

Amniotic Membrane and Amniotic Fluid

Policy # 00458

Original Effective Date: 08/19/2015

Current Effective Date: 07/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

Note: Recombinant and Autologous Platelet Derived Growth Factors for Wound Healing and Other Non Orthopedic Conditions is addressed separately in medical policy 00262.

Note: Bioengineered Skin and Soft Tissue Substitutes is addressed separately in medical policy 00572.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider treatment of diabetic foot ulcers using the following human amniotic membrane (HAM) products, Affinity^{®‡}, AmnioBand^{®‡} Membrane, AmnioExcel^{®‡}, Biovance^{®‡}, EpiCord^{®‡}, Epifix^{®‡}, Grafix^{™‡}, and NuShield^{®‡}, to be **eligible for coverage**** in following situations:

- Initial treatment may be approved when the following criteria are met:
 - For nonhealing and not clinically infected diabetic foot ulcers (non-healing of diabetic wounds is defined as less than a 20% decrease in wound area with standard wound care for at least 2 weeks); **AND**
 - Patient agrees to comply with adequate mechanical offloading; **AND**
 - For up to 4 applications over 6 weeks period per wound; **OR**
- Additional applications after initial 6 weeks may be eligible for coverage when the following criteria are met:
 - Not clinically infected diabetic foot ulcers; **AND**
 - Documented objective evidence of wound healing (e.g. development and presence of healthy granulation tissue with progressive wound contracture or decreasing depth); **AND**
 - Approved HAM product is applied no more frequently than in one-week intervals; **AND**
 - Patient remains compliant with adequate mechanical offloading; **AND**

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- Continued treatment may be approved for up to 4 additional applications over 6 more weeks, per wound treated.

Based on review of available data, the Company may consider a human amniotic product commercially available specifically for ophthalmic use (with or without suture or glue), e.g., Prokera[®], AmbioDisk[™], AmnioGraft[®], Artacent Ocular, Vendaje Optic[™], for the treatment of any of the following ophthalmic indications to be **eligible for coverage**:**

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

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers use of human amniotic membrane (HAM) products when criteria above are not met including using more than 8 applications beyond 12 weeks for diabetic foot ulcers to be **not medically necessary**.**

Based on review of available data, the Company considers human amniotic membrane grafts available for ophthalmic use when criteria above are not met to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers use of human amniotic membrane (HAM) for all other indications not listed above to be **investigational*** including but not limited to:

- Treatment of lower-extremity ulcers due to venous insufficiency
- Repair following Mohs micrographic surgery.

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Based on review of available data, the Company considers injection of micronized or particulated human amniotic membrane for all indications, including but not limited to treatment of osteoarthritis and plantar fasciitis, to be **investigational**.*

Based on review of available data, the Company considers injection of human amniotic fluid for all indications to be **investigational**.*

Based on review of available data, the Company considers all other human amniotic products not listed above (e.g., derived from amnion, chorion, amniotic fluid, umbilical cord, Wharton's jelly, and products noted in Table PG2 in Policy Guidelines) to be **investigational**.*

Policy Guidelines

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

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

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]).

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.

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
AmbioDisk	Katena	V2790
AmnioExcel ^{®‡}	Integra	Q4137
AmnioGraft	Bio-Tissue	V2790
Artacent Ocular	Tides medical	V2790
Biovance ^{®‡}	Celularity	Q4154
Epicord ^{®‡}	MiMedx	Q4187
Epifix ^{®‡}	MiMedx	Q4186
Grafix ^{®‡} (Grafix core, Grafix prime)	Osiris	Q4132, Q4133
NuShield ^{®‡}	Organogenesis	Q4160
Prokera	Bio-Tissue	V2790

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Vendaje Optic	BioStem Technologies	V2790
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Table PG2 Other Amniotic Products with HCPCS Codes

