

Medical Policy



Title: Amniotic Membrane and Amniotic Fluid

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| Related Policies: | <ul style="list-style-type: none"> ▪ <i>Bio-Engineered Skin and Soft Tissue Substitutes</i> ▪ <i>Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)</i> ▪ <i>Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions</i> |
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Professional / Institutional

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

| Populations | Interventions | Comparators | Outcomes |
|---|--|---|---|
| keratopathy as a palliative measure in patients who are not candidates for a curative treatment (e.g., endothelial or penetrating keratoplasty) | <ul style="list-style-type: none"> Sutured or self-retained human amniotic membrane | <ul style="list-style-type: none"> Medical therapy Bandage contact lens | <ul style="list-style-type: none"> Symptoms Morbid events Functional outcomes Quality of life |
| <p>Individuals:</p> <ul style="list-style-type: none"> With partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient | <p>Interventions of interest are:</p> <ul style="list-style-type: none"> Sutured or self-retained human amniotic membrane | <p>Comparators of interest are:</p> <ul style="list-style-type: none"> Medical therapy Bandage contact lens | <p>Relevant outcomes include:</p> <ul style="list-style-type: none"> Symptoms Morbid events Functional outcomes Quality of life |
| <p>Individuals:</p> <ul style="list-style-type: none"> With moderate or severe Stevens-Johnson syndrome | <p>Interventions of interest are:</p> <ul style="list-style-type: none"> Sutured or self-retained human amniotic membrane | <p>Comparators of interest are:</p> <ul style="list-style-type: none"> Medical therapy Bandage contact lens | <p>Relevant outcomes include:</p> <ul style="list-style-type: none"> Symptoms Morbid events Functional outcomes Quality of life |
| <p>Individuals:</p> <ul style="list-style-type: none"> With persistent epithelial defects that do not respond to conservative therapy | <p>Interventions of interest are:</p> <ul style="list-style-type: none"> Sutured or self-retained human amniotic membrane | <p>Comparators of interest are:</p> <ul style="list-style-type: none"> Medical therapy Bandage contact lens | <p>Relevant outcomes include:</p> <ul style="list-style-type: none"> Symptoms Morbid events Functional outcomes Quality of life |
| <p>Individuals:</p> <ul style="list-style-type: none"> With severe dry eye with ocular surface damage and inflammation that does not respond to conservative therapy | <p>Interventions of interest are:</p> <ul style="list-style-type: none"> Sutured or self-retained human amniotic membrane | <p>Comparators of interest are:</p> <ul style="list-style-type: none"> Medical therapy Bandage contact lens | <p>Relevant outcomes include:</p> <ul style="list-style-type: none"> Symptoms Morbid events Functional outcomes Quality of life |
| <p>Individuals:</p> <ul style="list-style-type: none"> With moderate or severe acute ocular chemical burn | <p>Interventions of interest are:</p> <ul style="list-style-type: none"> Sutured or self-retained human amniotic membrane | <p>Comparators of interest are:</p> <ul style="list-style-type: none"> Medical therapy Bandage contact lens | <p>Relevant outcomes include:</p> <ul style="list-style-type: none"> Symptoms Morbid events Functional outcomes Quality of life |
| <p>Individuals:</p> <ul style="list-style-type: none"> With corneal perforation when corneal tissue is not immediately available | <p>Interventions of interest are:</p> <ul style="list-style-type: none"> Sutured human amniotic membrane | <p>Comparators of interest are:</p> <ul style="list-style-type: none"> Medical therapy Bandage contact lens | <p>Relevant outcomes include:</p> <ul style="list-style-type: none"> Symptoms Morbid events Functional outcomes Quality of life |
| <p>Individuals:</p> <ul style="list-style-type: none"> With pterygium repair when there is insufficient healthy | <p>Interventions of interest are:</p> <ul style="list-style-type: none"> Sutured or glued human amniotic | <p>Comparators of interest are:</p> <ul style="list-style-type: none"> Medical therapy Bandage contact lens | <p>Relevant outcomes include:</p> <ul style="list-style-type: none"> Symptoms Morbid events |

| Populations | Interventions | Comparators | Outcomes |
|---|--|---|--|
| tissue to create a conjunctival autograft | membrane | | <ul style="list-style-type: none"> • Functional outcomes • Quality of life |
| Individuals: <ul style="list-style-type: none"> • Who have undergone Mohs micrographic surgery for skin cancer on the face, head, neck, or dorsal hand | Interventions of interest are: <ul style="list-style-type: none"> • Human amniotic membrane | Comparators of interest are: <ul style="list-style-type: none"> • Autologous tissue-based surgical repair (full-thickness skin grafts and flaps) • Non-surgical treatment (e.g., secondary intention healing) | Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Morbid events • Functional outcomes • Quality of life |

DESCRIPTION

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

OBJECTIVE

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

BACKGROUND

Human Amniotic Membrane

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

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

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; product code: NQB). The FDA determined that this device was substantially equivalent to the Symblypharon 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.

POLICY

- A. Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered **medically necessary**.
1. Affinity® (Q4159)
 2. AmnioBand® Membrane (Q4151)
 3. AmnioExcel®
 4. Biovance® (Q4154)
 5. EpiCord® (Q4187)
 6. EpiFix® (Q4186)
 7. Grafix™ (Q4132, Q4133)
- B. Human amniotic membrane grafts with or without suture or glue, may be considered **medically necessary** for the treatment of the following ophthalmic indications:
1. Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy;
 2. Corneal ulcers and melts that do not respond to initial conservative therapy;
 3. Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment;
 4. Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty);
 5. Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient;
 6. Moderate or severe Stevens-Johnson syndrome;
 7. Persistent epithelial defects that do not respond as stated in policy guidelines.
 8. Severe dry eye (DEWS 3 or 4) with ocular surface damage and inflammation that remains symptomatic after Steps 1, 2, and 3 of the dry eye disease management algorithm (see Policy Guidelines);
 9. Moderate or severe acute ocular chemical burn;
 10. Corneal perforation when corneal tissue is not immediately available; or
 11. Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft
- C. Human amniotic membrane grafts with or without suture are considered **experimental / investigational** for all ophthalmic indications not outlined above.
- D. Injection of micronized or particulated human amniotic membrane is considered **experimental / investigational** for all indications, including, but not limited to, treatment of osteoarthritis and plantar fasciitis.
- E. Injection of human amniotic fluid is considered **experimental / investigational** for all indications.
- F. All other uses reviewed herein of the human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) not listed above are considered **experimental / investigational** (see policy guidelines).

