7.01.149	Amniotic Membrane and Amniotic Fluid		
Original Policy Date:	August 31, 2015	**Effective Date:**	March 1, 2024
Section:	7.0 Surgery	**Page:**	Page 1 of 69

Policy Statement

I. Treatment of nonhealing diabetic lower-extremity ulcers using **any** of the following human amniotic membrane products may be considered **medically necessary**.
   A. Affinity®
   B. AmnioBand® Membrane
   C. Biovance®
   D. EpiCord®
   E. EpiFix®
   F. Grafix™

II. Human amniotic membrane grafts ***with or without suture*** (Prokera®, AmbioDisk™) may be considered **medically necessary** for the treatment of **any** of the following **ophthalmic indications**:
   A. Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy (See Policy Guidelines)
   B. Corneal ulcers and melts that do not respond to initial conservative therapy (See Policy Guidelines)
   C. Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment
   D. Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty)
   E. Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient
   F. Moderate or severe Stevens-Johnson syndrome (SJS)
   G. Persistent epithelial defects that do not respond within 2 days to conservative therapy (see Policy Guidelines)
   H. Severe dry eye (Dry Eye WorkShop score [DEWS] 3 or 4) with ocular surface damage and inflammation that remains symptomatic after Steps 1, 2, and 3 of the dry eye disease (DED) management algorithm (see Policy Guidelines)
   I. Moderate or severe acute ocular chemical burn

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

IV. Human amniotic membrane grafts with or without suture are considered **investigational** for all ophthalmic indications not outlined above.

V. Injection of micronized or particulated human amniotic membrane is considered **investigational** for all indications, including but not limited to treatment of osteoarthritis (OA) and plantar fasciitis.

VI. Injection of human amniotic fluid is considered **investigational** for all indications.

VII. All other human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) not listed above are considered **investigational** (see policy guidelines).

VIII. All other indications not listed above are considered **investigational**, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency and repair following Mohs micrographic surgery.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

Conservative therapy for neurotrophic keratitis may include 5 days of pressure patching, therapeutic contact lens, topical lubricants, and topical antibiotics.

Conservative therapy for corneal ulcers and melts may include 2 days of patching, therapeutic contact lens, and topical antimicrobial agents.

A persistent epithelial defect is one that failed to close completely after 5 days of conservative treatment or has failed to demonstrate a decrease in size after 2 days of conservative treatment. Conservative treatment of a persistent epithelial defect may include 5 days of the following: topical lubricants, topical antibiotics, therapeutic contact lens, or patching.

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

Table PG1 Amniotic Products Listed in the Policy Statements

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

Table PG2 Other Amniotic Products with HCPCS Codes

Trade Name	Supplier	HCPCS Code
Allogen	Vivex Biomedical	Q4212
AlloWrap™	AlloSource	Q4150
AmnioAMP-MP	Stratus BioSystems	Q4250
Amnioarmor™	Tissue Transplant Technology	Q4188
AmnioBand® Particulate	MTF Wound Care	Q4168
AmnioExcel®	Derma Sciences	Q4137
Amnio-maxx or Manio-maxx lite	Royal Biologics	Q4239
Amniotext	Regenerative Labs	Q4245
Amniowound	Alpha Tissue	Q4181
Amnion bio or Axomembrane	Axolotl Biologix	Q4211
Amniocore™	Stability Biologics	Q4227
Amniocyte	Predictive Biotech	Q4242
AmnioMatrix®	Integra Life Sciences	Q4139
Amniply	International Tissue	Q4249
Amniorepair or AltiPly	Zimmer Biomet	Q4235

Trade Name	Supplier	HCPCS Code
Amniotext patch	Regenerative Labs	Q4247
AmnioWrap2™	Direct Biologics	Q4221
Articent ac (flowable)	Tides Medical	Q4189
Artacent ac (patch)	Tides Medical	Q4190
Artacent® Wound	Tides Medical	Q4169
Artacent® Cord	Tides Medical	Q4126
Ascent	StimLabs	Q4213
Axolotl ambien or Axolotl Cryo	Axolotl Biology	Q4215
BioDDryFlex®	BioD	Q4138
BioDfence™	Integra Life Science	Q4140
BioWound, BioWound Plus™, BioWound XPlus™	HRT[a]	Q4217
Cellesta/Cellesta duo	Ventris Medical	Q4184
Cellesta Cord	Ventris Medical	Q4214
Cellesta flowable	Ventris Medical	Q4185
Clarix®	Amniox Medical	Q4156
Clarix® Flo	Amniox Medical	Q4155
Cogenex flowable amnion	Ventris Medical	Q4230
Cogenex amniotic membrane	Ventris Medical	Q4229
Corecyte	Predictive Biotech	Q4240
Corplex	StimLabs	Q4232
Corplex P	StimLabs	Q4231
Coretext or Protext	Regenerative Labs	Q4246
Cryo-cord	Royal Biologics	Q4237
Cygnus	Vivex Biomedical	Q4170
Dermacyte	Merakris Therapeutics	Q4248
Dermavest™ or Plurivest	AediCell[a]	Q4153
Derm-maxx	Royal Biologics	Q4238
Epifix Injectable	MiMedx	Q4145
Floweramnioflo	Flower Orthopedics	Q4177
Floweramniopatch	Flower Orthopedics	Q4178
Fluid flow or Fluid GF	BioLab Sciences	Q4206
Genesis	Genesis Biologics	Q4198
Guardian/AmnioBand®	MTF Wound Care	Q4151
Interfyl®	Celularity	Q4171
Matrion	LifeNet Health	Q4201
Neopatch or Therion	CryoLife	Q4176
Neox® Cord	Amniox Medical	Q4148
Neox® Flo	Amniox Medical	Q4155
Neox® Wound	Amniox Medical	Q4156
Novachor	Organogenisis	Q4191
Novafix®	Triad Life Sciences	Q4208
Novafix DL	Triad Life Sciences	Q4254
NuShield	Organogenesis	Q4160
PalinGen® Membrane	Amnio ReGen Solutions	Q4173
PalinGen® SportFlow	Amnio ReGen Solutions	Q4174
Plurivest™	AediCell	Q4153
Polycyte	Predictive Biotech	Q4241
Procenta	Lucina BioSciences	Q4244
Reguard	New Life Medical	Q4255
Restorigin	UMTB Biomedical	Q4191
Restorigin Injectable	UMTB Biomedical	Q4192
Revita	StimLabs	Q4180
Revitalon™	Medline Industries	Q4157
Surgenex, Surfactor, and Nudyn	Surgenex	Q4233
Surgicord	Synergy Biologics	Q4218
SurgiGRAFT™	Synergy Biologics	Q4183
WoundEx®	Skye Biologics[a]	Q4163
WoundEx® Flow	Skye Biologics[a]	Q4162

Trade Name	Supplier	HCPCS Code
Woundfix, Woundfix Plus, Wounfix XPlus (see BioWound above)	HRT	Q4217
Xcellerate	Precise Bioscience	Q4234
Xwrap	Applied Biologics	Q4204

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

Tear Film and Ocular Surface Society staged management for dry eye disease (Jones et al, 2017)
Step 1:

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

Step 2:
If above options are inadequate consider:

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

Step 3:
If above options are inadequate consider:

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

Step 4:
If above options are inadequate consider:

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

Table PG3. Dry Eye Severity Grading Scheme

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	Sever 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, decrease 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/ 5min)	Variable	≤ 10	≤ 5	≤ 2

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

Coding

The following HCPCS codes are for specific products:

- **A2001**: InnovaMatrix AC, per sq cm
- **Q4132**: Grafix Core and GrafixPL Core, per sq cm
- **Q4133**: Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq cm
- **Q4137**: AmnioExcel, AmnioExcel Plus or BioDExcel, per sq cm
- **Q4138**: BioDFence DryFlex, per sq cm
- **Q4139**: AmnioMatrix or BioDMatrix, injectable, 1 cc
- **Q4140**: BioDFence, per sq cm
- **Q4145:** EpiFix, injectable, 1 mg
- **Q4148**: Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per sq cm
- **Q4150**: AlloWrap DS or dry, per sq cm
- **Q4151**: AmnioBand or Guardian, per sq cm
- **Q4153**: Dermavest and Plurivest, per sq cm
- **Q4154**: Biovance, per sq cm
- **Q4155**: Neox Flo or Clarix Flo 1 mg
- **Q4156**: Neox 100 or Clarix 100, per sq cm
- **Q4157**: Revitalon, per sq cm
- **Q4159**: Affinity, per sq cm
- **Q4160**: Nushield, per sq cm
- **Q4162**: WoundEx Flow, BioSkin Flow, 0.5 cc

- **Q4163:** WoundEx, BioSkin, per sq cm
- **Q4168**: AmnioBand, 1 mg
- **Q4169**: Artacent wound, per sq cm
- **Q4170**: Cygnus, per sq cm
- **Q4171**: Interfyl, 1 mg
- **Q4173**: PalinGen or PalinGen XPlus, per sq cm
- **Q4174**: PalinGen or ProMatrX, 0.36 mg per 0.25 cc
- **Q4176**: Neopatch or Therion, per sq cm
- **Q4177**: FlowerAmnioFlo, 0.1 cc
- **Q4178**: FlowerAmnioPatch, per sq cm
- **Q4180**: Revita, per sq cm
- **Q4181**: Amnio Wound, per sq cm
- **Q4183**: Surgigraft, per sq cm
- **Q4184**: Cellesta or Cellesta Duo, per sq cm
- **Q4185**: Cellesta flowable amnion (25 mg per cc); per 0.5 cc
- **Q4186**: Epifix, per sq cm
- **Q4187**: Epicord, per sq cm
- **Q4188**: AmnioArmor, per sq cm
- **Q4189**: Artacent AC, 1 mg
- **Q4190**: Artacent AC, per sq cm
- **Q4191**: Restorigin, per sq cm
- **Q4192**: Restorigin, 1 cc
- **Q4194**: Novachor, per sq cm
- **Q4198**: Genesis Amniotic Membrane, per sq cm
- **Q4199**: Cygnus matrix, per sq cm
- **Q4201**: Matrion, per sq cm
- **Q4204**: XWRAP, per sq cm
- **Q4208:** Novafix, per sq cm
- **Q4209:** SurGraft, per sq cm
- **Q4210:** Axolotl Graft or Axolotl DualGraft, per sq cm
- **Q4211:** Amnion Bio or AxoBioMembrane, per sq cm
- **Q4212:** AlloGen, per cc
- **Q4213:** Ascent, 0.5 mg
- **Q4214:** Cellesta Cord, per sq cm
- **Q4215:** Axolotl Ambient or Axolotl Cryo, 0.1 mg
- **Q4216:** Artacent Cord, per sq cm
- **Q4217:** WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm
- **Q4218:** SurgiCORD, per sq cm
- **Q4219:** SurgiGRAFT-DUAL, per sq cm
- **Q4220:** BellaCell HD or Surederm, per sq cm
- **Q4221:** Amnio Wrap2, per sq cm
- **Q4224:** Human Health Factor 10 Amniotic Patch (HHF10-P), per sq cm
- **Q4225:** AmnioBind, per sq cm
- **Q4227**: AmnioCoreTM, per sq cm
- **Q4229**: Cogenex Amniotic Membrane, per sq cm
- **Q4230**: Cogenex Flowable Amnion, per 0.5 cc
- **Q4231**: Corplex P, per cc
- **Q4232**: Corplex, per sq cm

- **Q4233**: SurFactor or NuDyn, per 0.5 cc
- **Q4234**: XCellerate, per sq cm
- **Q4235**: AMNIOREPAIR or AltiPly, per sq cm
- **Q4236**: carePATCH, per sq cm ***(Reinstated code effective 1/1/2023)***
- **Q4237**: Cryo-Cord, per sq cm
- **Q4239**: Amnio-Maxx or Amnio-Maxx Lite, per sq cm
- **Q4240**: CoreCyte, for topical use only, per 0.5 cc
- **Q4241**: PolyCyte, for topical use only, per 0.5 cc
- **Q4242**: AmnioCyte Plus, per 0.5 cc
- **Q4244**: Procenta, per 200 mg
- **Q4245**: AmnioText, per cc
- **Q4246**: CoreText or ProText, per cc
- **Q4247**: Amniotext patch, per sq cm
- **Q4248**: Dermacyte Amniotic Membrane Allograft, per sq cm
- **Q4251:** Vim, per sq cm
- **Q4252:** Vendaje, per sq cm
- **Q4253:** Zenith Amniotic Membrane, per sq cm
- **Q4256:** MLG-Complete, per sq cm
- **Q4257:** Relese, per sq cm
- **Q4258:** Enverse, per sq cm
- **Q4259:** Celera per sq cm
- **Q4260:** Signature apatch, per sq cm
- **Q4261:** Tag, per sq cm
- **Q4262:** Dual Layer Impax Membrane, per sq cm ***(Code effective 1/1/2023)***
- **Q4263:** SurGraft TL, per sq cm ***(Code effective 1/1/2023)***
- **Q4264:** Cocoon Membrane, per sq cm ***(Code effective 1/1/2023)***
- **Q4285:** NuDYN DL or NuDYN DL MESH, per sq cm ***(Code effective 10/1/2023)***
- **Q4286:** NuDYN SL or NuDYN SLW, per sq cm ***(Code effective 10/1/2023)***

If no specific HCPCS code exists for the product, an unlisted code such as the following would be used:

- **Q4100**: Skin substitute, not otherwise specified

There are no specific codes for AmnioFix or OrthoFlo. It might be reported using the code for another MiMedx product such as the following:

- **Q4145**: EpiFix, injectable, 1 mg
- **Q4100**: Skin substitute, not otherwise specified

The following HCPCS code is for a human amniotic allograft membrane used to repair tissue deficits and to reduce healing time for chronic and post-surgical wounds:

- **Q4205**: Membrane Graft or Membrane Wrap, per sq cm

The following HCPCS code is for a human amniotic flowable allograft that is intended for homologous use to support the repair of soft tissue injury:

- **Q4206**: Fluid Flow or Fluid GF, 1 cc

There is no specific code for this type of injection. It might be reported with one of the musculoskeletal system injection codes or the subcutaneous or intramuscular code:

- **20550**: Injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar "fascia")
- **20999**: Unlisted procedure, musculoskeletal system, general

- **96372**: Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular

There are codes for the placement of amniotic membrane on the ocular surface:

- **65778**: Placement of amniotic membrane on the ocular surface; without sutures
- **65779**: Placement of amniotic membrane on the ocular surface; single layer, sutured

Description

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

Related Policies

- Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions
- Bioengineered Skin and Soft Tissue Substitutes
- Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

1. "The HCT/P is minimally manipulated;

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

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

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

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

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

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

Rationale

Background

Human Amniotic Membrane

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

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

Fresh amniotic membrane contains collagen, fibronectin, and hyaluronic acid, along with a combination of growth factors, cytokines, and anti-inflammatory proteins such as interleukin-1 receptor antagonist.[1,] There is evidence that the tissue has anti-inflammatory, antifibroblastic, and antimicrobial properties. HAM is considered nonimmunogenic and has not been observed to cause a substantial immune response. It is believed that these properties are retained in cryopreserved HAM and HAM products, resulting in a readily available tissue with regenerative potential. In support, 1 HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.[2,]

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

Amniotic Fluid

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

Amniotic membrane and amniotic fluid are also being investigated as sources of pluripotent stem cells.[1,] Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type. The use of stem cells in orthopedic applications is addressed in Blue Shield of California Medical Policy: Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow).