Trade Name	Supplier	HCPCS Code
Abiomend Xplus Membrane and Abiomend Xplus Hydromembrane	Amnio Technology	Q4355
Abiomend Membrane and Abiomend Hydromembrane	Amnio Technology	Q4356
Absolv3 Membrane	Amnio Technology	Q4401
ACApatch ^{TM†}	RegenTX Partners	Q4325
Acelagraft ^{®‡}	N/A	Q4395
Acesso	Dynamic Medical Services	Q4311
Acesso ac	Dynamic Medical Services	Q4312
Acesso dl	Dynamic Medical Services	Q4293
Acesso tl	Dynamic Medical Services	Q4300
Acesso TrifACA	Dynamic Medical Services LLC dba Acesso Biologics	Q4386
Activate matrix	Nvision Biomedical Technologies	Q4301
A/c wrap	Biolab Holdings	Q4422
Advograft one	RMBB Health	Q4380
Advograft dual	RMBB Health	Q4382
Aeroguard	C5 Biomedical	Q4370
AlexiGuard DL-T	AlexiGen BioTech	Q4417
AlexiGuard SL-T	AlexiGen BioTech	Q4415
AlexiGuard TL-T	AlexiGen BioTech	Q4416
alloPLY ^{TM†}	RegenTX Partners	Q4323
Allogen	Vivex Biologics	Q4212
AlloWrap ^{TM†}	AlloSource	Q4150
AmchoMatrix	LifeCell International Pvt Ltd	Q4243
AmchoMatrixDL	Cellution Biologics Inc	Q4410
AmnioMatrixF4X	Cellution Biologics Inc.	Q4411
AmchoPlast ^{®‡}	RMBB Health	Q4316
Amchoplast excel	Cellution Biologics	Q4372
AmchoPlast FD ^{TM†}	LifeCell International Pvt Ltd.	Q4360
AmchoThick ^{TM†}	Cellution Biologics	Q4368
AmnioAMP-MP	Stratus BioSystems	Q4250
Amnioarmor ^{TM†}	Bone Bank Allografts	Q4188
AmnioBand ^{1®‡} Particulate	MTF Wound Care	Q4168
AmnioExcel ^{1®‡}	Intergra Lifesciences	Q4137
AmnioMatrixF3X	Cellution Biologics Inc	Q4409
Amnio-maxx or Manio-maxx lite	Royal Biologics	Q4239
Amnioplast 1	LifeCell International	Q4334
Amnioplast 2	LifeCell International	Q4335

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AmnioPlast 3™†	Cellution Biologics	Q4369
Amniotext	Regenerative Labs	Q4245
AmnioTX™†	RegenTX Partners	Q4324
Amnio tri-core amniotic	Stability Biologics	Q4295
Amnio quad-core	Stability Biologics	Q4294
Amniowound	Alpha Tissue	Q4181
Amnion bio or Axomembrane	Axolotl Biologix	Q4211
Amniocore™†	Stability Biologics	Q4227
Amniocore pro	Stability Biologics	Q4298
Amnicore pro+	Stability Biologics	Q4299
AmnioCore SL	Stability Biologics.	Q4367
Amniodefend ft matrix	Sequence LifeScience	Q4379
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™†	Biostem Technologies	Q4221
Amnio Burgeon Membrane and Hydromembrane	One BioTech LLC.	Q4363
Amnio Burgeon XPlus Membrane and XPlus Hydromembrane	One BioTech LLC.	Q4364
Amnio Burgeon Dual-Layer Membrane	One BioTech LLC.	Q4365
AmnioPlast Double	Cellution Biologics Inc	Q4391
Apollo FT	Dynamic Medical Services LLC dba Acesso Biologics	Q4385
ArdeoGraft	Surgenex	Q4333
Articent ac (flowable)	Tides Medical	Q4189
Artacent ac (patch)	Tides Medical	Q4190
Artacent®† Wound	Tides Medical	Q4169
Artacent c	Tides Medical	Q4336
Artacent®† Cord	Tides Medical	Q4216
Artacent trident	Tides Medical	Q4337
Artacent velos	Tides Medical	Q4338
Artacent vericlen	Tides Medical	Q4339
Ascension™†	Ascension Biologics	Q4390
Ascent	StimLabs	Q4213
Axolotl Graft™†	Axolotl Biologix	Q4331
Axolotl Graft™† Ultra	Axolotl Biologix	Q4383
Axolotl DualGraft™†	Axolotl Biologix	Q4332
Axolotl DualGraft™† Ultra	Axolotl Biologix	Q4384
Axolotl ambien or Axolotl Cryo	Axolotl Biologix	Q4215