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

POLICY GUIDELINES

- A. Nonhealing of diabetic wounds is defined as less than a 20% decrease in wound area with standard wound care for at least 2 weeks based on the entry criteria for clinical trials (e.g., Zelen et al, 2015).
- B. Non-healing of lower-extremity ulcers due to venous insufficiency is defined as less than a 30% decrease in wound area with standard wound care for at least 2 weeks, based on clinical trial entry criteria (Serena et al [2022]).
- C. This review covers products that do not require FDA approval or clearance. The list of products named in this review is not a complete list of all commercially available products. Table PG1 lists products included in the Policy statements, and Table PG2 lists other amniotic products that have an HCPCS code.
- D. 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.
- E. Conservative treatment is defined as use of topical lubricants and/or topical antibiotics and/or therapeutic contact lens and/or patching. Failure of multiple modalities should not be required prior to moving to human amniotic membrane grafts. An amniotic membrane graft requires less effort on the part of the patient to adhere to a treatment regimen and has a significant advantage in regard to treatments requiring multiple drops per day.

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

Table PG1 Amniotic Products Listed in the Policy Statements

| Trade Name | Supplier | HCPCS Code |
|---------------------|---|--------------|
| Affinity® | Organogenesis (previously NuTech Medical) | Q4159 |
| AmnioBand® Membrane | MTF Wound Care | Q4151 |
| AmnioExcel® | Integra | Q4137 |
| 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 |
| 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 |
| Amniotext patch | Regenerative Labs | Q4247 |
| AmnioWrap2™ | Direct Biologics | Q4221 |
| Artacent 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 |
| BioNextPATCH | BioNext Solutions | Q4228 |
| BioWound, BioWound Plus™, BioWound XPlus™ | HRT ^a | Q4217 |
| carePATCH | Extremity Care | Q4236 |
| 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 |

| Trade Name | Supplier | HCPCS Code |
|---------------------------|-----------------------|-------------------|
| 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 Protect | Regenerative Labs | Q4246 |
| Cryo-cord | Royal Biologics | Q4237 |
| Cygnus | Vivex Biomedical | Q4170 |
| Dermacyte | Merakris Therapeutics | Q4248 |
| Dermavest™ or Plurivest | AediCell [®] | 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 | Organogenesis | 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 |

| Trade Name | Supplier | HCPCS Code |
|---|-----------------------------|------------|
| 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 |
| 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)

Dry eye severity level DEWS 3 to 4

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

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

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through January 3, 2024.

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

DIABETIC LOWER-EXTREMITY ULCERS

AMNIOTIC MEMBRANE OR PLACENTAL MEMBRANE

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

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 cm ² and 15 cm ² | n=38, Grafix weekly for up to 8 weeks | n=37, Dermagraft (fibroblast-derived) weekly for up to 8 weeks |

| Study; Trial | Countries | Sites | Dates | Participants | Active Intervention | Comparator |
|---|------------------|--------------|--------------|--|-----------------------------|---|
| Tettelbach et al (2018) ⁸ , | U.S. | 11 | 2016-2018 | 155 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers | n=101 EpiCord plus SOC | n=54 SOC with alginate dressing |
| DiDomenico et al (2018) ⁹ , | | | | 80 patients with non-healing (4 weeks) diabetic foot ulcers | AmnioBand Membrane plus SOC | SOC |
| Snyder et al (2016) ¹⁰ , | | | | 29 patients with non-healing diabetic foot ulcers | AmnioExcel plus SOC | SOC |
| Zelen et al (2015, 2016) ^{11,12} , | | 4 | | 60 patients with less than 20% wound healing in a 2 week run-in period | EpiFix | Apligraf or SOC with collagen-alginate dressing |
| Tettelbach et al (2019) ¹³ , | U.S. | 14 | | 110 patients with non-healing (4 weeks) lower extremity ulcers | EpiFix | SOC with alginate dressing |
| Lavery et al (2014) ¹⁴ , | | | | 97 patients with chronic diabetic foot ulcers | Grafix Weekly | SOC |

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

Table 2. Summary of Key RCT Results

| Study | Wounds Healed | Wounds Healed | Time to Complete Healing | Adverse Events and Number of Treatments |
|-------------------------------------|----------------------|----------------------|---------------------------------|--|
| Serena et al (2020) ⁶ , | 12 Weeks (ITT) (%) | 16 Weeks (ITT) (%) | Median | |
| N | 76 | 76 | 76 | |
| Affinity | 55% | 58% | 11 weeks | |
| SOC | 29% | 29% | not attained by 16 weeks | |
| p-value | .02 | .01 | | |
| HR (95% CI) | | 1.75 (1.16 to 2.70) | | |
| Ananian et al (2018) ⁷ , | 8 Weeks (PP) n (%) | | | Patients with Index Ulcer Related Adverse Events n (%) |
| N | 62 | | | 75 |
| Grafix | 15 (48.4%) | | | 1 (5.9%) |
| Dermagraft | 12 (38.7%) | | | 4 (16.7%) |
| Diff (95% CI) | 9.68% (-10.7 to | | | |

| Study | Wounds Healed | Wounds Healed | Time to Complete Healing | Adverse Events and Number of Treatments |
|---|----------------------------|---------------------------|---------------------------------|--|
| | 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) | | |

| Study | Wounds Healed | Wounds Healed | Time to Complete Healing | Adverse Events and Number of Treatments |
|--|---|---|--------------------------|---|
| 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. | | |

| Study | Allocation^a | Blinding^b | Selective Reporting^c | Data Completeness^d | Power^e | Statistical^f |
|---|-------------------------------|--|--|--|------------------------------------|--------------------------------|
| 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 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 individuals who have lower-extremity ulcers due to venous insufficiency is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Three RCTs, 2 using EpiFix and 1 using AmnioBand, were identified on HAM for venous leg ulcers. Serena et al (2014) reported on an industry-sponsored multicenter open-label RCT that compared EpiFix d-HAM plus compression therapy with compression therapy alone for venous leg ulcers (see Tables 6 and 7).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.

Serena et al (2022) reported an industry-sponsored, multicenter, open-label RCT comparing once- or twice-weekly applications of HAM (AmnioBand Membrane) plus compression bandaging with compression bandaging alone in patients with chronic venous leg ulcers (Tables 6 through 9).²⁰ This HAM is a dehydrated aseptically processed product without terminal irradiation for sterilization. It is purported to retain the structural properties of the extracellular matrix that enhances wound healing. There were no significant differences in the proportion of wounds with percentage area reduction 40 percent at 4 weeks between all three study groups. A significantly greater proportion of patients assigned to weekly or twice-weekly HAM achieved the primary endpoint of blinded assessor-confirmed complete wound healing after 12 weeks of study treatment (75%) than those assigned to compression bandaging alone (30%; p=.001). Receiving HAM was independently associated with odds of complete healing at 12 weeks after adjusting for baseline wound area (odds ratio, 8.7; 95% CI, 2.2 to 33.6). Median reduction in wound area

from baseline was also significantly greater in patients assigned to HAM therapy (100%; interquartile range, 5.3%) than those assigned to compression bandaging alone (75%; interquartile range, 68.7%; $p=.012$). Adverse events were reported in 55%, 60%, and 75% of the once-weekly HAM, twice-weekly HAM, and standard-of-care groups, respectively. The most commonly reported adverse events were wound-related infections (36.7%) and new ulcer (31.6%). No adverse events were attributed to study treatment.