Literature Review

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in

some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Diabetic Lower-Extremity Ulcers
Patch or Flowable Amniotic Membrane or Placental Membrane

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

The question addressed in this evidence review is: Does amniotic membrane or placental membrane improve the net health outcome in patients with diabetic lower-extremity ulcers?

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

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

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

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

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

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

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 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. Human amniotic membrane (HAM) or placental membrane grafts improved healing compared to SOC by 22% (EpiCord vs. Alginate dressing) to 60% (EpiFix) in the intention-to-treat (ITT) analysis (see Table 2). In a 2018 trial, the cryopreserved placental membrane Grafix was found to be non-inferior to an advanced fibroblast-derived wound therapy (Dermagraft).

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator
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 cm2 and 15 cm2	n=38, Grafix weekly for up to 8 weeks	n=37, Dermagraft (fibroblast-derived) weekly for up to 8 weeks
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%)

Study	Wounds Healed	Wounds Healed	Time to Complete Healing	Adverse Events and Number of Treatments
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	.001	.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	<.001	<.001	<.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	.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	.003	<.001 vs. SOC		.003
Tettelbach et al (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		<.001	.019	.031
Difference in wounds healed between amniotic or placental membrane and SOC	Affinity 26% AmnioBand 55% AmnioExcel 33% EpiFix 60%	Affinity 28% EpiCord 22% Grafix 41%		

CI: confidence interval; DIFF: difference; HR: hazard ratio; ITT: intention-to-treat; NR: not reported; PP: per-protocol; RCT: randomized controlled trial; SOC: standard of care.
a. Power analysis indicated that 94 patients per arm would be needed. However, after a prespecified interim

analysis at 50% enrollment, the blinded review committee recommended the trial is stopped due to the efficacy of the treatment.

Limitations in study design and conduct are shown in Table 3. Studies without notable limitations reported power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and ITT analysis. Limitations from the RCT with AmnioExcel (Snyder et al, 2016) [10,] 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 gaps assessment.
ITT: intention to treat; SOC: standard of care.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2.

Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Prospective Single-arm or Registry Studies

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

Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about a third (n=47) were diabetic foot wounds.[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 8 weeks and a mean of 2.4 amniotic membrane applications.

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

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 patch or flowable 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 included power analysis, blinded assessment of wound healing, and ITT analysis. For the HAM products that have been sufficiently evaluated (i.e., Affinity, AmnioBand Membrane, Biovance, EpiCord, EpiFix, Grafix), results have shown improved outcomes compared with standard care, and outcomes that are at least as good as an established advanced wound care product. Improved health outcomes in the RCTs are supported by multicenter registries. No studies were identified that compared different amniotic or placental products, and indirect comparison between products is limited by variations in the patient populations.

Lower-Extremity Ulcers Due to Venous Insufficiency
Amniotic Membrane

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does amniotic membrane or placental membrane improve the net health outcome in patients with venous ulcers?

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

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

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

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

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

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

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

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

Review of Evidence
Two RCTs, both with EpiFix, were identified on HAM for venous leg ulcers. Serena et al (2014) reported on an industry-sponsored multicenter open-label RCT that compared EpiFix d-HAM plus compression therapy with compression therapy alone for venous leg ulcers (see Tables 6 and 7).[17,] The primary outcome in this trial was the proportion of patients with 40% wound closure at 4 weeks, which was achieved by about twice as many patients in the combined EpiFix group compared with the control group (see Table 8). However, a similar percentage of patients in the combined EpiFix group and the control group achieved complete wound closure during the 4-week study. There was no significant difference in healing for wounds given 1 versus 2 applications of amniotic membrane (62% vs. 63%, respectively). Strengths of this trial included adequate power and ITT analysis with last observation carried forward. Limitations included the lack of blinding for wound evaluation and use of 40% closure rather than complete closure. A 2015 retrospective study of 44 patients from this RCT (31 treated with amniotic membrane) found that wounds with at least 40% closure at 4 weeks (n=20)

had a closure rate of 80% by 24 weeks; however, this analysis did not take into account additional treatments after the 4-week randomized trial period.

A second industry-sponsored, multicenter, open-label RCT (Bianchi et al [2018; 2019]) evaluated the time to complete ulcer healing following weekly treatment with EpiFix d-HAM plus compression therapy or compression wound therapy alone (see Tables 6 and 7).[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=.01), and improved time to complete healing, as assessed by Kaplan-Meier analysis. In per-protocol analysis, healing within 12 weeks was reported for 60% of patients in the EpiFix group and 35% of patients in the control group (p<.013) (see Table 8). Intent-to-treat analysis found complete healing in 50% of patients in the EpiFix group compared to 31% of patients in the control group (p=.0473). There were several limitations of this trial (see Tables 8 and 9). In the per-protocol analysis, 19 (15%) patients were excluded from the analysis, and the proportion of patients excluded differed between groups (19% from the EpiFix group vs. 11% from the control group). There was also a difference between the groups in how treatment failures at 8 weeks were handled. Patients in the control group who did not have a 40% decrease in wound area at 8 weeks were considered study failures and treated with advanced wound therapies. The ITT analysis used last-observation-carried-forward for these patients and sensitivity analysis was not performed to determine how alternative methods of handling the missing data would affect results. Kaplan-Meier analysis suggested a modest improvement in the time to heal when measured by ITT analysis, but may be subject to the same methodological limitations.

Two additional studies, one with Amnioband and a second with Artacent, are listed on clinicaltrials.gov as completed in 2018, but results have not been published (see Table 14)

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)

ITT: Intent-to-treat; PP: per-protocol; RCT: randomized controlled trial; 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 (%)**		**Complete Wound Closure at 16 Weeks n (%)**	
			PP	**ITT**	**PP**	**ITT**
Serena et al (2014)[17,]						
EpiFix	62	11.3				
Control	32	12.9				
p-Value	.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			.013	.047	.007	.034

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

Table 8. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Serena et al (2014)[17,]					
Bianchi et al (2018, 2019)[18,19,]					1. Advanced wound therapy was allowed in the control group before the primary endpoint was reached.

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

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		

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

Biovance

As described above, Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about half (n=89) were venous ulcers.[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 2 multicenter RCTs with EpiFix. One RCT reported a larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure at 4 weeks did not differ between EpiFix and the SOC. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression. Although a significant difference in complete healing was reported, interpretation is limited by the differential loss to follow-up and exclusions between groups. Although a subsequent publication reported ITT analysis, the handling of missing data differed between the groups and sensitivity analysis was not performed. The methodological flaws in the design, execution, and reporting of both of these RCTs limit inference that can be drawn from the results. Two additional studies with other HAM products have been completed but not published, raising further questions about the efficacy of HAM for lower-extremity ulcers due to venous insufficiency. Therefore, corroboration with well-designed and well-conducted RCTs evaluating wound healing in patients with venous leg ulcers is needed to demonstrate efficacy. The corroborating RCTs should report ITT and sensitivity analysis, with analysis of all patients, including those who were off treatment or had protocol deviations and exclusions.

Osteoarthritis

ReNu™ Knee Injection in Patients with Osteoarthritis

In 2016, a feasibility study (N=6) was reported of cryopreserved human amniotic membrane (c-HAM) suspension with amniotic fluid-derived cells for the treatment of knee osteoarthritis.[20,] 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 patients who have plantar fasciitis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does injectable amniotic membrane improve the net health outcome in patients with plantar fasciitis?

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

Populations

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

Interventions

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

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

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

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

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

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

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

Systematic Review
A 2016 network meta-analysis of 22 RCTs (total N=1216 patients) compared injection therapies for plantar fasciitis.[21,] 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 polydeoxy-ribonucleotide. 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.[22,] A subsequent RCT by Cazell et al (2018) enrolled 145 patients and reported 3-month follow-up (see Table 10).[23,] In Cazzell et al (2018) amniotic membrane injection led to greater improvements in the VAS for pain and the Foot Functional Index between baseline and 3 months (see Table 11) compared to controls. VAS at 3 months had decreased to 17.1 in the AmnioFix group compared to 38.8 in the placebo control group, which would be considered a clinically significant difference.

Table 10. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Active Intervention	Comparator Intervention
Cazzell et al (2018)[23];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

NCT02427191: Micronized dHACM Injection as Compared to the Saline Placebo Injection in the Treatment of Plantar Fasciitis; 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 3mo (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)[23]; AIPF004	N=145	N=145	N=145	N=145
AmnioFix	54.1 (48.3 to 59.9)	35.7 (30.5 to 41.0)	30 (41.1%)	1 (0.6%)
Placebo	31.9 (24.8 to 39.1)	22.2 (17.1 to 27.4)	39 (54.2%)	3 (1.8%)
Diff (95% CI)	22.2 (13.1 to 31.3)	13.5 (6.2 to 20.8)		
p-Value	<.001	<.001		

CI: confidence interval; 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 extended follow-up will be reported in a separate publication.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Cazzell et al (2018)[23]; 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 gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 13. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Cazzell et al (2018)[23]; AIPF004		1. Single blinded trial, although outcomes were self-reported by blinded patients		1. Only the first 3 months of 12-month follow-up were reported.		

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

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

Section Summary: Plantar Fasciitis

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

Human Amniotic Membrane for Ophthalmologic Conditions

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

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

Clinical Context and Therapy Purpose

The purpose of HAM in patients who have neurotrophic keratitis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have neurotrophic keratitis?

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

Populations

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

Interventions

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

Comparators

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

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

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

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

Suri et al (2013) reported on 11 eyes of 11 patients with neurotrophic keratopathy that had not responded to conventional treatment.[24,] 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 patients who have corneal ulcers and melts is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net heath outcome in patients who have corneal ulcers and melts?

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

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

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

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

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

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

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

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

Review of Evidence
Liu et al (2019) conducted a systematic review of 17 studies (390 eyes) of amniotic membrane for corneal ulcers.[25,] All but 1 of the studies was conducted outside of the U.S. There was 1 RCT with 30 patients, the remainder of the studies were prospective or retrospective case series. Corneal healing was obtained in 97% (95% CI: 0.94 to 0.99, p=.089) of patients evaluated. In the 12 studies (222 eyes) that reported on vision, the vision improvement rate was improved in 113 eyes (53%, 95% CI: 0.42 to 0.65, p<.001).

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.[26,] Utilization of amniotic membrane was initiated in their institution in 2018, allowing a retrospective comparison of the 2 treatment groups. Complete epithelialization occurred more rapidly (3.56± 1.78 weeks vs. 5.87 ± 2.20 weeks, p=.01) and was reached in significantly more patients (72.7% vs. 23.1%, p=.04). The group treated with amniotic membrane plus the standard therapy had more patients with clinically significant (> 3 lines) improvement in visual acuity (81.8% vs 38.4%, p=.047) and greater total improvement in visual acuity (log MAR 0.7 ± 0.6 vs 1.6 ± 0.9, p=.016).

Suri et al (2013) reported on a series of 35 eyes of 33 patients who were treated with the self-retained ProKera HAM for a variety of ocular surface disorders.[24,] Nine of the eyes had non-healing corneal ulcers. Complete or partial success was seen in 2 of 9 (22%) patients with this indication.

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

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

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

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have corneal perforation when there is active inflammation after corneal transplant?

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

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

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

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

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

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

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

Review of Evidence
No evidence was identified for this indication.

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

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

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have bullous keratopathy and are not candidates for a curative treatment?

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

Populations

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

Interventions

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

Comparators

The following therapies are currently being used: stromal puncture.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Dos Santos Paris et al (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy.[27,] Forty patients with pain from bullous keratopathy who were either waiting for a corneal transplant or had no potential for sight in the affected eye were randomized to the 2 treatments. Symptoms had been present for approximately 2 years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with use of HAM only if the pain did not resolve.

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

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

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

Clinical Context and Therapy Purpose

The purpose of HAM in patients who have partial limbal stem cell deficiency is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have partial limbal stem cell deficiency?