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BioDDryFlex ^{®†}	BioD	Q4138
BioDfence ^{™†}	Integra Life Science	Q4140
Biolab membrane wrap lite flow	Biolab Holdings	Q4419
Biolab membrane wrap flow	Biolab Holdings	Q4418
Biolab membrane wrap solo	Biolab Holdings	Q4421
Biolab tri-membrane wrap flow	Biolab Holdings	Q4423
BioWound, BioWound Plus ^{™†} , BioWound XPlus ^{™†}	Skye Biologics	Q4217
Carbon life	Carbon Life Sciences	Q4207
CaregraFT ^{™†}	RegenTX Partners	Q4322
carePATCH	Extremity Care	Q4236
Cellesta/Cellesta duo	Ventris Medical	Q4184
Cellesta Cord	Ventris Medical	Q4214
Cellesta flowable	Ventris Medical	Q4185
CHORIOFIX ^{™†}	MiMedx	Q4412
ChoriPly	International Tissue Inc.	Q4359
Clarix ^{®†}	Amniox Medical	Q4156
Clarix ^{®†} Flo	Amniox Medical	Q4155
Cogenex flowable amnion	Ventris Medical	Q4230
Cogenex amniotic membrane	Ventris Medical	Q4229
Complete aa	Samaritan Biologics	Q4303
Complete aca	Legacy Medical	Q4302
Corecyte	Predictive Biotech	Q4240
Corplex	StimLabs	Q4232
Corplex P or Theracor P or Allacor P	StimLabs	A2035
Coretext or Protext	Regenerative Labs	Q4246
Cryo-cord	Royal Biologics	Q4237
Curamatrix	Xtant Medical	Q4440
Cygnus	Vivex Biomedical	Q4170
CYGNUS Disk	VIVEX Biologics (Vivex)	Q4362
CYGNUS Solo	Vivex Biologics	Q4413
Dermacyte	Merakris Therapeutics	Q4248
Dermacyte ^{®†} AC Matrix	Merakris Therapeutics	Q4343
Dermabind ch	Health Tec Wound Care	Q4288
Dermabind ch n or dermabind ch x	HealthTech Wound Care	Q4429
Dermabind dl	Health Tec Wound Care	Q4287
Dermabind dl n or dermabind dl + or dermabind dl x	HealthTech Wound Care	Q4427
DermaBind FM ^{™†}	Health Tec Wound Care	Q4313
Dermabind sl n or dermabind sl + or dermabind sl x	HealthTech Wound Care	Q4428
DermaBind SL Optic ^{™†}	HealthTech Wound Care	Q4223