Table 6. Summary of Key RCT Characteristics

| Study | Countries | Sites | Dates | Participants | Interventions | |
|---|-----------|-------|-----------|---|--|--|
| | | | | | Active | Comparator |
| Serena et al (2014) ¹⁷ , | U.S. | 8 | 2012-2014 | 84 patients with a full-thickness chronic VLU between 2 and 20 cm ² treated for at least 14 d | 1 (n=26) or 2 (n=27) applications of EpiFix plus standard wound therapy (n=53) | Standard wound therapy (debridement with alginate dressing and compression) (n=31) |
| Bianchi et al (2018, 2019) ^{18,19} , | U.S. | 15 | 2015-2017 | 128 patients with a full-thickness VLU of at least 30-d duration | Weekly EpiFix plus moist wound therapy plus compression (n=64 ITT; 52 PP) | Moist wound therapy plus compression (n=64 ITT; 57 PP) |
| Serena et al (2022) ²⁰ , | U.S. | 8 | 2015-2019 | 101 patients with full-thickness VLU (≥ 2 to < 20 cm ²) of > 1 -mo duration and failing > 1 mo of SOC treatment | Once-weekly (n=20) or twice-weekly (n=20) applications of Amnioband plus SOC compression bandaging | SOC compression bandaging alone (n=20) |

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

Table 7. Summary of Key RCT Results

| Study | Percent With 40% Wound Closure at 4 Weeks | Percent With Complete Wound Closure at 4 Weeks | Complete Wound Closure at 12 Weeks, n (%) | | Median (IQR) Percentage Area Reduction at 12 Weeks | Complete Wound Closure at 16 Weeks, n (%) | |
|---|---|--|---|---------|--|---|---------|
| | | | PP | ITT | | ITT | PP |
| 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) |

| Study | Percent With 40% Wound Closure at 4 Weeks | Percent With Complete Wound Closure at 4 Weeks | Complete Wound Closure at 12 Weeks, n (%) | | Median (IQR) Percentage Area Reduction at 12 Weeks | Complete Wound Closure at 16 Weeks, n (%) | |
|-------------------------------------|---|--|---|---------|--|---|---------|
| | | | | | | | |
| Control | | | 20 (35) | 20 (31) | | 25 (44) | 25 (39) |
| p-Value | | | .013 | .047 | | .007 | .034 |
| Serena et al (2022) ²⁰ , | | | | | | | |
| Amnioband | 75 | | | 30 (75) | 100 (5.3) | | |
| Control | 65 | | | 6 (30) | 75 (68.7) | | |
| p-Value | | | | .001 | .012 | | |

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

Table 8. Study Relevance Limitations

| Study | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|---|-------------------------|---------------------------|-------------------------|-----------------------|---|
| Serena et al (2014) ¹⁷ , | | | | | |
| Bianchi et al (2018, 2019) ^{18,19} , | | | | | 1. Advanced wound therapy was allowed in the control group before the primary endpoint was reached. |
| Serena et al (2022) ²⁰ , | | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive 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 | | |
| Serena et al (2022) ^{20,} | | 1. Open-label with blinded assessors | | | | 4. Incomplete reporting of regression including wound duration. |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive 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 and 1 multicenter RCT with AmnioBand Membrane. One RCT reported a larger percent wound closure at 4 weeks, but the percentage of patients with complete wound closure at 4 weeks did not differ between EpiFix and the SOC. A second RCT evaluated complete wound closure at 12 weeks after weekly application of EpiFix or standard dressings with compression. Although a significant difference in complete healing was reported, interpretation is limited by the differential loss to follow-up and exclusions between groups. Although a subsequent publication reported ITT analysis, the handling of missing data differed between the groups and sensitivity analysis was not performed. The methodological flaws in the design, execution, and reporting of both of these RCTs limit inference that can be drawn from the results. An additional RCT evaluated outcomes using AmnioBand Membrane, a dehydrated aseptically processed product without terminal irradiation for sterilization that s purported to retain the structural properties of the extracellular matrix that enhances wound healing. The application of HAM plus SOC resulted in significantly higher rates of complete wound closure at 12 weeks compared with SOC alone. This endpoint was confirmed by a blinded assessor panel in the ITT population. All 60 subjects received the allocated intervention, and none were lost to follow-up or exited because of protocol deviation. Adverse event rates were numerically greater in the biweekly HAM group but no adverse events were attributed to appeared to be similar between groups.

OSTEOARTHRITIS**ReNu™ Knee Injection in Patients with Osteoarthritis**

In 2016, a feasibility study (N=6) was reported of cryopreserved human amniotic membrane (c-HAM) suspension with amniotic fluid-derived cells for the treatment of knee osteoarthritis.²¹ A single intra-articular injection of the suspension was used, with follow-up at 1 and 2 weeks and at 3, 6, and 12 months posttreatment. Outcomes included the Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee scale, and a numeric pain scale. Statistical analyses were not performed for this small sample. No adverse events, aside from a transient increase in pain, were noted. RCTs are in progress.

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

Section Summary: Osteoarthritis

Current evidence is insufficient to support definitive conclusions on the utility of c-HAM in the treatment of knee osteoarthritis.

PLANTAR FASCIITIS**Clinical Context and Therapy Purpose**

The purpose of micronized amniotic membrane in individuals who have plantar fasciitis is to provide a treatment option that is an alternative to or an improvement on existing therapies. The following PICO was used to select literature to inform this review.

Populations

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

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

Randomized Controlled Trials

Zelen et al (2013) reported a preliminary study with 15 patients per group (placebo, 0.5 cc, and 1.25 cc) and 8-week follow-up.²³ A subsequent RCT by Cazell et al (2018) enrolled 145 patients and reported 3-month follow-up (see Table 10).²⁴ In Cazell 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) ²⁴ ; AIPF004 (NCT02427191) | U.S. | 14 | 2015-2018 | Adult patients with plantar fasciitis with VAS for pain > 45 | n=73; Single injection of AmnioFix 40 mg/ml | n = 72; Single injection of saline |

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

Table 11. Summary of Key RCT Results

| Study | Change in VAS-Pain Between Baseline and 3 mo (95% CI) | Change in FFI-R Between Baseline and 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) ²⁴ ; 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 authors stated that extended follow-up would be reported in a subsequent publication; no subsequent publications have been identified for this trial.