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

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

Keirkhah et al (2008) reported on the use of HAM in 11 eyes of 9 patients who had limbal stem cell deficiency.[28,] Patients underwent superficial keratectomy to remove the conjunctivalized pannus followed by HAM transplantation using fibrin glue. An additional ProKera patch was used in 7 patients. An improvement in visual acuity was observed in all but 2 patients. Pachigolla et al (2009) reported a series of 20 patients who received a ProKera implant for ocular surface disorders; 6 of the

patients had limbal stem cell deficiency with a history of chemical burn.[29,] Following treatment with ProKera, 3 of the 6 patients had a smooth corneal surface and improved vision to 20/40.[29,] The other 3 patients had final visual acuity of 20/400, counting fingers, or light perception.

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

No RCTs were identified on HAM for partial limbal stem cell deficiency. Improvement in visual acuity has been reported for some patients who have received HAM in conjunction with removal of the diseased limbus.

Moderate or Severe Stevens-Johnson Syndrome

Clinical Context and Therapy Purpose

The purpose of HAM in patients who have Stevens-Johnson syndrome is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have moderate or severe SJS?

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

One 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.[30,] The c-HAM was prepared locally and applied with fibrin glue rather than sutures.

Application of c-HAM in the early stages of SJS resulted in improved visual acuity (p=.042), better tear breakup time (p=.015), improved Schirmer test results (p<.001), and less conjunctival congestion (p=.03). In the c-HAM group at 180 days, there were no cases of corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. These outcomes are dramatically better than those in the medical therapy alone group, which had 11 (44%) cases with corneal haze (p=.001), 6 (24%) cases of corneal vascularization and conjunctivalization (p=.03), and 6 (24%) cases of trichiasis and metaplastic lashes.

Section Summary: Moderate or Severe Stevens-Johnson Syndrome

The evidence on HAM for the treatment of SJ Syndrome includes 1 RCT with 25 patients (50 eyes) that found improved symptoms and function with HAM compared to medical therapy alone.

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

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have persistent epithelial defects and ulcerations that do not respond to conservative therapy?

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

Populations

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

Interventions

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

Comparators

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

Outcomes

The general outcomes of interest are epithelial closure.

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Bouchard and John (2004) reviewed the use of amniotic membrane transplantation in the management of severe ocular surface disease.[31,] They noted that c-HAM has been available since 1995, and has become an established treatment for persistent epithelial defects and ulceration refractory to conventional therapy. However, there was a lack of controlled studies due to the rarity of the diseases and the absence of standard therapy. They identified 661 reported cases in the peer-reviewed literature. Most cases reported assessed the conjunctival indications of pterygium, scars and symblepharon, and corneal indications of acute chemical injury and postinfectious keratitis.

Section Summary: Persistent Epithelial Defects and Ulceration that Do Not Respond to Conservative Therapy

No RCTs were identified on persistent epithelial defects and ulceration.

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

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have severe dry eye with ocular surface damage and inflammation?

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

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

Review of Evidence

John et al (2017) reported on an RCT with 20 patients with moderate-to-severe dry eye disease who were treated with Prokera c-HAM or maximal conventional treatment.[32,] 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 (DREAM) study (McDonald et al [2018]) was a retrospective series of 84 patients (97 eyes) with severe dry eye despite maximal medical therapy who were treated with Prokera self-retained c-HAM.[33,] A majority of patients (86%) had superficial punctate keratitis. Other patients had filamentary keratitis (13%), exposure keratitis (19%), neurotrophic keratitis (2%), and corneal epithelial defect (7%). Treatment with Prokera for a mean of 5.4 days (range, 2 to 11) resulted in an improved ocular surface and reduction in the DEWS score from 3.25 at baseline to 1.44 at 1 week, 1.45 at 1 month and 1.47 at 3 months (p=.001). Ten percent of eyes required repeated treatment. There was no significant difference in the number of topical medications following c-HAM treatment.

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

The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an 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 patients who have acute ocular burns is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of sutured or self-retained HAM improve the net health outcome in patients who have moderate or severe acute ocular chemical burns?

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

Populations

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

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

Comparators
The following therapies are currently being used: medical therapy (e.g., topical antibiotics, lubricants, steroids and cycloplegics, oral vitamin C, doxycycline).

Outcomes
The general outcomes of interest are visual acuity, corneal epithelialization, corneal clarity, and corneal vascularization.
Changes in symptoms may be measured in days, while changes in the ocular surface would be measured at 1 to 3 months.

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

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

Review of Evidence
An RCT of 100 patients with chemical or thermal ocular burns was published by Tandon et al (2011).[34,] Half of the patients (n=50) had moderate ocular burns and the remainder (n=50) had severe ocular burns. All but 8 of the patients had alkali or acid burns. Patients were randomized to HAM transplantation plus medical therapy or medical therapy alone. Epithelial healing, which was the primary outcome, was improved in the group treated with HAM, but there was no significant difference between the 2 groups for final visual outcome, symblepharon formation, corneal clarity or vascularization.

A second RCT that compared amniotic membrane plus medical therapy (30 eyes) to medical therapy alone (30 eyes) for grade IV ocular burn was reported by Eslani et al (2018).[35,] Medical therapy at this tertiary referral hospital included topical preservative-free lubricating gel and drops, chloramphenicol, betamethasone, homatropine, oral vitamin C, and doxycycline. There was no significant difference in the time to epithelial healing (amniotic membrane: 75.8 vs. 72.6 days) or in visual acuity between the 2 groups (2.06 logMAR for both groups). There was a trend for a decrease in corneal neovascularization (p=.108); the study was not powered for this outcome.

A third RCT by Tamhane et al (2005) found no difference between amniotic membrane and medical therapy groups in an RCT of 37 patients with severe ocular burns.[36,]

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

Corneal Perforation When Corneal Tissue is Not Immediately Available

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does the use of sutured HAM improve the net health outcome in patients who have corneal perforation?

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

Populations

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

Interventions

The therapy being considered is sutured HAM.

Comparators

The following therapies are currently being used: conservative management.

Outcomes

The general outcomes of interest are eye pain.

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

No RCTs were identified on corneal perforation.

Section Summary: Corneal Perforation When Corneal Tissue is Not Immediately Available

The standard treatment for corneal perforation is corneal transplantation, however, sutured HAM may be used as a temporary covering for this severe defect when corneal tissue is not immediately available.

Following Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft

Clinical Context and Therapy Purpose

The purpose of HAM in patients who have pterygium repair is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of sutured or glued HAM improve the net health outcome in patients who have pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft (e.g., extensive, double, or recurrent pterygium)?

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

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

Interventions
The therapy being considered is sutured or glued HAM.

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

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

Pterygium recurrence would be measured at 1 to 3 months.

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

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

Review of Evidence
RCTs have been reported on the use of amniotic membrane following pterygium repair. In 2013, the American Academy of Ophthalmology published a technology assessment on options and adjuvants for pterygium surgery.[37,] Reviewers identified 4 RCTs comparing conjunctival or limbal autograft procedure with amniotic membrane graft, finding that conjunctival or limbal autograft was more effective than HAM graft in reducing the rate of pterygium recurrence. A 2016 Cochrane review of 20 RCTs (total N=1866 patients) arrived at the same conclusion.[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 patients who have undergone Mohs microsurgery for skin cancer is to provide a treatment option that is an alternative to or an improvement on existing procedures.

The question addressed in this evidence review is: Does amniotic membrane improve the net health outcome in patients requiring repair following Mohs microsurgery?

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

Populations

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

Interventions

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

Comparators

Comparators of interest include surgical repair using autologous tissue (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 postprocedure morbidity and mortality, surgical complications, development of a non-healing wound, and quality of life.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

No RCTs were identified for this indication.

Nonrandomized Studies

Toman et al (2022) conducted an observational study that compared repair using a dehydrated human amnion/chorion membrane product (Epifix) with surgical repair using autologous tissue in patients who underwent same-day repair following Mohs microsurgery for removal of skin cancer on the face, head, or neck (Table 14).[39,] 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)[39,]	Retrospective, observational Propensity-score matching used to identify matched pairs	US	2014-2018	Patients who underwent Mohs microsurgery for removal of a basal or squamous cell carcinoma and required same day repair for moderate- to high-risk defects on the face, head, and neck. Mean age 78.0 years; 76.9% male 100% white	n = 143	n = 143	Unclear; 9 months or later for postoperative cosmetic outcomes.

dHACM: dehydrated human amnionic/chorionic membrane.

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

Study	dHACM repair n = 143	Autogolous tissue Repair n = 143	P
Toman et al (2022)[39,]			
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)[39],	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)[39],	1. Not randomized	1, 2. Not blinded		7. Data extracted from medical records could be incomplete/ inaccurate; 10 of 153 patients excluded because no match identified		

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

Section Summary: Repair Following Mohs Microscopic Surgery

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

Summary of Evidence

Diabetic Lower-Extremity Ulcers

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

Lower-Extremity Ulcers due to Venous Insufficiency

For individuals who have lower-extremity ulcers due to venous insufficiency who receive a patch or flowable formulation of HAM, the evidence includes 2 RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The published evidence on HAM for the treatment of venous leg ulcers includes 2 multicenter RCTs with EpiFix. One RCT reported a larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure at 4 weeks did not differ between EpiFix and the standard of care. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression, but interpretation is limited by methodologic concerns. Two additional studies with other HAM products have been completed but not published, raising further questions about the efficacy of HAM for venous insufficiency ulcers. Therefore, corroboration with well-designed and well-conducted RCTs evaluating wound healing is needed to demonstrate efficacy for this indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Osteoarthritis

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

Plantar Fasciitis

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 the visual analog score for pain and the Foot Functional Index compared to placebo controls. The primary limitation of the study is that this is an interim report with 12-month results pending. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ophthalmic Conditions

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

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

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

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

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

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

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

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

For individuals who have bullous keratopathy and who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty) who receive HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. An RCT found no advantage of sutured HAM over the simpler stromal puncture procedure for the treatment of pain from bullous keratopathy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

Moderate or Severe Stevens-Johnson Syndrome

For individuals who have moderate or severe Stevens-Johnson syndrome who receive HAM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. The evidence on HAM for the treatment of Stevens-Johnson syndrome (includes 1 RCT with 25 patients [50 eyes]) found improved symptoms and function with HAM compared to

medical therapy alone. Large RCTs are unlikely due to the severity and rarity of the disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

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

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

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

Moderate or Severe Acute Ocular Chemical Burns

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

Corneal Perforation When Corneal Tissue is Not Immediately Available

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

Pterygium Repair When There is Insufficient Healthy Tissue to Create a Conjunctival Autograft

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

Repair Following Mohs Micrographic Surgery

For individuals who have undergone Mohs micrographic surgery for skin cancer on the face, head, neck, or dorsal hand who receive human amniotic/chorionic membrane, the evidence includes a nonrandomized, comparative study and no RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A retrospective analysis using data from medical records compared a dehydrated human amnionic/chorionic membrane product (dHACM, Epifix) to repair using autologous surgery in 143 propensity-score matched pairs of patients requiring same-day

reconstruction after Mohs microsurgery for skin cancer on the head, face, or neck. A greater proportion of patients who received dHACM repair experienced zero complications (97.9% vs. 71.3%; p<.0001; relative risk 13.67; 95% CI 4.33 to 43.12). Placental allograft reconstructions developed less infection (p=.004) and were less likely to experience poor scar cosmesis (p<.0001). This study is limited by its retrospective observational design. Well-designed and conducted prospective studies are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

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

Clinical Input From Physician Specialty Societies and Academic Medical Centers

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

2019 Input

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

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

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

Further details from clinical input are included in the Appendix.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to

guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Society for Vascular Surgery et al.

In 2016, the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine made the following recommendation: "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amnionic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."[40,]

Tear Film and Ocular Surface Society

In 2017, the Tear Film and Ocular Surface Society published the Dry Eye Workshop II (DEWS) management and therapy report.[23,] 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.[41] The Society concluded that there was level 1 evidence that cellular and acellular skin equivalents improve diabetic foot ulcer healing, noting that, "healthy living skin cells assist in healing DFUs [diabetic foot ulcers] by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed." References from 2 randomized controlled trials on amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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	Dec 2022
NCT03390920[a]	Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions	200	Jun 2030
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
NCT04553432[a]	Dry Eye OmniLenz Application of Omnigen Research Study	70	Jul 2022
NCT04599673	Prospective Analysis of Intraoperative AMNIOGEN® Injection in Patients With Rotator Cuff Tear	100	Sep 2022
NCT04636229[a]	A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients With Osteoarthritis of the Knee	474	Dec 2023
NCT03864939	Randomized Pilot Study to Improve Postprostatectomy Incontinence and Potency by Application of Dried Human Amnion Graft	328	Apr 2025
NCT03855514[a]	A Prospective, Multicenter, Randomized, Controlled Clinical Study Of NuShield® and Standard of Care (SOC) Compared to SOC Alone For The Management Of Diabetic Foot Ulcers	200	Dec 2021
Unpublished			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02609594[a]	A Multi-center Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Amnioband Human Amniotic Membrane and Standard of Care vs. Standard of Care Alone in the Treatment of Venous Leg Ulcers	240	Dec 2018 (status unknown)
NCT02838784[a]	The Efficacy and Safety of Artacent™ for Treatment Resistant Lower Extremity Venous and Diabetic Ulcers: A Prospective Randomized Study	134	Dec 2018 (status unknown)
NCT03441607[a]	Safety & Efficacy of Micronized Human Amnion Chorion Membrane Biologic (mHACMb) FloGraft (Micronized Human Amnion Chorion Membrane)® in Adults With Pain Due to Osteoarthritis of the Knee	320	Mar 2019 (status unknown)
NCT02318511[a]	An Investigation of ReNu™ Knee Injection: Monitoring the Response of Knee Function and Pain in Patients With Osteoarthritis	200	Feb 2019 (completed)
NCT03379324[a]	A Prospective, Randomized Study Comparing Outcomes Following Arthroscopic Double-row Rotator Cuff Repair With and Without the Addition of a Cryopreserved, Liquid, Injectable Amnion Allograft	260	Sep 2019 (status unknown)
NCT03414268[a]	A Phase 3, Prospective, Double-Blinded, Randomized Controlled Trial of the Micronized dHACM Injection As Compared To Saline Placebo Injection In The Treatment Of Plantar Fasciitis	276	Apr 2021 (active, not recruiting)
NCT02982226[a]	A Comparative Study of Injectable Human Amniotic Allograft (ReNu™) Versus Corticosteroids for Plantar Fasciitis: A Prospective, Randomized, Blinded Study	150	Apr 2021 (active, not recruiting)
NCT03414255[a]	A Phase 3, Prospective, Double-Blinded, Randomized Controlled Trial Of The Micronized dHACM Injection As Compared To Saline Placebo Injection In The Treatment Of Achilles Tendonitis	158	May 2021 (active, not recruiting)
NCT03485157[a]	A Phase 2B, Prospective, Double-blinded, Randomized Controlled Trial of the Micronized Human Amnion Chorion Membrane Injection as Compared to Saline Placebo Injection in the Treatment of Osteoarthritis of the Knee	466	Oct 2021

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

Appendix 1

2019 Clinical Input

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

Respondents

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 a 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 specialty society and/or physician

member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA nor any Blue Plan.