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DermaBind TL + or dermabind tl X	HealthTech Wound Care	Q4426
Dermavest ^{TM†} or Plurinvest	AediCell ^a	Q4153
Dual Layer Amnio Burgeon X-Membrane	One BioTech LLC.	Q4366
DuoAmnion ^{TM†}	Samaritan Biologics	Q4327
Duograft aa	RegenTX Partners	Q4376
Duograft ac	RegenTX Partners	Q4375
E-Graft ^{TM†}	Skye Biologics	Q4318
Emerge matrix	Sequence Life Science	Q4297
Enclose tl matrix	Sequence LifeScience	Q4351
Epifix Injectable	MiMedx	Q4145
EPIXPRESS	MiMedx Group, Inc.	Q4361
Floweramnioflo	Flower Orthopedics	Q4177
Floweramniopatch	Flower Orthopedics	Q4178
Fluid flow or Fluid GF	BioLab Sciences	Q4206
Genesis	Genesis Biologics	Q4198
GRAFIX DUO	Smith and Nephew	Q4392
Grafix plus	Smith & Nephew	Q4304
Instagraft	Xtant Medical	Q4439
Interfyl ^{®†}	Celularity	Q4171
Lamellas	Keyport Management	Q4292
Lamellas xt	Keyport Management	Q4291
Mantle dl matrix	Sequence LifeScience	Q4349
Matrion	LifeNet Health	Q4201
Matrix HD Allograft Dermis	Royal Wound-X, Inc	Q4345
Membrane wrap-hydro	BioLab Sciences	Q4290
Membrane wrap-lite	BioLab Holdings	Q4373
MOST ^{TM†}	Samaritan Biologics	Q4328
Natalin ^{®†}	Celularity Inc.	Q4396
Neoguard	C5 Biomedical	Q4371
Neopatch or Therion	CryoLife	Q4176
NeoThelium 4L	Neostim, LLC dba NSM Biologics	Q4388
NeoThelium 4L+	Neostim, LLC dba NSM Biologics	Q4389
NeoThelium FT	Neostim, LLC dba NSM Biologics	Q4387
Neox ^{®†} Cord	Amniox Medical	Q4148
Neox ^{®†} Flo	Amniox Medical	Q4155
Neox ^{®†} Wound	Amniox Medical	Q4156
Novachor	Organogenesis	Q4194
Novafix ^{®†}	Triad Life Sciences	Q4208
Novafix DL	Triad Life Sciences	Q4254
NuDYN ^{®†} DL MESH	Fida Pharma USA	Q4285
NuDYN ^{®†} SLW	Fida Pharma USA	Q4286
NuForm ^{TM†}	Organogenesis Inc	Q4420
Overlay sl matrix	Sequence LifeScience	Q4352

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PalinGen ^{®†} Dual-Layer Membrane	Amnio Technology	Q4354
PalinGen ^{®†} Membrane	Amnio Technology	Q4173
PalinGen ^{®†} SportFlow	Amnio Technology	Q4174
Palisade dm matrix	Sequence LifeScience	Q4350
PelloGraft	Surgenex	Q4320
Plurivest ^{™†}	AediCell	Q4153
Polycyte	Predictive Biotech	Q4241
Polygon3 Membrane	Amnio Technology	Q4400
Pretect	Stimlabs	Q4438
Procenta	Extremity Care	Q4310
Rampart dl matrix	Sequence LifeScience	Q4347
Ranati ac membrane	Pinnacle Transplant Technologies	Q4436
Ranati membrane	Pinnacle Transplant Technologies	Q4435
Rebound matrix	Sequence LifeScience	Q4296
Reeva FT	Legacy Medical	Q4314
Regenelink	LifeLink Foundation	Q4315
Reguard	New Life Medical	Q4255
Renew ft matrix	Sequence LifeScience	Q4378
RenoGraft	Surgenex	Q4321
Restorigin	Parametrics Medical	Q4191
Restorigin Injectable	Parametrics Medical	Q4192
Revita	StimLabs	Q4180
Revitalon ^{™†}	Medline Industries	Q4157
Revival ac	Samaritan Biologics	Q4437
Revive ft	Acesso Biologics	Q4424
Revive tl	Acesso Biologics	Q4425
Revoshield + amniotic barrier	Revogen Biologics	Q4289
SanoGraft	Surgenex	Q4319
Shelter dm matrix	Sequence LifeScience	Q4346
Sentry sl matrix	Sequence LifeScience	Q4348
SimpliChor	Xtant Medical	Q4414
SimpliGraft	Xtant Medical	Q4340
Simplimax	Xtant Medical	Q4341
Singlay ^{™†}	Samaritan Biologics	Q4329
Summit AAA	N/A	Q4397
Summit AC	Legacy Medical	Q4398
Summit FX	Legacy Medical	Q4399
Surgenex, Surfactor, and Nudyn	Surgenex	Q4233
SurGraft ACA	Surgenex, LLC	Q4394
SurGraft AC	Surgenex, LLC	Q4393
Surgicord	Synergy Biologics	Q4218
SurgiGRAFT ^{™†}	Synergy Biologics	Q4183
Theracor	Stimlabs LLC	A2049
TheraMend	Lux Therapeutics	Q4342
Trigraft ft	RegenTX Partners	Q4377