Table 12. Study Relevance Limitations

| Study | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|--|-------------------------|---------------------------|--|-----------------------|--|
| Cazzell et al (2018) ²⁴ ; AIPF004 | | | 3. Placebo injections were used. A control delivered at a similar intensity as the investigational treatment would be corticosteroid injections. | | 1, 2. Follow-up to 12 mo to be reported in a subsequent publication. |

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

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

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.

the intervention of interest.

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

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

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

Table 13. Study Design and Conduct Limitations

| Study | Allocation ^a | Blinding ^b | Selective Reporting ^c | Data Completeness ^d | Power ^e | Statistical ^f |
|--|-------------------------|---|----------------------------------|---|--------------------|--------------------------|
| Cazzell et al (2018) ²⁴ ; AIPF004 | | 1. Single blinded trial, although outcomes were self-reported by blinded patients | | 1. Only the first 3 months of 12-month follow-up were reported. | | |

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

a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2.

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

Section Summary: Plantar Fasciitis

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

Human Amniotic Membrane for Ophthalmologic Conditions

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

taken into consideration in evaluating the evidence. The following indications apply to both sutured and self-retained HAM unless specifically noted.

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

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- 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.²⁵ The mean duration of treatment prior to ProKera

insertion was 51 days. Five of the 11 patients (45.5%) were considered to have had a successful outcome.

Section Summary: Neurotrophic Keratitis with Ocular Surface Damage and Inflammation that Does Not Respond to Conservative Therapy

An RCT of 30 patients showed no benefit of sutured HAM graft compared to tarsorrhaphy or bandage contact lens.

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

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

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.²⁶ 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.²⁷ Utilization of amniotic membrane was initiated in their institution in 2018, allowing a retrospective comparison of the 2 treatment groups. Complete epithelialization occurred more rapidly (3.56 ± 1.78 weeks vs. 5.87 ± 2.20 weeks, $p=.01$) 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.²⁵ Nine of the eyes had non-healing corneal ulcers. Complete or partial success was seen in 2 of 9 (22%) patients with this indication.

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

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

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

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

Comparators

The following therapies are currently being used: medical therapy.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

No evidence was identified for this indication.

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

No evidence was identified for this indication.

BULLOUS KERATOPATHY IN PATIENTS WHO ARE NOT CANDIDATES FOR A CURATIVE TREATMENT (EG, ENDOTHELIAL OR PENETRATING KERATOPLASTY)**Clinical Context and Therapy Purpose**

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

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

Populations

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

Interventions

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

Comparators

The following therapies are currently being used: stromal puncture.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Dos Santos Paris et al (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy.²⁸ Forty patients with pain from bullous keratopathy who were either waiting for a corneal transplant or had no potential for sight in the affected eye were randomized to the 2 treatments. Symptoms had been present for approximately 2 years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with use of HAM only if the pain did not resolve.

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

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

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

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

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

Keirkhah et al (2008) reported on the use of HAM in 11 eyes of 9 patients who had limbal stem cell deficiency.²⁹ 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.³⁰ Following treatment with ProKera, 3 of the 6 patients had a smooth corneal surface and improved vision to 20/40.³⁰ The other 3 patients had final visual acuity of 20/400, counting fingers, or light perception.

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

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

MODERATE OR SEVERE STEVENS-JOHNSON SYNDROME**Clinical Context and Therapy Purpose**

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

One RCT from India by Sharma et al (2016) assigned 25 patients (50 eyes) with acute ocular Stevens-Johnson syndrome to c-HAM plus medical therapy (antibiotics, steroids, or lubricants) or medical therapy alone.³¹ The c-HAM was prepared locally and applied with fibrin glue rather than sutures. Application of c-HAM in the early stages of 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 individuals who have persistent epithelial defects and ulcerations is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

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

Interventions

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

Comparators

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

Outcomes

The general outcomes of interest are epithelial closure.

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- 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.³² They noted that c-HAM has been available since 1995, and has become an established treatment for persistent epithelial defects and ulceration refractory to conventional therapy. However, there was a lack of controlled studies due to the rarity of the diseases and the absence of standard therapy. They identified 661 reported cases in the peer-reviewed literature. Most cases reported assessed the conjunctival indications of pterygium, scars and symblepharon, and corneal indications of acute chemical injury and postinfectious keratitis.

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

No RCTs were identified on persistent epithelial defects and ulceration.

SEVERE DRY EYE DISEASE WITH OCULAR SURFACE DAMAGE AND INFLAMMATION THAT DOES NOT RESPOND TO CONSERVATIVE THERAPY**Clinical Context and Therapy Purpose**

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

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

Populations

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

Interventions

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

Comparators

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

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

The treatment outcomes in the DRy Eye Amniotic Membrane (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.³⁴ A majority of patients (86%) had superficial punctate keratitis. Other patients had filamentary keratitis (13%), exposure keratitis (19%), neurotrophic keratitis (2%), and corneal epithelial defect (7%). Treatment with Prokera for a mean of 5.4 days (range, 2 to 11) resulted in an improved ocular surface and reduction in the DEWS score from 3.25 at baseline to 1.44 at 1 week, 1.45 at 1 month and 1.47 at 3 months ($p=.001$). Ten percent of eyes required repeated treatment. There was no significant difference in the number of topical medications following c-HAM treatment.

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

The evidence on HAM for severe dry eye with ocular surface damage and inflammation includes an RCT with 20 patients and a retrospective series of 84 patients (97 eyes). Placement of self-retained HAM for 2 to 11 days reduced symptoms and restored a smooth corneal surface and corneal nerve density for as long as 3 months.

MODERATE OR SEVERE ACUTE OCULAR CHEMICAL BURNS

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

An RCT of 100 patients with chemical or thermal ocular burns was published by Tandon et al (2011).³⁵ 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).³⁶ Medical therapy at this tertiary referral hospital included topical preservative-free lubricating gel and drops, chloramphenicol, betamethasone, homatropine, oral vitamin C, and doxycycline. There was no significant difference in the time to epithelial healing (amniotic membrane: 75.8 vs. 72.6 days) or in visual acuity between the 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.³⁷

Section Summary: Moderate or Severe Acute Ocular Chemical Burns

Evidence includes 3 RCTs with a total of 197 patients with acute ocular chemical burns who were treated with HAM transplantation plus medical therapy or medical therapy alone. Patients in the

HAM group had a faster rate of epithelial healing in 1 of the 3 trials, without a significant benefit for other outcomes. The other 2 trials did not find an increase in the rate of epithelial healing in patients with severe burns.

CORNEAL PERFORATION WHEN CORNEAL TISSUE IS NOT IMMEDIATELY AVAILABLE

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is sutured HAM.

Comparators

The following therapies are currently being used: conservative management.

Outcomes

The general outcomes of interest are eye pain.

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

No RCTs were identified on corneal perforation.

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

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

FOLLOWING PTERYGIUM REPAIR WHEN THERE IS INSUFFICIENT HEALTHY TISSUE TO CREATE A CONJUNCTIVAL AUTOGRAFT**Clinical Context and Therapy Purpose**

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

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

Populations

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

Interventions

The therapy being considered is sutured or glued HAM.