Clinical Input Ratings

Respondent Profile

	Specialty Society				
#	Name of Organization			Clinical Specialty	
1	American Academy of Ophthalmology			Ophthalmology	
	Physician				
#	Name	Degree	Institutional Affiliation	Clinical Specialty	Board Certification and Fellowship Training
Identified by Mass Society of Eye Physicians and Surgeons					
2	Mark Latina	MD	Tufts University School of Medicine	Ophthalmology	Ophthalmology, Glaucoma Fellowship trained

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than $1,000, health care related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than $350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	No		No		No		No	
2	No		No		No		No	

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response. NR = not reported

Responses

- We are seeking your opinion on whether using human amniotic membrane graft either without or with suture fixation for the below indications provide a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:
  - Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
  - Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals who may be appropriate for human amniotic membrane graft with versus without suture fixation for this indication;
  - Supporting evidence from the authoritative scientific literature (please include PMID).

#	Indications	Rationale
1	Neurothrophic 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 5 days of conservative treatment, or (2) has failed to demonstrate a decrease in size after 2 days of conservative treatment. Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. 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

#	Indications	Rationale
		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. Khokhar (Cornea 2005;24:654. PMID 16015082) found an increased but nonsignificant rate of epithelial healing with sutured HAM compared to more invasive interventions such as tarsorrhaphy for neurotrophic corneal ulceration in a small randomized clinical trial (RCT). A larger trial might have demonstrated a significant difference but the disease is uncommon enough to make such a trial difficult to perform. For the same reason, there have been no trials directly comparing sutured and non-sutured HAM for neurotrophic keratopathy. This reflects not only the uncommon nature of the disease but also the lack of interest in subjecting patients to the more invasive and expensive sutured HAM procedure when clinical experience indicates that non-sutured HAM is effective in a significant number of patients. Other uncontrolled series and case reports supporting effectiveness of HAM for neurotrophic keratopathy: Chen HJ. Br J Ophthalmol 2000;84:63. PMID 10906085 Ivekovic B. Coll Anthropol 2002;26:47. PMID 12137322 Suri K. Eye Contact Lens 2013;39:341. PMID 23945524 Uhlig CE. Acta Ophthalmol 2015;93:e481. PMID 25773445
2	Neurothrophic keratitis	Neurotrophic keratitis is a degenerative corneal disease induced by an impairment of corneal innervation and often manifested by corneal persistent epithelial defects (PED). Neurotrophic PED is characterized by painless epithelial breakdown, inflammation of the underlying stroma, and poor healing. The disease progression often leads to spontaneous corneal melting and perforation. In my practice, conventional treatments including topical medications, bandage contact lens, eye patching, and tarsorrhaphy usually fail to promote healing. If delayed healing was achieved, there is still a high risk of corneal scarring. Cryopreserved amniotic membrane (AM) has successfully been used to enhance healing in patients with Neurotrophic keratitis. [1-8] Besides the known actions of the AM in controlling inflammation and promoting healing, it is also rich in nerve growth factors that facilitate the recovery of the corneal nerves and enhancement of corneal wound healing. 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. 1. Chen H-J, Pires RTF, Tseng SCG. Amniotic membrane transplantation for severe neurotrophic corneal ulcers. Br. J. Ophthalmol. 2000; 84:826–833. [PubMed: 10906085] 2. IvekoviÄ‡ B, Tedeschi-Reiner E, Petric I, et al. Amniotic membrane transplantation for ocular surface reconstruction in neurotrophic corneal ulcer a. Coll Antropol. 2002;26(1):47-54. [PMID: 12137322] 3. Khokhar S, Natung T, Sony P, et al. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. Cornea. 2005;24:654–660. [PMID: 16015082] 4. Pachigolla G, Prasher P, Di Pascuale MA, et al. Evaluation of the role of ProKera in the management of ocular surface and orbital disorders. Eye Contact Lens. 2009; 35(4):172-175 [PMID: 19474753] 5. Suri K, Kosker M, Raber I, et al. Sutureless Amniotic Membrane ProKera for Ocular Surface Disorders. Short-Term Results. Eye Contact Lens. 2013;39:341-347 [PMID: 23945524] 6. Uhlig CE, Frings C, Rohloff N, et al. Long-term efficacy of glycerine-processed amniotic membrane transplantation in patients with corneal ulcer. Acta Ophthalmol. 2015;93(6):e481-7. [PMID:25773445]

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		7. Röck T, Bartz-Schmidt KU, Röck D. Management of a neurotrophic deep corneal ulcer with amniotic membrane transplantation in a patient with functional monocular vision: A case report. Medicine (Baltimore). 2017;96(50):e8997. [PMID: 29390295] 8. Morkin, M. I. and P. Hamrah. "Efficacy of self-retained cryopreserved amniotic membrane for treatment of neuropathic corneal pain." Ocul Surf 2018, 16(1): 132-138. [PMID: 29032001]
1	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. A number of these were summarized in a review by Bouchard (Ocul Surf 2004;2:201. PMID 17216092). Cited below are selected reports supporting the efficacy of HAM for the treatment of corneal ulcers and melts, including several published since Bouchard's review: Kruse FE. Ophthalmology 1999;106:1504. PMID: 10442895 Hanada K. Am J Ophthalmol 2001;131:324. PMID 11239864 Chen HC. Cornea 2006;25:564. PMID 16783145 Sheha H. Cornea 2009;28:1118. PMID 19770726 Tok OY. Int J Ophthalmol 2015;18:938. PMID 26558205 Sharma N. Indian J Ophthalmol 2018;66:816. PMID 29785990 Prabhasawat P. Br J Ophthalmol 2001;85:1455. PMID 11734521 Solomon A. Ophthalmology 2002;109:694. PMID 11927426 Uhlig CE. Am J Ophthalmol Case Rep 2018;10:296. PMID 29780958
2	Corneal ulcers and melts	Cryopreserved amniotic membrane (AM) has successfully been used to control inflammation and promote healing in corneal ulcers of varying etiology. [1-9] 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. 1. Kruse FE, Rohrschneider K, Völcker HE. Multilayer amniotic membrane transplantation for reconstruction of deep corneal ulcers. Ophthalmology. 1999;106(8):1504-10; discussion 1511. [PMID: 10442895] 2. Hanada K, Shimazaki J, Shimmura S, et al. Multilayered amniotic membrane transplantation for severe ulceration of the cornea and sclera. Am. J. Ophthalmol. 2001; 131(3):324–331. [PubMed: 11239864] 3. Chen HC, Tan HY, Hsiao CH, et al. Amniotic membrane transplantation for persistent corneal ulcers and perforations in acute fungal keratitis. Cornea. 2006 Jun;25(5):564-72. [PMID: 16783145] 4. Barequet IS, Habot-Wilner Z, Keller N, Smollan G, Ziv H, Belkin M, Rosner M. Effect of amniotic membrane transplantation on the healing of bacterial keratitis. Invest Ophthalmol Vis Sci. 2008 Jan;49(1):163-7. [PMID: 18172088] 5. Sheha H, Liang L, Li J, et al. Sutureless amniotic membrane transplantation for severe bacterial keratitis. Cornea 2009; 28(10): 1118-1123. [PMID: 19770726] 6. Tok OY, Tok L, Atay IM, et al. Toxic keratopathy associated with abuse of topical anesthetics and amniotic membrane transplantation for treatment. Int J Ophthalmol. 2015; 18;8(5):938-44. [PMID: 26558205] 7. Sheha H, Tighe S, Cheng AMS, et al. A stepping stone in treating dendritic keratitis. Am J Ophthalmol Case Rep. 2017; 6(7):55-58. [PMID: 29260079]

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		8. Zhong J, Wang B, Li S, et al. Full-thickness conjunctival flap covering surgery combined with amniotic membrane transplantation for severe fungal keratitis. Exp Ther Med. 2018;15(3):2711-2718. [PMID: 29456673] 9. Sharma N, Singhal D, Maharana PK, et al. Continuous intraoperative optical coherence tomography-guided shield ulcer debridement with tuck in multilayered amniotic membrane transplantation. Indian J Ophthalmol. 2018;66(6):816-819. [PMID: 29785990]
1	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. The rare nature of these cases guarantees that there will be no large RCTs performed for this indication. A number of clinical series and case reports supporting the efficacy of HAM for corneal perforation are cited here: Prabhasawat P. Br J Ophthalmol 2001;85:1455. PMID 11734521 Solomon A. Ophthalmology 2002;109:694. PMID 11927426 Rodriguez-Ares MT. Cornea 2004;23:577. PMID 15256996 Hick S. Cornea 2005;24:369. PMID 15829790 Uhlig CE. Am J Ophthalmol Case Rep 2018;10:296. PMID 29780958
2	Corneal perforation	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 [7] used multiple layers of AM with tissue glue in 10 patients with large corneal perforations up to 5 mm and noted 90% success in complete closure of perforation. AM offers the advantage of avoiding potential corneal graft rejection and postoperative astigmatism of tectonic corneal grafts. I personally did not use AM for this indication, but based on the literature, multiple layers of AM for this indication provides a clinically meaningful improvement in net health outcome. 1. Prabhasawat P, Tesavibul N, Komolsuradej W. Single and multilayer amniotic membrane transplantation for persistent corneal epithelial defect with and without stromal thinning and perforation. Br J Ophthalmol. 2001;85(12):1455-63. [PMID: 11734521] 2. Solomon A, Meller D, Prabhasawat P, et al. Amniotic membrane grafts for nontraumatic corneal perforations, descemetoceles, and deep ulcers. Ophthalmology. 2002; 109(4):694–703. [PubMed: 11927426] 3. Rodriguez-Ares MT, Tourino R, Lopez-Valladares MJ, et al. Multilayer amniotic membrane transplantation in the treatment of corneal perforations. Cornea. 2004; 23(6):577–583. [PubMed: 15256996] 4. Hick S, Demers PE, Brunette I, et al. Amniotic membrane transplantation and fibrin glue in the management of corneal ulcers and perforations: a review of 33 cases. Cornea. 2005; 24(4):369–377. [PubMed: 15829790] 5. Xie HT, Zhao D, Liu Y, et al. Umbilical Cord Patch Transplantation for Corneal Perforations and Descemetoceles. J Ophthalmol. 2017;2017:2767053. [PMID: 28660079] 6. Uhlig CE, Müller VC. Resorbable and running suture for stable fixation of amniotic membrane multilayers: A useful modification in deep or perforating sterile corneal ulcers. Am J Ophthalmol Case Rep. 2018; 19 (10):296-299. [PMID: 29780958] 7. Kim HK, Park HS. Fibrin glue-assisted augmented amniotic membrane transplantation for the treatment of large noninfectious corneal perforations. Cornea 2009; 28(2), 170–176.[PMID: 19158560]
1	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

#	Indications	Rationale
		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. There are additional reports demonstrating the efficacy of HAM for bullous keratopathy: Pires RTF. Arch Ophthalmol 1999;117:1291. PMID 10532436 Espana EM. J Cataract Refract Surg 2003;29:279. PMID 12648638 Chansanti O. J Med Assoc Thai 2005;9:S57. PMID 16681053 Srinivas S. Eur J Ophthalmol 2007;17:7. PMID 17294377 Georgiadis NS. Clin Exp Ophthalmol 2008;36:130. PMID 18352868 Chawla B. Eur J Ophthalmol 2008;18:998. PMID 18988175 Altiparmak UE. Am J Ophthalmol 2009;147:442. PMID 19019342 Stefaniu GI. J Med Life 2014;7:88. PMID 25870682 Siu GD. Int Ophthalmol 2015;35:777. PMID: 255866
2	Bullous keratopathy	Cryopreserved amniotic membrane (AM) is recommended for Bullous keratopathy with poor visual potential. AM achieves immediate pain relief, reduced inflammation, and complete healing. [1-12] Chansanti et al [4] noted postoperative relief of pain in 14 eyes (82.4%) and complete corneal epithelial healing in 15 eyes (88.2%) after AMT. Sonmez et al. [5] performed anterior stromal micropuncture and AMT in 5 eyes with painful bullous keratopathy [40]. All showed an intact, smooth corneal epithelial surface 1 month after the procedure, and there were no patients that developed recurrent bullae formation during an average follow-up period of 21 months. Siu et al [12] reported a long term symptomatic relief of bullous keratopathy with amniotic membrane transplant in a total of 21 eyes of 20 patients. The majority of eyes experienced pain reduction (94 %), with a significant mean pain score difference of 6.8 ± 2.6, 2-tail p < 0.001 (99 % CI 4.9-8.7). The mean preoperative and postoperative pain scores were 7.3 ± 2.9 and 0.5 ± 1.0, respectively. 16 eyes (76 %) were completely pain free, and 10 eyes (47 %) remained symptom free after a mean follow-up of 39.0 ± 36.3 months (range 5-171 months). The median epithelial healing time was 2 weeks (range 1-20 weeks). 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. 1. Pires RTF, Tseng SCG, Prabhasawat P et al. Amniotic membrane transplantation for symptomatic bullous keratopathy. Arch.Ophthalmol. 1999; 117, 1291-1297.[PMID: 10532436] 2. Mrukwa-Kominek E, Gierek-Ciaciura S, Rokita-Wala I, et al. Use of amniotic membrane transplantation for treating bullous keratopathy. Klin Oczna. 2002;104(1):41-6. Polish. [PMID: 12046309] 3. Espana EM, Grueterich M, Sandoval H et al. Amniotic membrane transplantation for bullous keratopathy in eyes with poor visual potential. J.Cat.Refract.Surg. 2003; 29, 279-284. 4. Chansanti O, Horatanaruang O. The results of amniotic membrane transplantation for symptomatic bullous keratopathy. J Med.Assoc.Thai. 88 Suppl 2005; 9, S57-S62. 5. Sonmez B, Kim BT, Aldave AJ. Amniotic membrane transplantation with anterior stromal micropuncture for treatment of painful bullous keratopathy in eyes with poor visual potential. Cornea 26(2), 227–229 (2007). 6. Srinivas S, Mavrikakis E, Jenkins C. Amniotic membrane transplantation for painful bullous keratopathy. Eur J Ophthalmol. 2007;17(1):7-10. [PMID: 17294377]