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Tri-Membrane Wrap ^{TM†}	BioLab	Q4344
TOTAL ^{TM†}	Samaritan Biologics	Q4330
Vendaje ac	BioStem Technologies	Q4279
VitoGraft	Surgenex	Q4317
WoundEx ^{®†}	Skye Biologics	Q4163
WoundEx ^{®†} Flow	Skye Biologics	Q4162
Woundfix, Woundfix Plus, Wounfix XPlus (see BioWound above)	Skye Biologics	Q4217
WoundPlus ^{TM†}	Skye Biologics	Q4326
Xceed tl matrix	RMBB Health	Q4353
Xcellerate	Precise Bioscience	Q4234
Xwrap	Applied Biologics	Q4204
XWRAP Fenestra ^{®†}	Applied Biologics	Q4406
XWRAP Fenestra Plus ^{®†}	Applied Biologics	Q4405
XWRAP Hydro ^{®†}	Applied Biologics	Q4408
XWRAP Hydro Plus ^{®†}	Applied Biologics	Q4404
XWRAP Plus ^{®†}	Applied Biologics, LLC.	Q4357
XWRAP Dual ^{®†}	Applied Biologics, LLC.	Q4358
XWRAP Dual Plus ^{®†}	Applied Biologics	Q4403
XWRAP Tribus ^{®†}	Applied Biologics	Q4407
XWRAP 2.0 ^{®†}	Applied Biologics	Q4402

HRT: Human Regenerative Technologies; MTF: Musculoskeletal Transplant Foundation

^a Processed by HRT and marketed under different trade name.

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

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- 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)

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

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Background/Overview

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. 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.

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. 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. 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. 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. Pluripotent stem cells can be cultured and are capable of differentiation toward any cell type.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

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

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, Title 21, parts 1270 and 1271. In 2017, the FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps).

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:

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- a. Is for autologous use;
- b. Is for allogeneic use in a first-degree or second-degree blood relative; or
- c. Is for reproductive use."

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

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

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

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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.

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Summary of Evidence

Diabetic Lower-Extremity Ulcers

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

Lower-Extremity Ulcers due to Venous Insufficiency

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

Osteoarthritis

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

Plantar Fasciitis

For individuals who have plantar fasciitis who receive an injection of amniotic membrane, the evidence includes preliminary studies and a larger (N=145) patient-blinded comparison of

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

Ophthalmic Conditions

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

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

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

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

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

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

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

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

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

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

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

Moderate or Severe Stevens-Johnson Syndrome

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

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

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

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

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

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density for as long as 3 months. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Moderate or Severe Acute Ocular Chemical Burns