Comparators

The following therapies are currently being used: conjunctival autograft.

Outcomes

The general outcomes of interest are a recurrence of pterygium.

Pterygium recurrence would be measured at 1 to 3 months.

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.³⁸ 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.³⁹

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

Systematic reviews of RCTs have been published that found that conjunctival or limbal autograft is more effective than HAM graft in reducing the rate of pterygium recurrence.

REPAIR FOLLOWING MOHS MICROSCOPIC SURGERY

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

Comparators

Comparators of interest include surgical repair using autologous tissue (eg, local flaps and full-thickness skin grafts) and healing without surgery. Second intention healing (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).⁴⁰ Propensity-score matching using retrospective data from medical records was used to identify 143 matched pairs. The primary endpoint was the incidence of postoperative morbidity, including the rate of infection, bleeding/hematoma, dehiscence, surgical reintervention, or development of a nonhealing wound. Postoperative cosmetic outcomes were assessed at 9 months or later and included documentation of suboptimal scarring, scar revision treatment, and patient satisfaction.

Results are summarized in Table 15, and study limitations in Tables 16 and 17. A greater proportion of patients who received dHACM repair experienced zero complications (97.9% vs. 71.3%; $p < .0001$; relative risk 13.67; 95% CI 4.33 to 43.12). Placental allograft reconstructions developed less infection ($p = .004$) and were less likely to experience poor scar cosmesis ($P < .0001$). Confidence in these findings is limited, however, by the study's retrospective design and potential for bias due to missing data. Additionally, the study's relevance is limited due to a lack of diversity in the study population and no comparison to non-surgical treatment options.

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

| Study | Study Type | Country | Dates | Participants | Repair using dHACM | Repair using autologous tissue | Follow-Up |
|------------------------------------|--|---------|-----------|--|--------------------|--------------------------------|---|
| Toman et al (2022) ⁴⁰ , | Retrospective, observational Propensity-score matching used to identify | US | 2014-2018 | Patients who underwent Mohs microsurgery for removal of a basal or squamous cell carcinoma and | n = 143 | n = 143 | Unclear; 9 months or later for postoperative cosmetic outcomes. |

| Study | Study Type | Country | Dates | Participants | Repair using dHACM | Repair using autologous tissue | Follow-Up |
|-------|---------------|---------|-------|--|--------------------|--------------------------------|-----------|
| | matched pairs | | | 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 | | | |

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 | Autologous tissue Repair n = 143 | P |
|-------------------------------------|-------------------------|-------------------------------------|--------|
| Toman et al (2022) ⁴⁰ , | | | |
| 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 |

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

Table 16. Study Relevance Limitations

| Study | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Duration of Follow-up ^e |
|-----------------------------------|---|---------------------------|---|---|------------------------------------|
| Toman et al (2022) ^{40,} | 4. Study participants were 100% white, over two-thirds male | | 2. No comparison to non-surgical options (eg, second intention healing) | 1. Not all outcomes mentioned in methods had results reported (eg, patient satisfaction with scar appearance) | |

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

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (eg, proposed as an adjunct but not tested as such); 5. Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 17. Study Design and Conduct Limitations

| Study | Allocation ^a | Blinding ^b | Selective Reporting ^c | Data Completeness ^d | Power ^e | Statistical ^f |
|-----------------------------------|-------------------------|-----------------------|----------------------------------|---|--------------------|--------------------------|
| Toman et al (2022) ^{40,} | 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.

SUPPLEMENTAL INFORMATION

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

Clinical Input From Physician Specialty Societies and Academic Medical Centers

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

2019 Input

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

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

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

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, amniotic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."⁴¹

Tear Film and Ocular Surface Society

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

Step 1:

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

Step 2:

If above options are inadequate consider:

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

- Topical secretagogues
- Topical non-glucocorticoid immunomodulatory drugs (such as cyclosporine)
- Topical LFA-1 antagonist drugs (such as lifitegrast)
- Oral macrolide or tetracycline antibiotics

Step 3:

If above options are inadequate consider:

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

Step 4:

If above options are inadequate consider:

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

Wound Healing Society

In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.⁴² The Society concluded that there was level 1 evidence that cellular and acellular skin equivalents improve diabetic foot ulcer healing, noting that, “healthy living skin cells assist in healing DFUs [diabetic foot ulcers] by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed.” References from 2 randomized controlled trials on amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

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

Table 18. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|---|---------------------------|------------------------|
| <i>Ongoing</i> | | | |
| NCT04457752 ^a | A Randomised Controlled Multicentre Clinical Trial, Evaluating the Efficacy of Dual Layer Amniotic Membrane (Artacent®) and Standard of Care Versus Standard of Care Alone in the Healing of Chronic Diabetic Foot Ulcers | 124 | Mar 2023 |
| NCT03390920 ^a | Evaluation of Outcomes With Amniotic Fluid for Musculoskeletal Conditions | 200 | Jan 2030 |
| NCT04553432 ^a | Dry Eye OmniLenz Application of Omnigen Research Study | 130 | Jul 2023 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|--|---------------------------|------------------------|
| NCT04636229 ^a | A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients With Osteoarthritis of the Knee | 474 | Dec 2023 |
| NCT06000410 ^a | A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients With Osteoarthritis of the Knee | 474 | Mar 2026 |
| NCT05842057 ^a | Phase 2 Randomized Trial: Human Amnion Membrane Allograft and Early Return of Erectile Function After Radical Prostatectomy (HAMMER) | 240 | Aug 2028 |
| NCT06150209 ^a | A Controlled Data Collection and Prospective Treatment Study to Evaluate the Efficacy of Vendaje in the Management of Foot Ulcers in Diabetic Patients | 100 | Jun 2025 |
| NCT05796765 ^a | A Phase 2B, Prospective, Double-Blind, Randomized Controlled Trial of the Micronized DHACM Injectable Product Compared to Saline Placebo Injection for the Treatment of Osteoarthritis of the Knee | 471 | Jan 2025 |
| Unpublished | | | |
| NCT03855514 ^a | A Prospective, Multicenter, Randomized, Controlled Clinical Study Of NuShield® and Standard of Care (SOC) Compared to SOC Alone For The Management Of Diabetic Foot Ulcers | 200 | Dec 2021 |
| NCT04612023 | A Prospective, Double-Blinded, Randomized Controlled Trial of an Amniotic Membrane Allograft Injection Comparing Two Doses (1 mL and 2 mL Injection) and a Placebo (Sterile Saline) in the Treatment of Osteoarthritis of the Knee | 90 | Jul 2022 |
| NCT04599673 | Prospective Analysis of Intraoperative AMNIOGEN® Injection in Patients With Rotator Cuff Tear | 100 | Sep 2022 |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