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		7. Georgiadis NS, Ziakas NG, Boboridis KG, et al. Cryopreserved amniotic membrane transplantation for the management of symptomatic bullous keratopathy. Clin Exp Ophthalmol. 2008;36(2):130-5. [PMID: 18352868] 8. Chawla B, Tandon R. Sutureless amniotic membrane fixation with fibrin glue in symptomatic bullous keratopathy with poor visual potential. Eur J Ophthalmol. 2008;18(6):998-1001. [PMID: 18988175] 9. Altiparmak UE, Oflu Y, Yildiz EH, et al. Prospective comparison of two suturing techniques of amniotic membrane transplantation for symptomatic bullous keratopathy. Am J Ophthalmol. 2009;147(3):442-446.e1. [PMID:19019342] 10. Gregory ME, Spiteri-Cornish K, Hegarty B, et al. Combined amniotic membrane transplant and anterior stromal puncture in painful bullous keratopathy: clinical outcome and confocal microscopy. Can J Ophthalmol. 2011;46(2):169-74. [PMID: 21708086] 11. Stefaniu GI, Chiotoroiu SM, Secureanu FA, et al. Use of amniotic membrane in bullous keratopathy palliative care. J Med Life. 2014;7 Spec No. 2:88-91. [PMID: 25870682] 12. Siu GD, Young AL, Cheng LL. Long-term symptomatic relief of bullous keratopathy with amniotic membrane transplant. Int Ophthalmol. 2015;35(6):777-83. [PMID: 25586624]
1	Pterygium repair	Sutured HAM has been fairly extensively studied as an alternative to conjunctival autograft or bare sclera technique in pterygium surgery (Kaufman SC. Ophthalmology 2013;120:201. PMID 23062647. Clearfield, Cochrane Database Syst Rev 2016;2:CD011349. PMID 26867004). 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. Non-sutured HAM is effective at promoting epithelial healing in patients who have persistent epithelial defects (see below) after pterygium surgery and should be covered in these cases.
2	Pterygium repair	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. [1-16] However, some debate still continues regarding which graft offers the better outcome. In a prospective study, Prabhasawat et al [1] first reported a recurrence rate of 10.9% in primary pterygium (n = 54) after excision and AMT. Solomon et al [2] subsequently modified the technique of AMT and achieved a low recurrence rate of 3% in 33 cases of primary pterygium. Another surgical parameter is the use of MMC. Rosen et al [16] reported a considerably low recurrence rate (3.6%) when used AM graft without sutures along with reduced exposure to MMC. 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 provides 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. 1. Prabhasawat P, Barton K, Burkett G, et al. Comparison of conjunctival autografts, amniotic membrane grafts and primary closure for pterygium excision. Ophthalmology 1997; 104, 974-985. [PMID: 9186439] 2. Ma DH-K, See L-C, Liau S-B, et al. Amniotic membrane graft for primary pterygium: comparison with conjunctival autograft and topical mitomycin C treatment. Br.J.Ophthalmol. 2000; 84, 973-978.[PMID: 10966947] 3. Solomon A, Espana EM, Tseng SCG. Amniotic membrane transplantation for reconstruction of the conjunctival fornices. Ophthalmology. 2003; 110:93–100. [PubMed: 12511352]

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		4. Jain S, Rastogi A. Evaluation of the outcome of amniotic membrane transplantation for ocular surface reconstruction in symblepharon. Eye. 2004; 18(12):1251–1257. [PubMed: 15184952] 5. Zhou SY, Chen JQ, Chen LS, et al. Long-term results of amniotic membrane transplantation for conjunctival surface reconstruction. Zhonghua Yan. Ke. Za Zhi. 2004; 40(11):745–749. [PubMed: 15634481] 6. Keklikci U, Celik Y, Cakmak SS, et al. Conjunctival-limbal autograft, amniotic membrane transplantation, and intraoperative mitomycin C for primary pterygium. Ann Ophthalmol (Skokie). 2007;39(4):296-301. [PMID: 18025649] 7. Kucukerdonmez C, Akova YA, Altinors DD. Comparison of conjunctival autograft with amniotic membrane transplantation for pterygium surgery: surgical and cosmetic outcome. Cornea. 2007:26(4):407-413. [PMID: 17457187] 8. Kucukerdonmez C, Akova YA, Altinors DD. Vascularization is more delayed in amniotic membrane graft than conjunctival autograft after pterygium excision. Am.J.Ophthalmol 2007; 143(2), 245-249. [PMID: 17173849] 9. Fallah MR, Golabdar MR, Amozadeh J, et al. Transplantation of conjunctival limbal autograft and amniotic membrane vs mitomycin C and amniotic membrane in treatment of recurrent pterygium. Eye 2008; 22(3), 420-424. [PMID: 17159974] 10. Kheirkhah A, Casas V, Sheha H, et al. Role of conjunctival inflammation in surgical outcome after amniotic membrane transplantation with or without fibrin glue for pterygium. Cornea 2008; 27(1), 56-63. [PMID: 18245968] 11. Kheirkhah A, Blanco G, Casas V, et al. Surgical strategies for fornix reconstruction based on symblepharon severity. Am. J. Ophthalmol. 2008; 146(2):266– 275. [PubMed: 18514608] 12. Park JH, Jeoung JW, Wee WR, et al. Clinical efficacy of amniotic membrane transplantation in the treatment of various ocular surface diseases. Cont Lens Anterior Eye. 2008 Apr;31(2):73-80. [PMID: 18249149] 13. KatÄ±rcÄ±oglu YA, Altiparmak U, Engur Goktas S, et al. Comparison of Two Techniques for the Treatment of Recurrent Pterygium: Amniotic Membrane vs Conjunctival Autograft Combined with Mitomycin C. Semin Ophthalmol. 2015;30(5-6):321-7. [PMID: 24506693] 14. Zhao D, Yin HY, Cheng A, et al. Sealing of the gap between the conjunctiva and tenon capsule to improve symblepharon surgery. Am J Ophthalmol. 2015;160(3):438-446.e1. [PMID: 26093286] 15. Tanaka TS, Demirci H. Cryopreserved Ultra-Thick Human Amniotic Membrane for Conjunctival Surface Reconstruction After Excision of Conjunctival Tumors. Cornea. 2016;35(4):445-50. [PMID: 26807897] 16. Rosen R. Amniotic Membrane Grafts to Reduce Pterygium Recurrence. Cornea. 2018;37(2):189-193. [PMID: 28976415]
1	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.
2	Limbal stem cell deficiency	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 [1-4]. To avoid suture-related disadvantages and complications, Kheirkhah et al. [5] recently reported

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		successful reconstruction of the corneal surface in nine patients with nearly total LSCD using fibrin glue. Kheirkhah et al. [56] further reported successful use of minimal conjunctival limbal autograft in conjunction with AM for total limbal stem cell deficiency. 1. Tseng SCG, Prabhasawat P, Barton K, et al. Amniotic membrane transplantation with or without limbal allografts for corneal surface reconstruction in patients with limbal stem cell deficiency. Arch. Ophthalmol. 1998;116, 431–441. [PMID: 9565039] 2. Anderson DF, Ellies P, Pires RT, et al. Amniotic membrane transplantation for partial limbal stem cell deficiency. Br. J. Ophthalmol. 2001; 85(5), 567–575. [PMID: 11316719] 3. Gomes JA, dos Santos MS, Cunha MC, et al. Amniotic membrane transplantation for partial and total limbal stem cell deficiency secondary to chemical burn. Ophthalmology 2003; 110(3), 466–473. [PMID: 12623806] 4. Sangwan VS, Matalia HP, Vemuganti GK, et al. Amniotic membrane transplantation for reconstruction of corneal epithelial surface in cases of partial limbal stem cell deficiency. Indian J. Ophthalmol. 2004; 52(4), 281–285. [PMID: 15693318] 5. Kheirkhah A, V. Casas V. Raju K et al. Sutureless amniotic membrane transplantation for partial limbal stem cell deficiency. Am.J.Ophthalmol. 2008; 145(5): 787-794. [PMID: 18329626] 6. Kheirkhah, A., Raju VK and S. C. Tseng. "Minimal conjunctival limbal autograft for total limbal stem cell deficiency." Cornea 2008; 27(6): 730-733. [PMID: 18580269]
1	Stevens-Johnson	Sutureless HAM plus medical therapy has been demonstrated in a small RCT to be more effective than medical therapy alone in treatment of Stevens-Johnson syndrome (Sharma N. Ophthalmology 2016;123:484. PMID 26686968). 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. Additional literature demonstrating good visual outcomes with both sutured and sutureless HAM in a disease that prior to introduction of HAM was typically blinding includes: Shammas MC. Am J Ophthalmol 2010;149:203. PMID 20005508 Gregory DM. Ocular Surf 2008;6:40. PMID 18418506 Shay E. Surv Ophthalmol 2009;54:686. PMID 19699503 Gregory DM. Ophthalmology 2011;118:908. PMID 21440941 Shay E. Cornea 2010;29:359. PMID 20098313 Tomlins PJ. Cornea 2013;32:365. PMID 22677638 Kolomeyer AM. Eye Contact Lens 2013;39:e7. PMID 22683916 Ma KN. Ocular Surf 2016;14:31. PMID 26387869
2	Stevens-Johnson	Amniotic membrane with sutures has been used to suppress inflammation, promote healing, and prevent scarring in patients with acute Stevens Johnson Syndrome (SJS) with or without toxic epidermal necrolysis (TEN) [1-6]. The conventional management at intensive care and burn units are usually reserved for life-threatening problems, and thus are frequently inadequate to address ocular inflammation and ulceration. As a result, patients suffering are frequently left with a blinding disease owing to scarring-induced late complications. Gregory et al. [7] and Shay et al. [8] have reviewed the literature and found that AMT performed within 2 weeks after the onset of disease effectively aborts inflammation and facilitates rapid healing in AM-covered areas, thus preventing pathogenic cicatricial complications at the chronic stage in 12 eyes. Several case reports and case series [6-12] demonstrated the effectiveness of AM without sutures (ProKera) at the acute stage of SJS/ TEN, and noted restoration of normal vision. Gregory et al [9] further reported restoration of vision in 10 consecutive cases using AM with and without sutures. However, because this devastating ocular surface disease usually elicits inflammation and ulceration in such hidden areas as the lid margin, the tarsus, and the fornix, AM extended to cover the entire ocular surface is necessary.[10] Ma et al [13] developed a novel technique for using large AM graft without suture to cover the entire ocular surface in patients with acute SJS. 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.