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

Corneal Perforation When Corneal Tissue is Not Immediately Available

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

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

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

Repair Following Mohs Micrographic Surgery

For individuals who have undergone Mohs micrographic surgery for skin cancer on the face, head, neck, or dorsal hand who receive human amniotic/chorionic membrane, the evidence includes a nonrandomized, comparative study and no RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, and quality of life. A retrospective analysis using data from medical records compared a dehydrated human amniotic/chorionic membrane product (dHACM, Epifix) to repair using autologous surgery in 143 propensity-score matched pairs of patients requiring same-day reconstruction after Mohs microsurgery for skin cancer on the head, face, or neck. A greater proportion of patients who received dHACM repair experienced zero complications (97.9% vs. 71.3%; $p < .0001$; relative risk 13.67; 95% CI 4.33 to 43.12). Placental allograft reconstructions developed less infection ($p = .004$) and were less likely to experience poor scar cosmesis ($p < .0001$). This study is limited by its retrospective observational design. Well-designed and conducted prospective studies are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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Supplemental Information

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.

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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."

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. 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)

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT07159282	A Multicenter, Prospective, Controlled Clinical Trial Evaluating the Efficacy of a Single Layer Placental-based Allograft and Standard of Care in	60	Aug 2027

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	the Management of Nonhealing Diabetic Foot Ulcers		
NCT06704893	The Efficacy of Amniotic Suspension Allograft Injection in the Treatment of Knee Osteoarthritis: a Randomized Double-blind Controlled Trial	160	Dec 2027
NCT06600724 ^a	A Multicenter, Prospective, Randomized Controlled Modified Platform Trial Evaluating PURION Processed Lyophilized Human Amnion/Chorion Membrane (ppLHACM) and Standard of Care Versus Standard of Care Alone in the Treatment of Nonhealing Diabetic Foot Ulcers	170	Aug 2026
NCT04457752 ^a	A Randomised Controlled Multicentre Clinical Trial, Evaluating the Efficacy of Dual Layer Amniotic Membrane (Artacent®)‡ and Standard of Care Versus Standard of Care Alone in the Healing of Chronic Diabetic Foot Ulcers	124	Mar 2023
NCT03390920 ^a	Evaluation of Outcomes with Amniotic Fluid for Musculoskeletal Conditions	200	Jan 2030
NCT04553432 ^a	Dry Eye OmniLenz Application of Omnigen Research Study	79 (actual)	Jul 2023
NCT05842057 ^a	Phase 2 Randomized Trial: Human Amnion Membrane Allograft and Early Return of Erectile Function After Radical Prostatectomy (HAMMER)	240118 (actual)	Aug 2028
NCT06150209 ^a	A Controlled Data Collection and Prospective Treatment Study to Evaluate the Efficacy of Vendaje in the Management of Foot Ulcers in Diabetic Patients	100	Jun 2025
NCT05796765 ^a	A Phase 2B, Prospective, Double-Blind, Randomized Controlled Trial of the Micronized DHACM Injectable Product Compared to Saline Placebo Injection for the Treatment of Osteoarthritis of the Knee	43 (terminated)	Dec 2023
Unpublished			
NCT03855514 ^a	A Prospective, Multicenter, Randomized, Controlled Clinical Study Of NuShield®‡ and Standard of Care (SOC) Compared to SOC Alone for the Management of Diabetic Foot Ulcers	200	Dec 2021

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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
NCT04636229 ^a	A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients with Osteoarthritis of the Knee	516 (actual)	Aug 2025
NCT06000410 ^a	A Phase 3 Prospective, Multicenter, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of Amniotic Suspension Allograft (ASA) in Patients with Osteoarthritis of the Knee	594 (actual)	Nov 2025