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

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

| CPT/HCPCS | |
|------------------|---|
| 65778 | Placement of amniotic membrane on the ocular surface; without sutures |
| 65779 | Placement of amniotic membrane on the ocular surface; single layer, sutured |
| A2001 | Innovamatrix ac, per square centimeter |
| 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 square centimeter |
| Q4181 | Amnio Wound, per sq cm |

| CPT/HCPCS | |
|------------------|---|
| Q4183 | Surgigraft, per sq cm |
| Q4184 | Cellesta, per sq cm |
| Q4185 | Cellesta flowable amnion (25 mg per cc); per 0.5 cc |
| Q4186 | Epifix, per sq cm |
| Q4187 | Epicord, per sq cm |
| Q4188 | AmnioArmor, per sq cm |
| Q4189 | Artacent AC, 1 mg |
| Q4190 | Artacent AC, per sq cm |
| Q4191 | Restorigin, per sq cm |
| Q4192 | Restorigin, 1 cc |
| Q4194 | Novachor, per sq cm |
| Q4198 | Genesis Amniotic Membrane, per sq cm |
| Q4199 | Cygnus matrix, per square centimeter |
| Q4201 | Matrion, per sq cm |
| Q4204 | XWRAP, per sq cm |
| Q4205 | Membrane graft or membrane wrap, per square centimeter |
| Q4206 | Fluid flow or fluid GF, 1 cc |
| Q4208 | Novafix, per square centimeter |
| Q4209 | Surgraft, per square centimeter |
| Q4210 | Axolotl graft or axolotl dualgraft, per square centimeter |
| Q4211 | Amnion bio or Axobiomembrane, per square centimeter |
| Q4212 | Allogen, per cc |
| Q4213 | Ascent, 0.5 mg |
| Q4214 | Cellesta cord, per square centimeter |
| Q4215 | Axolotl ambient or axolotl cryo, 0.1 mg |
| Q4216 | Artacent cord, per square centimeter |
| Q4217 | Woundfix, BioWound, Woundfix Plus, BioWound Plus, Woundfix Xplus or BioWound Xplus, per square centimeter |
| Q4218 | Surgicord, per square centimeter |
| Q4219 | Surgigraft-dual, per square centimeter |
| Q4220 | BellaCell HD or Surederm, per square centimeter |
| Q4221 | Amniowrap2, per square centimeter |
| Q4224 | Human health factor 10 amniotic patch (hhf10-p), per square centimeter |
| Q4225 | Amniobind or dermabind tl, per square centimeter |
| Q4227 | Corplex, per square centimeter |
| Q4229 | Cogenex Amniotic Membrane |
| Q4230 | Cogenex Flowable Amnion, per 0.5 cc |
| Q4231 | Corplex P, per cubic centimeter |
| Q4232 | Corplex, per square centimeter |
| Q4233 | SurFactor or NuDyn, per 0.5 cc |
| Q4234 | XCellerate, per square centimeter |
| Q4235 | Amniorepair, altiPLY, per square centimeter |
| Q4236 | Carepatch, per square centimeter (reactivated 01-01-2023) |
| Q4237 | Cryo-Cord, per square centimeter |
| Q4238 | Derm-maxx, per square centimeter |

| CPT/HCPCS | |
|------------------|--|
| Q4239 | Amnio-Maxx, Amnio-Maxx Lite, per square centimeter |
| Q4240 | Amniotext patch, per square centimeter |
| Q4241 | PolyCyte, per 0.5 mL |
| Q4242 | AmnioCyte Plus, per 0.5 mL |
| Q4245 | AmnioText, per square centimeter |
| Q4246 | CoreText, ProText, per cc |
| Q4247 | Amniotext patch, per square centimeter |
| Q4248 | Dermacyte Matrix, per sq cm |
| Q4249 | Amniplay, for topical use only, per square centimeter |
| Q4250 | Amnioamp-mp, per square centimeter |
| Q4251 | Vim, per square centimeter |
| Q4252 | Vendaje, per square centimeter |
| Q4253 | Zenith amniotic membrane, per square centimeter. |
| Q4254 | Novafix dl, per square centimeter |
| Q4255 | Reguard, for topical use only, per square centimeter |
| Q4256 | Mlg-complete, per square centimeter |
| Q4257 | Relese, per square centimeter |
| Q4258 | Enverse, per square centimeter |
| Q4259 | Celera dual layer or celera dual membrane, per square centimeter |
| Q4260 | Signature apatch, per square centimeter |
| Q4261 | Tag, per square centimeter |
| Q4262 | Dual layer impax membrane, per square centimeter |
| Q4263 | Surgraft tl, per square centimeter |
| Q4264 | Cocoon membrane, per square centimeter |
| Q4265 | Neostim tl, per square centimeter |
| Q4266 | Neostim membrane, per square centimeter |
| Q4267 | Neostim dl, per square centimeter |
| Q4268 | Surgraft ft, per square centimeter |
| Q4269 | Surgraft xt, per square centimeter |
| Q4270 | Complete sl, per square centimeter |
| Q4271 | Complete ft, per square centimeter |
| Q4272 | Esano a, per square centimeter |
| Q4273 | Esano aaa, per square centimeter |
| Q4274 | Esano ac, per square centimeter |
| Q4275 | Esano aca, per square centimeter |
| Q4276 | Orion, per square centimeter |
| Q4277 | Woundplus membrane or e-graft, per square centimeter |
| Q4278 | Epieffect, per square centimeter |
| Q4279 | Vendaje ac, per square centimeter |
| Q4280 | Xcell amnio matrix, per square centimeter |
| Q4281 | Barrera sl or barrera dl, per square centimeter |
| Q4282 | Cygnus dual, per square centimeter |
| Q4283 | Biovance tri-layer or biovance 3l, per square centimeter |
| Q4284 | Dermabind sl, per square centimeter |
| Q4285 | Nudyn dl or nudyn dl mesh, per square centimeter |

| CPT/HCPCS | |
|------------------|--|
| Q4286 | Nudyn sl or nudyn slw, per square centimeter |
| Q4287 | Dermabind dl, per square centimeter |
| Q4288 | Dermabind ch, per square centimeter |
| Q4289 | Revoshield + amniotic barrier, per square centimeter |
| Q4290 | Membrane wrap-hydro, per square centimeter |
| Q4291 | Lamellas xt, per square centimeter |
| Q4292 | Lamellas, per square centimeter |
| Q4293 | Acesso dl, per square centimeter |
| Q4294 | Amnio quad-core, per square centimeter |
| Q4295 | Amnio tri-core amniotic, per square centimeter |
| Q4296 | Rebound matrix, per square centimeter |
| Q4297 | Emerge matrix, per square centimeter |
| Q4298 | Amniocore pro, per square centimeter |
| Q4299 | Amnicore pro+, per square centimeter |
| Q4300 | Acesso tl, per square centimeter |
| Q4301 | Activate matrix, per square centimeter |
| Q4302 | Complete aca, per square centimeter |
| Q4303 | Complete aa, per square centimeter |
| Q4304 | Grafix plus, per square centimeter |
| Q4305 | American amnion ac tri-layer, per square centimeter |
| Q4306 | American amnion ac, per square centimeter |
| Q4307 | American amnion, per square centimeter |
| Q4308 | Sanopellis, per square centimeter |
| Q4309 | Via matrix, per square centimeter |
| Q4310 | Procenta, per 100 mg |

