring or globe perforation with patient movement. HAM typically offers long-lasting pain relief in these cases, obviating the need for corneal transplantation with its associated increased risks (rejection, infection) and costs.” (AAO)

- “Based on the literature, AM is considered as a longer-term treatment for bullous keratopathy patients with poorer visual prognosis. AM without sutures may also be used as an interim measure for patients awaiting corneal transplant. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

Pterygium repair

- “While HAM is more effective at preventing recurrences than bare sclera technique, and subject to fewer serious complications than mitomycin C, conjunctival autograft has been shown to be more effective than HAM in terms of reducing recurrences. However, there are patients with extensive, double, or recurrent pterygia in which there is insufficient healthy tissue to create a conjunctival autograft. In these patients, sutured or non-sutured (glued) HAM is the material of choice for covering the conjunctival defect left after removal of the pterygium as the recurrence rate is lower than if the sclera is left bare. Sutured and glued HAM should be covered for these cases” (AAO)
- “The most daunting challenge of pterygium surgery is the high rate of recurrence, as high as 88%. Surgical techniques in more recent years, in which scleral defects are covered with conjunctival autograft or cryopreserved amniotic membrane (AM) with or without mitomycin C (MMC), have resulted in much better outcomes, with less recurrence rates and minimal complications.…In my opinion, AM is as effective as conjunctival autograft in preventing pterygium recurrence, and can be considered as a preferred grafting procedure for pterygium repair. The use of AM provide the following benefits: save donor conjunctiva, minimize surgical trauma, reduce surgery time, reduce postoperative pain, reduce inflammation, facilitate faster recovery and healing. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

Limbal stem cell deficiency

- “Limbal stem cell deficiency is an uncommon, serious disorder leading to conjunctivalization, irregularity, and opacity of the corneal surface. Total limbal stem cell deficiency typically requires a limbal stem cell transplant to restore the ocular surface. These vascularized transplants require prolonged systemic immunosuppression and the attendant risks to support graft survival and prevent recurrence of the disease. Partial limbal stem cell deficiency may respond to selective removal of the diseased tissue without a transplant when a limited portion of the ocular surface is involved. In more extensive cases where selective removal alone is not sufficient, HAM in conjunction with superficial keratectomy to remove the diseased tissue can provide long-term restoration of a smooth and transparent ocular surface and improved visual acuity without having to resort to a transplant (Kheirkhah AV. Am J Ophthalmol 2008;145:787. PMID 18329626). Due to the rarity of this disease, it is unlikely that RCTs will ever be performed. Comparisons to limbal stem cell transplants are unlikely to be performed because of the risks of systemic immune suppression. HAM should be covered in conjunction with superficial keratectomy for cases of limbal stem cell deficiency.” (AAO)
- “Patients with Limbal stem cell deficiency (LSCD) suffer from severe loss of vision due to vascularized cornea scarring and non-healing epithelial defect. Their vision cannot be corrected by conventional penetrating keratoplasty. Previous studies have shown that in eyes with partial LSCD, AM promotes expansion of remaining limbal epithelial stem cells.” (Dr. Latina)

Stevens-Johnson

- “Sutureless or sutured HAM, depending on the severity of the disease, in conjunction with medical therapy has become the accepted management technique for the treatment of moderate or severe Stevens-Johnson. Both should be covered for this indication. The severity of the disease and its infrequency makes it unlikely that a large RCT will be performed.” (AAO)
- “In my opinion, and based on the literature, the use of AM with sutures is preferred to prevent long term lid related complications. The use of AM without suture is still helpful in emergency settings when the patient condition does not allow for surgical intervention. Collectively, the use of AM for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

Persistent epithelial defects

- “HAM is an effective treatment for persistent epithelial defects due to a number of underlying causes. While not a first-line treatment, both sutured and non-sutured HAM are appropriate in patients with epithelial defects that fail to show a response within 2 days of initiation of conservative therapy. Conservative therapy is considered to be any one or more of the following: topical lubricants and/or antibiotics, therapeutic contact lens, or patching. If there is a failure to respond to any one of these modalities, HAM is an appropriate second step…The uncommon nature of the diseases associated with persistent epithelial defects and the lack of a standard therapeutic regimen account for the lack of RCTs.” (AAO)
- “Persistent epithelial defect (PED) is often caused by microtrauma, neurotrophic keratopathy and exposure. Conventional treatment includes correcting the underlying condition, suppressing the inflammation, and promoting the healing process using tears. If conventional treatment fails after 2 weeks, these patients are prone to further complications and corneal scarring and haze. Because PED also be ‘neurotrophic,’ please refer to Neurotrophic keratitis indication. As stated above, conventional treatments usually fail to promote prompt healing in these conditions and the eyes are prone to delayed healing, corneal ulceration, scarring, and infection. These complications in turn result in poor patient outcomes, visual detriment, and a greater frequency of office visits and associated costs…Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