#	Indications	Rationale
		1. John T, Foulks GN, John ME, et al. Amniotic membrane in the surgical management of acute toxic epidermal necrolysis. Ophthalmology 2002; 109(2), 351–360. [PMID: 11825823] 2. Kobayashi A, Yoshita T, Sugiyama K et al. Amniotic membrane transplantation in acute phase of toxic epidermal necrolysis with severe corneal involvement. Ophthalmology 2006; 113(1), 126–132. [PMID: 16324747] 3. Di Pascuale MA, Espana EM, Liu DT et al. Correlation of corneal complications with eyelipid cicatricial pathologies in patients with Steven-Johnson syndrome and toxic epidermal necrolysi syndrome. Ophthalmology 2005; 112(5), 904–912. [PMID: 15878074] 4. Muqit MM, Ellingham RB, Daniel C. Technique of amniotic membrane transplant dressing in the management of acute Stevens–Johnson syndrome. Br. J. Ophthalmol. 2007; 91(11), 1536. [PMID: 17947270] 5. Tandon A, Cackett P, Mulvihill A, et al. Amniotic membrane grafting for conjunctival and lid surface disease in the acute phase of toxic epidermal necrolysis. J. AAPOS 2007; 11(6), 612–613. [PMID: 17681814] 6. Shammas MC, Lai EC, Sarkar JS, et al. Management of acute Stevens–Johnson syndrome and toxic epidermal necrolysis utilizing amniotic membrane and topical corticosteroids. Am. J. Ophthalmol. 2010; 149(2), 203–213. [PMID: 20005508] 7. Gregory DG. The ophthalmologic management of acute Stevens–Johnson syndrome. Ocul. Surf. 2008; 6(2), 87–95. [PMID: 18418506] 8. Shay E, Kheirkhah A, Liang L, et al. Amniotic membrane transplantation as a new therapy for the acute ocular manifestations of Stevens–Johnson syndrome and toxic epidermal necrolysis. Surv. Ophthalmol. 2009; 54(6), 686–696. [PMID: 19699503] 9. Gregory, DG. Treatment of Acute Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis Using Amniotic Membrane: A Review of 10 Consecutive Cases. Ophthalmology 2011; 118:908–914. [PMID: 21440941] 10. Shay E, Khadem JJ and Tseng SC. Efficacy and limitation of sutureless amniotic membrane transplantation for acute toxic epidermal necrolysis. Cornea 2010; 29(3): 359-361. [PMID: 20098313] 11. Tomlins, PJ., Parulekar MV, and Rauz S. ""Triple-TEN" in the Treatment of Acute Ocular Complications From Toxic Epidermal Necrolysis." Cornea 2013; 32(3): 365-369. [PMID: 22677638] 12. Kolomeyer AM, Do BK, Tu Y, et al. Placement of ProKera in the management of ocular manifestations of acute Stevens-Johnson syndrome in an outpatient. Eye Contact Lens. 2013;39: e7-11. [PMID: 22683916] 13. Ma KN, Thanos A, Chodosh J, et al. A Novel Technique for Amniotic Membrane Transplantation in Patients with Acute Stevens-Johnson Syndrome. Ocul Surf. 2016;14(1):31-6. [PMID: 26387869]
1	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. Persistent epithelial defects are often a precursor to corneal stromal melting and ulceration. Many of the comments and citations in the above "Section b. corneal ulcers and melts" are applicable here. 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. However, the following publications demonstrate the effectiveness of HAM for this indication. Prabhasawat P. Br J Ophthalmol 2001;85:1455. PMID 11734521 Lee SH. Am J Ophthalmol 97;123:303. PMID 9063239 Letko E. Arch Ophthalmol 2001;119:659. PMID 11346392 Gris O. Cornea 2002;21:22. PMID 11805502 Seitz B. Eye (London) 2009;23:840. PMID 18535612 Dekaris I. Coll Antropol 2010;34 Suppl 2:15. PMID 21305721

#	Indications	Rationale
2	Persistent epithelial defects	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. The following publications [1-6] show the effectiveness of AM with and without sutures in promoting healing in PEDs. Therefore, using AM either without or with suture fixation for this indication provides a clinically meaningful improvement in net health outcome. 1. Lee SH, Tseng SC. Amniotic membrane transplantation for persistent epithelial defects with ulceration. Am J Ophthalmol. 1997;123(3):303-12. [PMID:9063239] 2. Letko E, Stechschulte SU, Kenyon KR, et al. Amniotic membrane inlay and overlay grafting for corneal epithelial defects and stromal ulcers. Arch Ophthalmol. 2001;119(5):659-63. [PMID: 11346392] 3. Gris O, del Campo Z, Wolley-Dod C, et al. Amniotic membrane implantation as a therapeutic contact lens for the treatment of epithelial disorders. Cornea. 2002;21(1):22-7. [PMID: 11805502] 4. Seitz B, Das S, Sauer R, et al. Amniotic membrane transplantation for persistent corneal epithelial defects in eyes after penetrating keratoplasty. Eye (Lond). 2009;23(4):840-8. [PMID: 18535612] 5. Dekaris I, MraviciÄ‡ I, BarisiÄ‡ A, et al. Amniotic membrane transplantation in the treatment of persistent epithelial defect on the corneal graft. Coll Antropol. 2010;34 Suppl 2:15-9. [PMID: 21305721] 6. Nguyen, P., K. Rue, M. Heur, et al. "Ocular surface rehabilitation: Application of human amniotic membrane in high-risk penetrating keratoplasties." Saudi J Ophthalmol 2014; 28(3): 198-202. [PMID: 25278797]
1	Severe dry eye	As noted in the BCBS review, non-sutured HAM has been demonstrated in an RCT to be more effective than conservative therapy in patients with moderate to severe dry eye disease (John T. J Ophthalmol 2017;2017:6404918. PMID 28894606). Also noted in the review was a small series of 10 patients with moderate to severe dry eye that were non-responsive to conventional therapy (Cheng AM. Ocul Surf 2016;14:56. PMID 26387870). These patients improved with placement of non-sutured HAM. A more recent, larger retrospective review of patients with severe dry eye disease unresponsive to traditional therapy and then treated with non-sutured HAM showed that 88% of subjects demonstrated significant improvement of symptoms extending beyond the period of treatment with HAM (McDonald MD. Clin Ophthalmol 2018;12:677. PMID 29670328). 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.
2	Severe dry eye	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

#	Indications	Rationale
		protection devices and/ or surgical intervention. In fact, Prokera has been reported to manage ocular signs and symptoms of DED. In a retrospective study by Cheng et al,[1] Prokera was placed for 5 days (Range: 2-8 days) in 15 eyes of 10 patients with moderate to severe DED. The dry eye severity ranged from Grade 1 to 4 according to the Report of the International Dry Eye Work Shop (DEWS) 2007.[2] All patients experienced symptomatic relief for a mean period of 4.2 months (Range: 0.3-6.8). Such improvement was accompanied by reduction of Ocular Surface Disease Index (OSDI) symptom scores, the use of topical medications, conjunctival hyperemia, and corneal staining as well as improvement in the quality of vision.11 In a single site prospective, randomized, and controlled study conducted by John et al [3], Prokera together with standard of care was placed in 10 patients for 3.4 ± 0.7 days (Range: 3-5 days) while standard of care was instituted in another 10 patients as the control. All 20 patients presented with moderate to severe DED with DEWS Grade 2-4. Compared to the control arm of 10 patients receiving standard of care, the treatment arm of 10 patients receiving Prokera together with standard of care resulted in reduction of symptoms based on SPEED score and signs such as superficial punctate keratitis (SPK) measured by fluorescein staining, leading to an overall reduction of the mean DEWS severity score from 2.9 ± 0.3 at baseline to 1.1 ± 0.3 at 1 month and 1.0 ± 0.0 at 3 months, respectively (both p ≤ 0 001).These palliative benefits are correlated with an increase of corneal nerve density measured by in vivo confocal microscopy from 12,241 ± 5,083 µm/mm2 at baseline to 16,364 ±3,734 µm/mm2 at 1 month, and 18,827 ±5,453 µm/mm2 at 3 months(both p=0.015). The increase of corneal nerve density is also correlated with an increase of corneal sensitivity measured by a monofilament in the Bonnet-Crochet esthesiometer. A lasting benefit for more than 3 months after one placement of Prokera was also demonstrated in a retrospective study by McDonald et al [4] in 97 eyes of 84 of patients with moderate to severe DED (DEWS 2-4), of which the majority presented with symptoms of ocular discomfort, blurry vision, ocular pain, redness, and light sensitivity. Most of the cases manifested the ocular sign of SPK due to exposure keratitis, filamentary keratitis, epithelial defect, and neurotrophic keratitis. A single placement of Prokera for 5.4 ± 2.8 days leads to notable improvement of DED symptoms and reduction of ocular signs in 74 subjects (88%) as evidenced by notable reduction of the mean DEWS severity score from 3.25 to 1.44 at 1 week, 1.45 at 1 month, and 1.47 at 3 months. 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. 1. Cheng AM, Zhao D, Chen R, et al. Accelerated Restoration of Ocular Surface Health in Dry Eye Disease by Self-Retained Cryopreserved Amniotic Membrane. Ocul Surf. 2016 Jan;14(1):56-63. [PMID: 26387870] 2. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007; 5: 75-92. 3. John T, Tighe S, Sheha H, et al. Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease. J Ophthalmol. 2017;6404918. [PMC5574308] 4. McDonald MB, Sheha H, Tighe S, et al. Treatment outcomes in the Dry Eye Amniotic Membrane (DREAM) study. Clin Ophthalmol. 2018 Apr 9;12:677-681. [PMID: 29670328]
1	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. Though control groups are lacking, several of these reports are fairly large series and were not addressed directly in the BCBS review:

#	Indications	Rationale
		Westekemper H. Br J Ophthalmol 2017;101:103. PMID 27150827 Meller D. Ophthalmology 2000;107:980. PMID 10811094 Ucakhan OO. Cornea 2002;21:169. PMID 11862088 Arora R. Eye 2005;19:273. PMID 15286672 Tamhane A. Ophthalmology 2005;112:1963. PMID: 16198422 Tejwani S. Cornea 2007;26:21. PMID 17198009 Prabhasawat P. J Med Assoc Thai 2007;90:319. PMID 17375638 Kheirkhah A. Arch Ophthalmol 2008;126:1059. PMID 18695099 Tandon R. Br J Ophthalmol 2011;95:199. PMID: 20675729
2	Acute ocular chemical burn	Previous studies have demonstrated the importance of early intervention with cryopreserved amniotic membrane (AM) in mild and moderate chemical burns.[1-10] Specifically, Miller et al [7] used AM as a patch graft with sutures in 13 eyes of patients with acute chemical burn grade II-IV (within 2 weeks of the injury) and epithelial healing occurred within 2-5 weeks. Prabhasawat et al [8] also showed that AM as a patch graft performed within 5 days of grades II and III chemical burns promoted faster epithelial healing and less corneal haze than if performed after 5 days. These results were confirmed by Tandon et al [9] who demonstrated the efficacy of sutured AM in eyes with acute ocular burns in a prospective, randomized, controlled clinical trial of 100 patients with grade II to IV acute ocular burns. Patients were randomized to receive AM or conventional medical treatment. The rate of epithelial healing was significantly better in the AM group than the group with standard medical therapy alone. Kheirkhah et al [10] noted a similar positive outcome when AM without sutures (Prokera) was used within 8 days of chemical burn injury. Based on the above, the use of AM with or without sutures in acute chemical burn is considered a medical necessity to control inflammation, prevent further damage, reduce scarring and restore visual function. 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. 1. Kim JS, Kim JC, Na BK, et al. Amniotic membrane patching promotes healing and inhibits protease activity on wound healing following acute corneal alkali burns. Exp Eye Res. 2000;70:329Y337. [PMID: 10712819] 2. Sridhar MS, Bansal AK, Sangwan VS, et al. Amniotic membrane transplantation in acute chemical and thermal injury. Am J Ophthalmol. 2000;130:134Y137. [PMID: 10712819] 3. Ucakhan OO, Koklu G, Firat E. Nonpreserved human amniotic membrane transplantation in acute and chronic chemical eye injuries. Cornea. 2002;21:169Y172. 4. Arora R, Mehta D, Jain V. Amniotic membrane transplantation in acute chemical burns. Eye. 2005;19:273Y278. [PMID: 11862088] 5. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. Ophthalmology. 2005;112:1963Y1969. [PMID: 16198422] 6. Tejwani S, Kolari RS, Sangwan VS, et al. Role of amniotic membrane graft for ocular chemical and thermal injuries. Cornea. 2007;26:21Y26. [PMID: 17198009] 7. Meller D, Pires RTF, Mack RJS, et al. Amniotic membrane transplantation for acute chemical or thermal burns. Ophthalmology. 2000;107:980Y990. [PMID: 10811094] 8. Prabhasawat P, Tesavibul N, Prakairungthong N, et al. Efficacy of amniotic membrane patching for acute chemical and thermal ocular burns. J Med Assoc Thai. 2007;90:319Y326. PMID: [17375638] 9. Tandon R, Gupta N, Kalaivani M, et al. Amniotic Membrane Transplantation as an Adjunct to Medical Therapy in Acute Ocular Burns. Br J Ophthalmol. 2011;95(2):199-204. [PMID: 20675729] 10. Kheirkhah A, Johnson DA, Paranjpe DR, et al. Temporary sutureless amniotic membrane patch for acute alkaline burns. Arch Ophthalmol. 2008;126:1059Y1066. [PMID: 18695099]

NR = not reported

- Based on the evidence and your clinical experience for using **human amniotic membrane with suture fixation** for the clinical indications described below:

- Respond YES or NO for each clinical indication whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND
- Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	Indications	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Neurothrophic keratitis	Yes					X
2	Neurothrophic keratitis	Yes				X	
1	Corneal ulcers and melts	Yes					X
2	Corneal ulcers and melts	Yes					X
1	Corneal perforation	Yes					X
2	Corneal perforation	Yes					X
1	Bullous keratopathy	Yes					X
2	Bullous keratopathy	Yes				X	
1	Pterygium repair	Yes					X
2	Pterygium repair	Yes					X
1	Limbal stem cell deficiency	Yes					X
2	Limbal stem cell deficiency	Yes				X	
1	Stevens-Johnson	Yes					X
2	Stevens-Johnson	Yes					X
1	Persistent epithelial defects	Yes					X
2	Persistent epithelial defects	Yes					X
1	Severe dry eye	Yes				X	
2	Severe dry eye	Yes				X	
1	Acute ocular chemical burn	Yes					X
2	Acute ocular chemical burn	Yes					X

NR = not reported

- Based on the evidence and your clinical experience for using **human amniotic membrane with suture fixation** for the clinical indications described below:
  - Respond YES or NO for each clinical indication whether this intervention is consistent with generally accepted medical practice; AND
  - Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	Indications	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Neurothrophic keratitis	Yes					X
2	Neurothrophic keratitis	Yes				X	
1	Corneal ulcers and melts	Yes					X
2	Corneal ulcers and melts	No				X	
1	Corneal perforation	Yes					X
2	Corneal perforation	Yes					X
1	Bullous keratopathy	Yes					X
2	Bullous keratopathy	No				X	
1	Pterygium repair	Yes					X
2	Pterygium repair	Yes					X
1	Limbal stem cell deficiency	Yes				X	
2	Limbal stem cell deficiency	Yes					X
1	Stevens-Johnson	Yes					X
2	Stevens-Johnson	Yes					X
1	Persistent epithelial defects	Yes					X
2	Persistent epithelial defects	No				X	
1	Severe dry eye	Yes				X	
2	Severe dry eye	No					X