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| 03-20-2017 | Policy added to the bcbsks.com web site. |
| 01-01-2019 | Updated Description section. In Policy section: <ul style="list-style-type: none"> ▪ In Item A 1, added "Q4168". ▪ In Item A 3, removed "Q4131" and added "Q4145, Q4186". ▪ Added new Item B, "FDA-approved sutured and non-sutured human amniotic membrane grafts may be considered medically necessary for the treatment of the following ophthalmic indications: 1. Neurotrophic keratitis 2. Corneal ulcers and melts 3. Pterygium repair 4. Stevens-Johnson syndrome 5. Persistent epithelial defects (with documented pain for ≥5 days) 6. Acid or alkaline burn. ▪ Added new Item C, "FDA-approved sutured and non-sutured human amniotic membrane grafts are considered experimental / investigational for the treatment of all other ophthalmic conditions including but not limited to dry eye syndrome, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy." ▪ In Item D (previous Item B), added "including but not limited to treatment of osteoarthritis and plantar fasciitis" to read "Injection of micronized or particulated human amniotic membrane is considered experimental / investigational for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis." ▪ In Item F (previous Item D), removed "human amniotic membrane products and" and added "including but not limited to treatment of lower-extremity ulcers due to venous |

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| | <p>insufficiency" to read "All other human amniotic membrane products and indications not listed above are considered experimental / investigational, including but not limited to treatment of lower-extremity ulcers due to venous insufficiency."</p> <ul style="list-style-type: none"> ▪ Updated Policy Guidelines. |
| | Updated Rationale section. |
| | <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT codes: 65778, 65779. ▪ Added new HCPCS codes: Q4183, Q4184, Q4185, Q4186, Q4187, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4201, Q4204. ▪ Removed deleted HCPCS code: Q4131. ▪ Revised nomenclature to HCPCS codes: Q4132, Q4133, Q4137, Q4148, Q4156, Q4162, Q4163. ▪ Added ICD-10 codes: H11.001, H11.002, H11.003, H11.011, H11.012, H11.013, H11.021, H11.022, H11.023, H11.031, H11.032, H11.033, H11.041, H11.042, H11.043, H11.051, H11.052, H11.053, H11.061, H11.062, H11.063, H16.011, H16.012, H16.013, H16.021, H16.022, H16.023, H16.031, H16.032, H16.033, H16.041, H16.042, H16.043, H16.051, H16.052, H16.053, H16.061, H16.062, H16.063, H16.121, H16.122, H16.123, H16.231, H16.232, H16.233, H18.831, H18.832, H18.833, T26.11XA, T26.11XD, T26.11XS, T26.12XA, T26.12XD, T26.12XS, T26.31XA, T26.31XD, T26.31XS, T26.32XA, T26.32XD, T26.32XS, T26.51XA, T26.51XD, T26.51XS, T26.52XA, T26.52XD, T26.52XS, T26.61XA, T26.61XD, T26.61XS, T26.62XA, T26.62XD, T26.62XS, T26.81XA, T26.81XD, T26.81XS, T26.82XA, T26.82XD, T26.82XS. |
| | Updated References section. |
| 02-18-2019 | <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A 3, removed "Q4145". |
| 03-27-2019 | Updated Description section. |
| | <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A, added new Item A 3, "Epicord (Q4187)". |
| | Updated Rationale section. |
| | <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Removed ICD-10 codes: T26.51XA, T26.51XD, T26.51XS, T26.52XA, T26.52XD, T26.52XS. |
| | Updated References section. |
| 05-21-2019 | <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A 1, removed HCPCS code Q4168. |
| 09-27-2019 | Policy published to the bcbsks.com website on 08-28-2019 with an effective date of 09-27-2019. |
| | <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added ICD-10 codes: H18.891, H18.892, H18.893. |
| | Updated References section. |
| 10-01-2019 | <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added HCPCS Codes: Q4205, Q4206, Q4208, Q4209, Q4210, Q4211, Q4212, Q4213, Q4214, Q4215, Q4216, Q4217, Q4218, Q4219, Q4221 |
| 07-01-2020 | <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added HCPCS Codes: Q4176, Q4177, Q4178, Q4181, Q4227, Q4228, Q4229, Q4230, Q4231, Q4232, Q4233, Q4234, Q4235, Q4236, Q4237, Q4239, Q4240, Q4241, Q4242, Q4244, Q4245, Q4246, Q4247, Q4248 |
| 07-16-2021 | Updated Description section |
| | <p>In Policy section <u>Added item A.1</u> <u>In Item B</u></p> |

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| | <ul style="list-style-type: none"> • Removed: "FDA-approved sutured and non-sutured human amniotic membrane grafts may be considered medically necessary for the treatment of the following ophthalmic indications: <ol style="list-style-type: none"> 1. Neurotrophic keratitis 2. Corneal ulcers and melts 3. Pterygium repair 4. Stevens-Johnson syndrome 5. Persistent epithelial defects (with documented pain for ≥ 5 days) 6. Acid or alkaline burn" • Added: "Human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) or glue may be considered medically necessary for the treatment of the following ophthalmic indications: <ol style="list-style-type: none"> 1. Neurotrophic keratitis with ocular surface damage and inflammation that does not respond to conservative therapy; 2. Corneal ulcers and melts that do not respond to initial conservative therapy; 3. Corneal perforation when there is active inflammation after corneal transplant requiring adjunctive treatment; 4. Bullous keratopathy as a palliative measure in patients who are not candidates for curative treatment (e.g., endothelial or penetrating keratoplasty); 5. Partial limbal stem cell deficiency with extensive diseased tissue where selective removal alone is not sufficient; 6. Moderate or severe Stevens-Johnson syndrome; 7. Persistent epithelial defects that do not respond as stated in policy guideline #2; 8. Severe dry eye (DEWS 3 or 4) with ocular surface damage and inflammation that remains symptomatic after Steps 1, 2, and 3 of the dry eye disease management algorithm (see Policy Guidelines); or 9. Moderate or severe acute ocular chemical burn." 10. Corneal perforation when corneal tissue is not immediately available; or 11. Pterygium repair when there is insufficient healthy tissue to create a conjunctival autograft <p><u>In Item C</u></p> <ul style="list-style-type: none"> • Removed: "FDA approved sutured and non-sutured human amniotic membrane grafts are considered experimental / investigational for the treatment of all other ophthalmic conditions including, but not limited to, dry eye syndrome, corneal perforation, bullous keratopathy, limbus stem cell deficiency, and after photorefractive keratectomy." • Added: "Human amniotic membrane grafts with or without suture are considered experimental / investigational for all ophthalmic indications not outlined above." <p><u>Added</u></p> <ul style="list-style-type: none"> • <u>Item F</u> • <u>Policy Guidelines</u> |
| | Updated Rationale section |
| | <p>In Coding section:</p> <ul style="list-style-type: none"> • Added HCPCS Codes: Q4180, Q4220, Q4238, Q4249, Q4250, Q4254, Q4255 • Added ICD 10 Diagnosis codes: H18.11, H18.12, H18.13, H18.30, H18.52, I87.2, L51.1, T26.50XA, T26.50XD, T26.50XS, T26.51XA, T26.51XD, T26.51XS, T26.52XA, T26.52XD, T26.52XS • Removed ICD 10 Diagnosis codes: H16.121, H16.122, H16.123, L97.212, L97.213, L97.214, L97.222, L97.223, L97.224, L97.312, L97.313, L97.314, L97.322, L97.323, L97.324, L97.412, L97.413, L97.414, L97.422, L97.423, L97.424, L97.512, L97.513, L97.514, L97.522, L97.523, L97.524, L97.812, L97.813, L97.814, L97.822, L97.823, |