Severe dry eye

- “Traditional dry eye therapy typically consists of frequent application of lubricants, hot compresses, and environmental controls to increase humidity. Patients may not respond to traditional dry eye therapy due to the severity of the disease or due to inability to control the environment or administer drops frequently. Topical drugs such as cyclosporine and lifitegrast may be helpful in these cases but they may take months to take effect. If the patient's daily activities are significantly affected by dry eye signs and symptoms, HAM may provide rapid relief while waiting for long-term medications to take effect. HAM is unlikely to be of benefit for mild dry eye disease or disease that responds to conservative therapy. Because HAM limits acuity it is only viable as a short-term therapy. Sutured HAM is not typically used for severe dry eye alone but may be necessary in the face of one or more concomitant diseases discussed in the other sections. Our recommendation is that non-sutured HAM be covered in patients with persistent symptoms or persistent corneal staining that does not respond to traditional dry eye therapy.” (AAO)

- “Dry eye disease (DED) is a multifactorial disease comprised of tear film insufficiency and associated ocular surface disorder such as superficial epithelial defect. Treatment of DED depends on the etiology and the level of severity. Although artificial tears, immunosuppressants and punctal occlusion are commonly used for tear film insufficiency, ocular surface involvement with a defect are usually refractory and may require eye protection devices and/ or surgical intervention... In my practice, a single placement of Amniotic Membrane (non-sutured) was also effective in reducing signs and symptoms of DED for a period lasting more than three months. Therefore, amniotic membrane without sutures should be considered for severe dry eye with ocular surface damage and inflammation.” (Dr. Latina)

Acute ocular chemical burn

- “Ocular chemical burns represent a diverse array of clinical conditions and severity, making high quality RCTs difficult or impossible to perform. The Cochrane review cited in the BCBS review (Clare G. Cochrane Database Syst Rev 2012;9:CD009379. PMID 22972141) reflects this difficulty. However, it is clear that there are subsets of patients that respond to either sutured or non-sutured HAM based in its ability to reduce inflammation and promote epithelial healing. Particularly in moderate and severe burns where the prognosis with traditional therapy is poor, sutured and non-sutured HAM are important alternatives that should be covered. There are multiple reports of good outcomes in these cases.” (AAO)
- “In my opinion, and based on the literature, the use of AM without sutures is preferred to prevent surgical trauma and suture related complications in such compromised eyes. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome.” (Dr. Latina)

PRACTICE GUIDELINES AND POSITION STATEMENTS

Society for Vascular Surgery et al

The Society for Vascular Surgery (2016) in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine made the following recommendation: "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of four 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."(41)

Tear Film and Ocular Surface Society

The Tear Film and Ocular Surface Society (2017) published the DEWS [Dry Eye Workshop] II management and therapy report.(24) The report evaluated the evidence on treatments for dry eye and provided the following treatment algorithm for dry eye disease management:

Step 1:

- Education regarding the condition, its management, treatment and prognosis
- Modification of local environment
- Education regarding potential dietary modifications (including oral essential fatty acid supplementation)

- Identification and potential modification/elimination of offending systemic and topical medications
- Ocular lubricants of various types (if meibomian gland dysfunction is present, then consider lipid containing supplements)
- Lid hygiene and warm compresses of various types

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

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

Step 4:
If above options are inadequate consider:
- Topical corticosteroid for longer duration
- Amniotic membrane grafts
- Surgical punctal occlusion
- Other surgical approaches (e.g., tarsorrhaphy, salivary gland transplantation)

Wound Healing Society
In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.(42) 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 dehydrated amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