#	Indications	YES / NO	Low Confidence	Intermediate Confidence	High Confidence
1	Acute ocular chemical burn	Yes			X
2	Acute ocular chemical burn	Yes			X

NR = not reported

- Based on the evidence and your clinical experience for using **human amniotic membrane without suture fixation** for the clinical indications described below:
  - Respond YES or NO for each clinical indication whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND
  - Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	Indications	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Neurothrophic keratitis	Yes					X
2	Neurothrophic keratitis	Yes					X
1	Corneal ulcers and melts	Yes					X
2	Corneal ulcers and melts	Yes					X
1	Corneal perforation	No					X
2	Corneal perforation	No				X	
1	Bullous keratopathy	Yes					X
2	Bullous keratopathy	Yes					X
1	Pterygium repair	Yes					X
2	Pterygium repair	Yes			X		
1	Limbal stem cell deficiency	Yes				X	
2	Limbal stem cell deficiency	Yes					X
1	Stevens-Johnson	Yes					X
2	Stevens-Johnson	Yes					X
1	Persistent epithelial defects	Yes					X
2	Persistent epithelial defects	Yes					X
1	Severe dry eye	Yes				X	
2	Severe dry eye	Yes					X
1	Acute ocular chemical burn	Yes					X
2	Acute ocular chemical burn	Yes					X

NR = not reported

- Based on the evidence and your clinical experience for using human amniotic membrane without suture fixation for the clinical indications described below:
  - Respond YES or NO for each clinical indication whether this intervention is consistent with generally accepted medical practice; AND
  - Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	Indications	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
			1	2	3	4	5
1	Neurothrophic keratitis	Yes					X
2	Neurothrophic keratitis	Yes				X	
1	Corneal ulcers and melts	Yes					X
2	Corneal ulcers and melts	Yes					X
1	Corneal perforation	No					X
2	Corneal perforation	No				X	
1	Bullous keratopathy	Yes					X
2	Bullous keratopathy	Yes				X	
1	Pterygium repair	Yes					X
2	Pterygium repair	No				X	

#	Indications	YES / NO	Low Confidence	Intermediate Confidence	High Confidence
1	Limbal stem cell deficiency	Yes		X	
2	Limbal stem cell deficiency	Yes		X	
1	Stevens-Johnson	Yes			X
2	Stevens-Johnson	Yes			X
1	Persistent epithelial defects	Yes			X
2	Persistent epithelial defects	Yes		X	
1	Severe dry eye	Yes		X	
2	Severe dry eye	Yes			X
1	Acute ocular chemical burn	Yes			X
2	Acute ocular chemical burn	Yes			X

NR = not reported

- Additional narrative rationale or comments regarding clinical pathway and/or any relevant scientific citations (including the PMID) supporting your clinical input on this topic.

#	Additional Comments
1	Specific citations are included above in the comments for each of the individual indications.
2	Amniotic Membrane is available either as an outpatient clinic based only protective bandage contact lens AM patch, or as an ASC or hospital based operating room surgical inlay tissue substitute and is an established treatment for several severe ocular surface diseases. It is most commonly used in patients whose condition is refractory to conventional therapies, such as Corneal Ulcers and Melts, Neurotrophic Keratitis, severe anterior basement membrane dystrophy, and especially difficult-to-heal Persistent Epithelial Defects (PED). I use Prokera (BioTissue) to treat ocular surface diseases because based on the clinical presentation and the failure of conventional therapy, it is medically necessary in order to achieve the best clinical outcome. Prokera is a cryopreserved (not) sutureless AM and is the only such AM cleared by the FDA (2003). It is indicated for use "where the ocular surface is damaged, or the underlying corneal stroma is inflamed." The Prokera self-retaining ring makes it possible to non-surgically insert AM into the eye like a very large contact lens and thereby secure the membrane in place. As such, Prokera represents a significant improvement over the use of AM grafts that require the more invasive, time consuming, and costly suturing procedure. Clinically, use of amniotic membranes serve two primary roles: reduction of inflammation and promotion of wound healing. These are critical functions to accelerating and facilitating optimal clinical outcomes for the patient. Other therapies that provide these mechanisms do exist but either come with drawbacks (side effects such as thinning of the conjunctiva, time to effect) or address one function but not the other (in some cases, therapies may be counterproductive for the other critical clinical need).

NR = not reported

- Is there any evidence missing from the attached draft review of evidence that demonstrates clinically meaningful improvement in net health outcome?

#	YES / NO	Citations of Missing Evidence
1	Yes	See specific citations in above comments on each of the individual indications.
2	No	In general- amniotic membrane is an important Therapy for ocular surface disease which is unresponsive to conventional therapies. In my experience Amniotic membrane grafts have significantly improved the clinical course of many patients, that would have otherwise resulted in vision loss and saved patients from more extensive surgical procedures.

References

1. Parolini O, Soncini M, Evangelista M, et al. Amniotic membrane and amniotic fluid-derived cells: potential tools for regenerative medicine?. Regen Med. Mar 2009; 4(2): 275-91. PMID 19317646
2. Koob TJ, Rennert R, Zabek N, et al. Biological properties of dehydrated human amnion/chorion composite graft: implications for chronic wound healing. Int Wound J. Oct 2013; 10(5): 493-500. PMID 23902526
3. Shimberg M, Wadsworth K. The use of amniotic-fluid concentrate in orthopaedic conditions. J Bone Joint Surg. 1938;20(I):167-177.
4. U.S. Food and Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use Guidance for Industry and Food and Drug Administration Staff. 2017 https://www.regulations.gov/document?D=FDA-2017-D-6146-0003 Accessed January 10, 2022
5. Food and Drug Administration. 510(k) Summary: ProKeraTM Bio-Tissue Inc. (K032104). 2003; https://www.accessdata.fda.gov/cdrh_docs/pdf3/K032104.pdf. Accessed January 10, 2022.
6. Serena TE, Yaakov R, Moore S, et al. A randomized controlled clinical trial of a hypothermically stored amniotic membrane for use in diabetic foot ulcers. J Comp Eff Res. Jan 2020; 9(1): 23-34. PMID 31691579
7. Ananian CE, Dhillon YS, Van Gils CC, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. Wound Repair Regen. May 2018; 26(3): 274-283. PMID 30098272
8. Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. Int Wound J. Feb 2019; 16(1): 122-130. PMID 30246926
9. DiDomenico LA, Orgill DP, Galiano RD, et al. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients. Int Wound J. Dec 2018; 15(6): 950-957. PMID 30019528
10. Snyder RJ, Shimozaki K, Tallis A, et al. A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcer. Wounds. Mar 2016; 28(3): 70-7. PMID 26978860
11. Zelen CM, Gould L, Serena TE, et al. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. Int Wound J. Dec 2015; 12(6): 724-32. PMID 25424146
12. Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. Int Wound J. Apr 2016; 13(2): 272-82. PMID 26695998
13. Tettelbach W, Cazzell S, Reyzelman AM, et al. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. Int Wound J. Feb 2019; 16(1): 19-29. PMID 30136445
14. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix((R)) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. Int Wound J. Oct 2014; 11(5): 554-60. PMID 25048468
15. Smiell JM, Treadwell T, Hahn HD, et al. Real-world Experience With a Decellularized Dehydrated Human Amniotic Membrane Allograft. Wounds. Jun 2015; 27(6): 158-69. PMID 26061491

16. Frykberg RG, Gibbons GW, Walters JL, et al. A prospective, multicentre, open-label, single-arm clinical trial for treatment of chronic complex diabetic foot wounds with exposed tendon and/or bone: positive clinical outcomes of viable cryopreserved human placental membrane. Int Wound J. Jun 2017; 14(3): 569-577. PMID 27489115
17. Serena TE, Carter MJ, Le LT, et al. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. Wound Repair Regen. Nov-Dec 2014; 22(6): 688-93. PMID 25224019
18. Bianchi C, Cazzell S, Vayser D, et al. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix (R)) allograft for the treatment of venous leg ulcers. Int Wound J. Feb 2018; 15(1): 114-122. PMID 29024419
19. Bianchi C, Tettelbach W, Istwan N, et al. Variations in study outcomes relative to intention-to-treat and per-protocol data analysis techniques in the evaluation of efficacy for treatment of venous leg ulcers with dehydrated human amnion/chorion membrane allograft. Int Wound J. Jun 2019; 16(3): 761-767. PMID 30864259
20. Vines JB, Aliprantis AO, Gomoll AH, et al. Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis. J Knee Surg. Aug 2016; 29(6): 443-50. PMID 26683979
21. Tsikopoulos K, Vasiliadis HS, Mavridis D. Injection therapies for plantar fasciopathy ('plantar fasciitis'): a systematic review and network meta-analysis of 22 randomised controlled trials. Br J Sports Med. Nov 2016; 50(22): 1367-1375. PMID 27143138
22. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. Foot Ankle Int. Oct 2013; 34(10): 1332-9. PMID 23945520
23. Cazzell S, Stewart J, Agnew PS, et al. Randomized Controlled Trial of Micronized Dehydrated Human Amnion/Chorion Membrane (dHACM) Injection Compared to Placebo for the Treatment of Plantar Fasciitis. Foot Ankle Int. Oct 2018; 39(10): 1151-1161. PMID 30058377
24. Suri K, Kosker M, Raber IM, et al. Sutureless amniotic membrane ProKera for ocular surface disorders: short-term results. Eye Contact Lens. Sep 2013; 39(5): 341-7. PMID 23945524
25. Liu J, Li L, Li X. Effectiveness of Cryopreserved Amniotic Membrane Transplantation in Corneal Ulceration: A Meta-Analysis. Cornea. Apr 2019; 38(4): 454-462. PMID 30702468
26. Yin HY, Cheng AMS, Tighe S, et al. Self-retained cryopreserved amniotic membrane for treating severe corneal ulcers: a comparative, retrospective control study. Sci Rep. Oct 12 2020; 10(1): 17008. PMID 33046729
27. Paris Fdos S, Goncalves ED, Campos MS, et al. Amniotic membrane transplantation versus anterior stromal puncture in bullous keratopathy: a comparative study. Br J Ophthalmol. Aug 2013; 97(8): 980-4. PMID 23723410
28. Kheirkhah A, Casas V, Raju VK, et al. Sutureless amniotic membrane transplantation for partial limbal stem cell deficiency. Am J Ophthalmol. May 2008; 145(5): 787-94. PMID 18329626
29. Pachigolla G, Prasher P, Di Pascuale MA, et al. Evaluation of the role of ProKera in the management of ocular surface and orbital disorders. Eye Contact Lens. Jul 2009; 35(4): 172-5. PMID 19474753
30. Sharma N, Thenarasun SA, Kaur M, et al. Adjuvant Role of Amniotic Membrane Transplantation in Acute Ocular Stevens-Johnson Syndrome: A Randomized Control Trial. Ophthalmology. Mar 2016; 123(3): 484-91. PMID 26686968
31. Bouchard CS, John T. Amniotic membrane transplantation in the management of severe ocular surface disease: indications and outcomes. Ocul Surf. Jul 2004; 2(3): 201-11. PMID 17216092
32. John T, Tighe S, Sheha H, et al. Corneal Nerve Regeneration after Self-Retained Cryopreserved Amniotic Membrane in Dry Eye Disease. J Ophthalmol. 2017; 2017: 6404918. PMID 28894606
33. McDonald MB, Sheha H, Tighe S, et al. Treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study. Clin Ophthalmol. 2018; 12: 677-681. PMID 29670328

34. Tandon R, Gupta N, Kalaivani M, et al. Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns. Br J Ophthalmol. Feb 2011; 95(2): 199-204. PMID 20675729
35. Eslani M, Baradaran-Rafii A, Cheung AY, et al. Amniotic Membrane Transplantation in Acute Severe Ocular Chemical Injury: A Randomized Clinical Trial. Am J Ophthalmol. Mar 2019; 199: 209-215. PMID 30419194
36. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. Ophthalmology. Nov 2005; 112(11): 1963-9. PMID 16198422
37. Kaufman SC, Jacobs DS, Lee WB, et al. Options and adjuvants in surgery for pterygium: a report by the American Academy of Ophthalmology. Ophthalmology. Jan 2013; 120(1): 201-8. PMID 23062647
38. Clearfield E, Muthappan V, Wang X, et al. Conjunctival autograft for pterygium. Cochrane Database Syst Rev. Feb 11 2016; 2: CD011349. PMID 26867004
39. Toman J, Michael GM, Wisco OJ, et al. Mohs Defect Repair with Dehydrated Human Amnion/Chorion Membrane. Facial Plast Surg Aesthet Med. Jan-Feb 2022; 24(1): 48-53. PMID 34714143
40. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg. Feb 2016; 63(2 Suppl): 3S-21S. PMID 26804367
41. Lavery LA, Davis KE, Berriman SJ, et al. WHS guidelines update: Diabetic foot ulcer treatment guidelines. Wound Repair Regen. Jan-Feb 2016; 24(1): 112-26. PMID 26663430

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Reason/indication for human amniotic membrane/fluid product
  - Type, name, and amount of human amniotic membrane/fluid product

Post Service (in addition to the above, please include the following):

- Procedure report including type and name of product used

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	20550	Injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar "fascia")
	20999	Unlisted procedure, musculoskeletal system, general
	65778	Placement of amniotic membrane on the ocular surface; without sutures