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| | L97.824, T26.31XA, T26.31XD, T26.31XS, T26.32XA, T26.32XD, T26.32XS, T26.61XA, T26.61XD, T26.61XS, T26.62XA, T26.62XD, T26.62XS, T26.81XA, T26.81XD, T26.81XS, T26.82XA, T26.82XD, T26.82XS |
| | Updated Reference section |
| | Added Appendix |
| 10-08-2021 | In Coding section: Effective 10-01-2021 Added HCPCS codes: Q4251, Q4252, Q4253 Deleted HCPCS codes: Q4228, Q4236 (no longer being manufactured) |
| 01-03-2022 | In Coding Section Added HCPCS code A2001, Q4199 (effective 01-01-2022) |
| 04-01-2022 | In Coding Section Added: Q4224, Q4225, Q4256, Q4257, Q4258 (new codes 04-01-2022) |
| 04-08-2022 | Updated Description Section |
| | Updated Policy Section <ul style="list-style-type: none"> ▪ Section G "All other indications not listed above are considered experimental / investigational, including, but not limited to, treatment of lower-extremity ulcers due to venous insufficiency." added "and repair following Mohs micrographic surgery" to the end of the statement. |
| | Updated Rationale Section |
| | Updated Coding Section <ul style="list-style-type: none"> ▪ Removed coding bullets <ul style="list-style-type: none"> • There are specific HCPCS codes for some of these products. If no specific HCPCS code exists for the product, an unlisted code such as Q4100 would be used. • There are no specific codes for AmnioFix or OrthoFlo. It might be reported using the code for another MiMedx product such as Q4145 or the not otherwise specified code Q4100. • There is no specific code for this type of injection. It might be reported with one of the musculoskeletal system injection codes (e.g., 20550), the unlisted general musculoskeletal system code (20999), or if subcutaneous or intramuscular, the therapeutic injection code (96372). • There are codes for the placement of amniotic membrane on the ocular surface: 65778, 65779 ▪ Removed Code: Q4100 ▪ Added ICD-10 Codes: H04.121-H04.129, M17.10-M17.9 and M72.2 ▪ Converted ICD-10 codes to ranges |
| | Updated References Section |
| 01-03-2023 | Updated Coding Section <ul style="list-style-type: none"> ▪ Added codes Q4259, Q4260, Q4261 (eff. 07-01-2022) and Q4262, Q4263, Q4264 (eff. 01-01-2023) |
| 03-28-2023 | Updated Description Section |
| | Updated Rationale Section |
| | Updated Coding Section <ul style="list-style-type: none"> ▪ Added Q4236 (reactivated 01-01-2023), Q4265, Q4266, Q4267, Q4268, Q4269, Q4270, Q4271 (eff. 04-01-2023) ▪ Removed ICD-10 Codes |
| | Updated References Section |
| | Removed Appendix Section |
| 07-03-2023 | Updated Coding Section <ul style="list-style-type: none"> ▪ Added: Q4272, Q4273, Q4274, Q4275, Q4276, Q4277, Q4278, Q4280, Q4281, Q4282, Q4283 and Q4284 (eff. 7-1-2023) |

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| 10-02-2023 | Updated Coding Section <ul style="list-style-type: none"> Added: Q4285 and Q4286 (eff. 10-1-2023) |
| 01-01-2024 | Updated Coding Section <ul style="list-style-type: none"> Updated nomenclature for Q4225 Added Q4279, Q4287, Q4288, Q4289, Q4290, Q4291, Q4292, Q4293, Q4294, Q4295, Q4296, Q4297, Q4298, Q4299, Q4300, Q4301, Q4302, Q4303 and Q4304 (eff. 01-01-2024) |
| Posted 04-23-2024 Effective 05-23-2024 | Updated Description Section Update Policy Section <ul style="list-style-type: none"> Added A3: AmnioExcel® to statement A: "Treatment of nonhealing diabetic lower-extremity ulcers using the following human amniotic membrane products may be considered medically necessary." Removed "(Prokera®, AmbioDisk™)" from statement B: "Human amniotic membrane grafts with or without suture (Prokera®, AmbioDisk™) or glue, may be considered medically necessary for the treatment of the following ophthalmic indications:" Added to statement G "other human amniotic products (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, or Wharton's jelly) including but not limited to those in Table PG2 (see Policy Guidelines) for indications not listed above are considered experimental / investigational for indications reviewed herein," Updated Policy Guidelines <ul style="list-style-type: none"> Added "Non-healing of lower-extremity ulcers due to venous insufficiency is defined as less than a 30% decrease in wound area with standard wound care for at least 2 weeks, based on clinical trial entry criteria (Serena et al [2022])." And "This review covers products that do not require FDA approval or clearance. The list of products named in this review is not a complete list of all commercially available products. Table PG1 lists products included in the Policy statements, and Table PG2 lists other amniotic products that have an HCPCS code." Added: AmnioExcel® Integra Q4137 to PG1 Table Removed: AmnioBand® Particulate, MTF Wound Care, Q4168 and AmnioExcel®, Derma Sciences, Q4137 Updated Rationale Section Updated Coding Section <ul style="list-style-type: none"> Deleted Q4244 (eff. 04-01-2024) Added Q4305, Q4306, Q4307, Q4308, Q4309, Q4310 (eff. 04-01-2024) Updated Rationale Section |

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