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

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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	130	Jul 2024
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 2023
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	240	Aug 2028
NCT06150209[a]	A Controlled Data Collection and Prospective Treatment Study to Evaluate the Efficacy of Vendaje in the Management of Foot Ulcers in Diabetic Patients	100	Jun 2025
NCT05796765[a]	A Phase 2B, Prospective, Double-Blind, Randomized Controlled Trial of the Micronized DHACM Injectable Product Compared to Saline Placebo Injection for the Treatment of Osteoarthritis of the Knee	471	Jan 2025
Unpublished			
NCT02609594[a]	A Multi-center Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Amnioband Dehydrated Human Amniotic Membrane and Standard of Care vs. Standard of Care Alone in the Treatment of Venous Leg Ulcers	200	Dec 2021 (Recruiting)
NCT04612023	A Prospective, Double-Blinded, Randomized Controlled Trial of an Amniotic Membrane Allograft Injection Comparing Two Doses (1 mL and 2 mL Injection) and a Placebo (Sterile Saline) in the Treatment of Osteoarthritis of the Knee	90	Jul 2022
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.

Government Regulations

National:

There is not a National Determination for Amniotic Membranes or Amniotic Fluid for use in wound care.

Local:

LCD: Amniotic and Placental Derived Product Injections and/or Applications for Musculoskeletal Indications, Non-Wound. L39624. Original Effective Date: 11/12/23

Amniotic and Placental Derived Product Injections and/or Applications for Musculoskeletal Indications, Non-Wound *(This is a summary of the LCD and does not contain all information. Refer to LCD for further information.)*

Coverage Indications, Limitations, and/or Medical Necessity
This is a NON-coverage policy for all amniotic membrane, amniotic fluid or other placental derived product injections and/or applications as a means of managing musculoskeletal injuries, joint conditions, and all other conditions not stated below.

Based on these characteristics, amniotic and placental derived products are currently being studied and heavily marketed as allografts to serve as:

- scaffolds for tissue engineering
- membrane covering for certain burns, wounds, and ophthalmic corneal injuries
- micronized/particulated products suspended in an aqueous material to be applied topically or injected into joints, tendons, ligaments
- applications or injections performed intra-operatively to promote post-operative healing

These amniotic and placental-derived products are further being investigated for a multitude of indications, including but not limited to musculoskeletal conditions involving joint pain and back pain, chronic pain in general, dental conditions, alopecia, wounds, burns, and a plethora of others. In the quest to find alternative treatments for certain musculoskeletal conditions, the emergence of a class of substances being marketed as “orthobiologics” has become more prevalent in the pharmaceutical market. “Orthobiologics” are biological products aimed at treating musculoskeletal conditions purported to heal injury/trauma, slow degenerative processes and affect regeneration of tissues. The result ideally would be decreased pain and increased function. One such category of orthobiologics involves the incorporation of human amniotic and placental-derived products.

The Food and Drug Administration (FDA), under Sect. 361 of the Public Health Service Act (regulated by the Centers for Biologics Evaluation and Research CBER, an arm of the FDA) oversees the therapeutic use of “Human cells or tissue products” or “HCT/Ps”. Once these types of products are harvested, their processing and handling will determine whether the products fall under Section 361 guidance or default to the more regulated section 351 of the Public Health Service Act and/or the Federal Food, Drug, and Cosmetic Act. The regulatory pathway for pre-market FDA approval of new drugs, devices and/or biological products, requires registration as a New Drug application (NDA), a Premarket Approval (PMA) or other appropriate device premarket clearance such as 510(k), or a (BLA) Biologics License Approval.

Due to the ongoing development of new products and clinical trials, the field of FDA regulatory requirements is evolving. It is the expectation that the respective Medicare Administrative Contractor will continue to follow any guidance as it is issued by the FDA.

Lack of standard formulation, dose, frequency of administration, and standard of care in treatment with these products further complicates regulation and guidance determinations.

Despite this lack of standardization, numerous amniotic and placental-derived products have been released for use in treatment of musculoskeletal conditions. These conditions include, but are not limited to tendon/ligament injuries, musculoskeletal injuries, cartilage damage, osteoarthritis, or pain related to these conditions as well as adjunctive orthopedic surgical treatments. Due to the lack of component standardization, the remainder of this LCD will use the term amniotic and placental-derived products to mean ANY product derived from ANY combination of amniotic membrane/chorion/placenta/Wharton's jelly/umbilical cord/amniotic fluid/umbilical cord blood.

Although amniotic and placental-derived products are marketed to treat certain musculoskeletal conditions, there is limited available support for safety and efficacy from human clinical trials.

Application of Bioengineered Skin Substitutes (L34593) for services performed on or after 1/1/16 (Retired 3/1/16)

This LCD covers the use of skin substitutes and related products in the treatment of lower extremity ulcer disease. The LCD does not pertain or otherwise apply to the use of any skin substitutes or related products in the treatment of burns, skin cancer, or for true reconstructive surgery.