Type	Code	Description
	65779	Placement of amniotic membrane on the ocular surface; single layer, sutured
	96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
HCPCS	A2001	InnovaMatrix AC, per sq c
	Q4100	Skin substitute, not otherwise specified
	Q4132	Grafix Core and GrafixPL Core, per sq cm
	Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq cm
	Q4137	AmnioExcel, AmnioExcel Plus or BioDExcel, per sq cm
	Q4138	BioDFence DryFlex, per sq cm
	Q4139	AmnioMatrix or BioDMatrix, injectable, 1 cc
	Q4140	BioDFence, per sq cm
	Q4145	EpiFix, injectable, 1 mg
	Q4148	Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per sq cm
	Q4150	AlloWrap DS or dry, per sq cm
	Q4151	AmnioBand or Guardian, per sq cm
	Q4153	Dermavest and Plurivest, per sq cm
	Q4154	Biovance, per sq cm
	Q4155	Neox Flo or Clarix Flo 1 mg
	Q4156	Neox 100 or Clarix 100, per sq cm
	Q4157	Revitalon, per sq cm
	Q4159	Affinity, per sq cm
	Q4160	Nushield, per sq cm
	Q4162	WoundEx Flow, BioSkin Flow, 0.5 cc
	Q4163	WoundEx, BioSkin, per sq cm
	Q4168	AmnioBand, 1 mg
	Q4169	Artacent wound, per sq cm
	Q4170	Cygnus, per sq cm
	Q4171	Interfyl, 1 mg
	Q4173	PalinGen or PalinGen XPlus, per sq cm
	Q4174	PalinGen or ProMatrX, 0.36 mg per 0.25 cc
	Q4176	Neopatch or Therion, per sq cm
	Q4177	FlowerAmnioFlo, 0.1 cc
	Q4178	FlowerAmnioPatch, per sq cm
	Q4180	Revita, per sq cm
	Q4181	Amnio Wound, per sq cm
	Q4183	Surgigraft, per sq cm
	Q4184	Cellesta or Cellesta Duo, per sq cm
	Q4185	Cellesta Flowable Amnion (25 mg per cc); per 0.5 cc
	Q4186	Epifix, per sq cm
	Q4187	Epicord, per sq cm
	Q4188	AmnioArmor, per sq cm
	Q4189	Artacent AC, 1 mg
	Q4190	Artacent AC, per sq cm
	Q4191	Restorigin, per sq cm
	Q4192	Restorigin, 1 cc
	Q4194	Novachor, per sq cm
	Q4198	Genesis Amniotic Membrane, per sq cm
	Q4199	Cygnus matrix, per sq cm

Type	Code	Description
	Q4201	Matrion, per sq cm
	Q4204	XWRAP, per sq cm
	Q4205	Membrane Graft or Membrane Wrap, per sq cm
	Q4206	Fluid Flow or Fluid GF, 1 cc
	Q4208	Novafix, per sq cm
	Q4209	SurGraft, per sq cm
	Q4210	Axolotl Graft or Axolotl DualGraft, per sq cm
	Q4211	Amnion Bio or AxoBioMembrane, per sq cm
	Q4212	AlloGen, per cc
	Q4213	Ascent, 0.5 mg
	Q4214	Cellesta Cord, per sq cm
	Q4215	Axolotl Ambient or Axolotl Cryo, 0.1 mg
	Q4216	Artacent Cord, per sq cm
	Q4217	WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm
	Q4218	SurgiCORD, per sq cm
	Q4219	SurgiGRAFT-DUAL, per sq cm
	Q4220	BellaCell HD or Surederm, per sq cm
	Q4221	Amnio Wrap2, per sq cm
	Q4224	Human Health Factor 10 Amniotic Patch (HHF10-P), per sq cm
	Q4225	AmnioBind, per sq cm
	Q4227	AmnioCoreTM, per sq cm
	Q4229	Cogenex Amniotic Membrane, per sq cm
	Q4230	Cogenex Flowable Amnion, per 0.5 cc
	Q4231	Corplex P, per cc
	Q4232	Corplex, per sq cm
	Q4233	SurFactor or NuDyn, per 0.5 cc
	Q4234	XCellerate, per sq cm
	Q4235	AMNIOREPAIR or AltiPly, per sq cm
	Q4236	carePATCH, per sq cm
	Q4237	Cryo-Cord, per sq cm
	Q4238	Derm-Maxx, per sq cm
	Q4239	Amnio-Maxx or Amnio-Maxx Lite, per sq cm
	Q4240	CoreCyte, for topical use only, per 0.5 cc
	Q4241	PolyCyte, for topical use only, per 0.5 cc
	Q4242	AmnioCyte Plus, per 0.5 cc
	Q4244	Procenta, per 200 mg
	Q4245	AmnioText, per cc
	Q4246	CoreText or ProText, per cc
	Q4247	Amniotext patch, per sq cm
	Q4248	Dermacyte Amniotic Membrane Allograft, per sq cm
	Q4249	AMNIPLY, for topical use only, per sq cm
	Q4250	AmnioAmp-MP, per sq cm
	Q4251	Vim, per sq cm
	Q4252	Vendaje, per sq cm
	Q4253	Zenith Amniotic Membrane, per sq cm
	Q4254	Novafix DL, per sq cm
	Q4255	REGUaRD, for topical use only, per sq cm
	Q4256	MLG-Complete, per sq cm

Type	Code	Description
	Q4257	Relese, per sq cm
	Q4258	Enverse, per sq cm
	Q4259	Celera per sq cm
	Q4260	Signature apatch, per sq cm
	Q4261	Tag, per sq cm
	Q4262	Dual Layer Impax Membrane, per sq cm
	Q4263	SurGraft TL, per sq cm
	Q4264	Cocoon Membrane, per sq cm
	Q4265	NeoStim TL, per sq cm ***(Code effective 4/1/2023)***
	Q4266	NeoStim Membrane, per sq cm ***(Code effective 4/1/2023)***
	Q4267	NeoStim DL, per sq cm ***(Code effective 4/1/2023)***
	Q4268	SurGraft FT, per sq cm ***(Code effective 4/1/2023)***
	Q4269	SurGraft XT, per sq cm ***(Code effective 4/1/2023)***
	Q4270	Complete SL, per sq cm ***(Code effective 4/1/2023)***
	Q4271	Complete FT, per sq cm ***(Code effective 4/1/2023)***
	Q4272	Esano a, per square centimeter ***(Code effective 7/1/2023)***
	Q4273	Esano aaa, per square centimeter ***(Code effective 7/1/2023)***
	Q4274	Esano ac, per square centimeter ***(Code effective 7/1/2023)***
	Q4275	Esano aca, per square centimeter ***(Code effective 7/1/2023)***
	Q4276	Orion, per square centimeter ***(Code effective 7/1/2023)***
	Q4277	Woundplus membrane or e-graft, per square centimeter ***(Code effective 7/1/2023)***
	Q4278	Epieffect, per square centimeter ***(Code effective 7/1/2023)***
	Q4279	Vendaje AC, per sq cm ***(Code effective 1/1/2024)***
	Q4280	Xcell amnio matrix, per square centimeter ***(Code effective 7/1/2023)***
	Q4281	Barrera sl or barrera dl, per square centimeter ***(Code effective 7/1/2023)***
	Q4282	Cygnus dual, per square centimeter ***(Code effective 7/1/2023)***
	Q4283	Biovance tri-layer or biovance 3l, per square centimeter ***(Code effective 7/1/2023)***
	Q4284	Dermabind sl, per square centimeter ***(Code effective 7/1/2023)***
	Q4285	NuDYN DL or NuDYN DL MESH, per sq cm ***(Code effective 10/1/2023)***
	Q4286	NuDYN SL or NuDYN SLW, per sq cm ***(Code effective 10/1/2023)***
	Q4287	DermaBind DL, per sq cm ***(Code effective 1/1/2024)***
	Q4288	DermaBind CH, per sq cm ***(Code effective 1/1/2024)***
	Q4289	RevoShield+ Amniotic Barrier, per sq cm ***(Code effective 1/1/2024)***
	Q4290	Membrane Wrap-Hydro TM, per sq cm ***(Code effective 1/1/2024)***
	Q4291	Lamellas XT, per sq cm ***(Code effective 1/1/2024)***
	Q4292	Lamellas, per sq cm ***(Code effective 1/1/2024)***
	Q4293	Acesso DL, per sq cm ***(Code effective 1/1/2024)***
	Q4294	Amnio Quad-Core, per sq cm ***(Code effective 1/1/2024)***
	Q4295	Amnio Tri-Core Amniotic, per sq cm ***(Code effective 1/1/2024)***
	Q4296	Rebound Matrix, per sq cm ***(Code effective 1/1/2024)***
	Q4297	Emerge Matrix, per sq cm ***(Code effective 1/1/2024)***
	Q4298	AmniCore Pro, per sq cm ***(Code effective 1/1/2024)***
	Q4299	AmniCore Pro+, per sq cm ***(Code effective 1/1/2024)***
	Q4300	Acesso TL, per sq cm ***(Code effective 1/1/2024)***
	Q4301	Activate Matrix, per sq cm ***(Code effective 1/1/2024)***
	Q4302	Complete ACA, per sq cm ***(Code effective 1/1/2024)***

Type	Code	Description
	Q4303	Complete AA, per sq cm ***(Code effective 1/1/2024)***
	Q4304	GRAFIX PLUS, per sq cm ***(Code effective 1/1/2024)***

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
08/31/2015	BCBSA Medical Policy adoption
01/01/2016	Coding update
05/01/2016	Policy revision without position change
03/01/2017	Policy title change from "Amniotic Membrane and Amniotic Fluid Injections" Policy revision with position change
12/01/2017	Policy revision with position change
02/01/2018	Coding update
06/01/2018	Policy revision without position change
02/01/2019	Coding update
04/01/2019	Policy revision without position change
11/01/2019	Coding update
05/01/2020	Annual review. Policy statement, guidelines and literature updated.
08/01/2020	Coding update
04/01/2021	Annual review. Policy statement, guidelines and literature updated. Coding update.
11/01/2021	Coding update.
03/01/2022	Coding update.
05/01/2022	Annual review. Policy statement and literature updated.
06/01/2022	Coding update.
08/01/2022	Coding update.
03/01/2023	Coding update.
04/01/2023	Annual review. No change to policy statement. Literature review updated.
05/01/2023	Coding update.
08/01/2023	Coding update.
11/01/2023	Coding update.
03/01/2024	Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with

generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Amniotic Membrane and Amniotic Fluid 7.01.149 **Policy Statement:** I. Treatment of nonhealing diabetic lower-extremity ulcers using **any** of the following human amniotic membrane products may be considered **medically necessary**. A. Affinity® B. AmnioBand® Membrane C. Biovance® D. EpiCord® E. EpiFix® F. Grafix™ II. Human amniotic membrane grafts ***with or without suture*** (Prokera®, AmbioDisk™) may be considered **medically necessary** for the treatment of **any** of the following **ophthalmic indications**: A. Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy (See Policy Guidelines) B. Corneal ulcers and melts that do not respond to initial conservative therapy (See Policy Guidelines) C. Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment D. Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty) E. Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient F. Moderate or severe Stevens-Johnson syndrome (SJS) G. Persistent epithelial defects that do not respond within 2 days to conservative therapy (see Policy Guidelines) H. Severe dry eye (Dry Eye WorkShop score [DEWS] 3 or 4) with ocular surface damage and inflammation that remains	**Amniotic Membrane and Amniotic Fluid 7.01.149** **Policy Statement:** I. Treatment of nonhealing diabetic lower-extremity ulcers using **any** of the following human amniotic membrane products may be considered **medically necessary**. A. Affinity® B. AmnioBand® Membrane C. Biovance® D. EpiCord® E. EpiFix® F. Grafix™ II. Human amniotic membrane grafts ***with or without suture*** (Prokera®, AmbioDisk™) may be considered **medically necessary** for the treatment of **any** of the following **ophthalmic indications**: A. Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy (See Policy Guidelines) B. Corneal ulcers and melts that do not respond to initial conservative therapy (See Policy Guidelines) C. Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment D. Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty) E. Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient F. Moderate or severe Stevens-Johnson syndrome (SJS) G. Persistent epithelial defects that do not respond within 2 days to conservative therapy (see Policy Guidelines) H. Severe dry eye (Dry Eye WorkShop score [DEWS] 3 or 4) with ocular surface damage and inflammation that remains

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
symptomatic after Steps 1, 2, and 3 of the dry eye disease (DED) management algorithm (see Policy Guidelines) I. Moderate or severe acute ocular chemical burn	symptomatic after Steps 1, 2, and 3 of the dry eye disease (DED) management algorithm (see Policy Guidelines) I. Moderate or severe acute ocular chemical burn
III. Human amniotic membrane grafts ***with suture or glue*** may be considered **medically necessary** for the treatment of **either** of the following **ophthalmic indications**: A. Corneal perforation when corneal tissue is not immediately available B. Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft	III. Human amniotic membrane grafts ***with suture or glue*** may be considered **medically necessary** for the treatment of **either** of the following **ophthalmic indications**: A. Corneal perforation when corneal tissue is not immediately available B. Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft
IV. Human amniotic membrane grafts with or without suture are considered **investigational** for all ophthalmic indications not outlined above.	IV. Human amniotic membrane grafts with or without suture are considered **investigational** for all ophthalmic indications not outlined above.
V. Injection of micronized or particulated human amniotic membrane is considered **investigational** for all indications, including but not limited to treatment of osteoarthritis (OA) and plantar fasciitis.	V. Injection of micronized or particulated human amniotic membrane is considered **investigational** for all indications, including but not limited to treatment of osteoarthritis (OA) and plantar fasciitis.
VI. Injection of human amniotic fluid is considered **investigational** for all indications.	VI. Injection of human amniotic fluid is considered **investigational** for all indications.
VII. All other human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) not listed above are considered **investigational** (see policy guidelines).	VII. All other human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) not listed above are considered **investigational** (see policy guidelines).
VIII. All other indications not listed above are considered **investigational**, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency and repair following Mohs micrographic surgery.	VIII. All other indications not listed above are considered **investigational**, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency and repair following Mohs micrographic surgery.