Indications
Application of bioengineered skin substitutes will be covered when the following conditions are met and documented as appropriate for the individual patient:

1. Presence of neuropathic diabetic foot ulcers for greater than four (4) weeks duration
2. Presence of venous stasis ulcers of greater than (1) one-month duration that have failed to respond to documented conservative measures for greater than one (1) month duration
3. Presence of neuropathic diabetic foot ulcers that have failed to respond to documented conservative measures for greater than one (1) month duration. These measures must include appropriate steps to off-load pressure during treatment.
4. Presence of partial or full-thickness ulcers
5. Measurements of the initial ulcer size, the size following cessation of any conservative management and the size at the beginning of skin substitute treatment.

In all cases, the ulcer must be free of infection and underlying osteomyelitis. Documentation must be provided that these conditions have been successfully treated, resolved, prior to instituting skin substitute treatment.

Medicare accepts the Federal Drug Administration's (FDA) classification and description of any bioengineered skin substitute. Application of a Bioengineered Skin Substitute is covered when the following conditions are met and documented as appropriate for the individual patient:

1. Beneficiaries with diabetes under current medical management and controlled with stable HgbA1c level.
2. Venous stasis ulcers that have failed to heal, using conservative measures.
3. Neuropathic diabetic foot ulcers that have failed to heal, using conservative measures.
4. Ulcers that, do not involve tendon, muscle or joint capsule, or have bone exposure, extend through the dermis Unless specifically indicated within the FDA approved package insert.

5. Beneficiaries with adequate arterial blood supply to the foot evidenced by a palpable pulse on the foot (either dorsalis pedis or posterior tibial artery) or an Ankle Brachial Index (ABI) of 0.65 or greater.
6. Neuropathic diabetic foot ulcers that have been treated with appropriate steps to off-load pressure.
7. The ulcer must be free of infection and underlying osteomyelitis.

The following SKIN Substitutes are currently covered under Medicare in an inpatient hospital, outpatient hospital, ambulatory surgical center, or office setting:
Q4101 Skin substitute, apligraf, per square centimeter
Q4102 Skin substitute, oasis wound matrix, per square centimeter
Q4106 Skin substitute, dermagraft, per square centimeter
Q4107 Graftjacket, per square centimeter
Q4110 Skin substitute, primatrix, per square centimeter
Q4121 Theraskin per square centimeter
Q4131 EpiFix per square centimeter

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Orthopedic Applications of Stem Cell Therapy
- Recombinant and Autologous Platelet-Derived Growth Factors As A Treatment of Wound Healing and Other Non–Orthopedic Conditions
- Skin and Tissue Substitutes

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 7/15/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/19	12/11/18	NA	Amniotic membrane products previously addressed on Skin and Tissue Substitutes policy.
1/1/20	10/15/19	NA	Clarified inclusion of venous stasis ulcers under diabetic ulcer lower extremity ulcer language
1/1/21	10/20/20	NA	• Code updated per AMA • Epicord added as established
1/1/22	10/19/21		• Affinity added as established • Code update per AMA (Q4249, Q4250, Q4254, Q4255 - EI)
1/1/23	10/18/22		• Routine maintenance (slp) • Added exclusion for repair following Mohs micrographic surgery • Q4251-Q4253 added as EI
1/1/23[a]			• February adjustment[a] – Q4251-Q4253 (Vim, Vedaje, Zenith) added as EST and approved via email with mention at February JUMP (slp) • Change effective January 1, 2023 • Vendor Managed: NA
1/1/24	10/17/23		• Routine maintenance (slp) • Vendor Managed: N/A • Codes added as EI per code update recommendation: ○ Q4262-Q4278 ○ Q4280-4284
1/1/25	10/15/24		• Vendor Managed: N/A (slp) • Human added to title • CarePatch added to exclusions (Q4236) • Removed examples of membrane grafts with and without suture

			• Distinguished between Vendjae (EST) and Vendjae AC (EI) in the criteria • Note added to criteria referring the reader to PG Tables for clarification of products with assigned codes • Codes added as EI: Q4279, Q4287 through Q4333 • Deleted codes: Q4244, Q4277, Q4210
7/1/25	4/15/25		• Off cycle review – code correction for Prokera from 67759 to 67558.

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: AMNIOTIC MEMBRANE AND AMNIOTIC FLUID (HUMAN)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.