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 08/19/2015

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| 08/06/2015 | Medical Policy Committee review |
| 08/19/2015 | Medical Policy Implementation Committee approval. New policy. |
| 08/04/2016 | Medical Policy Committee review |
| 08/17/2016 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 08/03/2017 | Medical Policy Committee review |
| 08/23/2017 | Medical Policy Implementation Committee approval. AmnioBand Membrane, Biovance, Epifix, Grafix considered medically necessary for diabetic foot ulcers; all other products and indications are investigational. Sutured amniotic membrane grafts considered medically necessary for neurotrophic keratitis, corneal ulcers and melts, following pterygium repair, Stevens-Johnson syndrome, and persistent epithelial defects. Ophthalmic products added and discontinued product names removed from Table 1. |
| 05/03/2018 | Medical Policy Committee review |
| 05/16/2018 | Medical Policy Implementation Committee approval. Investigational indications clarified. |
| 04/04/2019 | Medical Policy Committee review |
| 04/24/2019 | Medical Policy Implementation Committee approval. EpiCord add to medically necessary statement for diabetic lower extremity ulcers. Sutured and non-sutured amniotic membrane may be considered medically necessary for specified ophthalmic conditions. |
| 08/01/2019 | Medical Policy Committee review |
| 08/14/2019 | Medical Policy Implementation Committee approval. Added criteria for non healing diabetic ulcers. |
| 08/06/2020 | Medical Policy Committee review |
| 08/12/2020 | Medical Policy Implementation Committee approval. 60-day provider notification required as proposed changes will result in more restrictive coverage criteria. Effective date is 11/01/2020.
Replaced “diabetic lower extremity ulcers” with “diabetic foot ulcers” in the eligible for coverage statement for treatment of nonhealing and not clinically infected diabetic foot ulcers. This change is proposed to make distinction/clarification between other lower extremity ulcers in diabetics and true non-healing diabetic foot ulcers. |

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	Added the requirement that “patient agrees to comply with adequate mechanical offloading” for initial placement and similarly for continued treatment eligible for coverage criteria for additional applications, adding that “patient remains compliant with adequate mechanical offloading”.
	Revised the Policy Guidelines definition of non-healing diabetic wounds was revised to “an ulcer that fails to demonstrate > 50% wound area reduction after a minimum of 4 weeks of standard wound therapy.” It replaces the previous definition that was worded as “fails to demonstrate 20% decrease in wound area with standard wound care for at least 2 weeks.”
08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. Brought back for clarification.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. AmnioGraft, Vendaje Optic and Artacent Ocular was added as eligible for coverage for HAM grafts with or without suture or glue. Added new investigational statement for repair following Mohs micrographic surgery.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. No change to coverage.
06/07/2023	Coding update
09/20/2023	Coding update
09/27/2023	Added NuDYN [®] DL MESH and NuDYN [®] SLW to the PG2 table listing investigational amniotic products that have an HCPCS code
01/01/2024	Table PG 2 updated due to new codes. Coding update: Add new HCPCS codes.
03/27/2024	Coding update
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. AmnioExcel added to the list of eligible for coverage products for the treatment of nonhealing diabetic lower-extremity ulcers. Products in table PG 1 revised.
06/14/2024	Coding update, PG1 and PG2 content and format revised.
10/01/2024	Coding update. PG 2 content updated.
01/01/2025	Coding update. PG 2 content updated.
04/01/2025	Coding update. PG 2 content updated.
06/05/2025	Medical Policy Committee review
06/11/2025	Medical Policy Implementation Committee approval. NuShield added to existing medically necessary policy statement for the treatment of nonhealing diabetic lower-extremity ulcers based on randomized controlled trials evidence. Removed NuShield and HCPCS Code Q4160 from PG 2 Table and moved it to PG 1 Table. Removed Derm-Maxx and HCPCS Code Q4238 from the PG 2 Table.
07/01/2025	Coding update. PG 2 content updated.
10/01/2025	Coding update. PG 2 content updated.
01/01/2026	Coding update. PG 2 content updated.
04/01/2026	Coding update
06/04/2026	Medical Policy Committee review
06/10/2026	Medical Policy Implementation Committee review

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08/20/2026 Medical Quality Management Committee approval. The following statements were changed from investigational to not medically necessary “Based on review of available data, the Company considers use of human amniotic membrane (HAM) products when criteria above are not met including using more than 8 applications beyond 12 weeks for diabetic foot ulcers to be not medically necessary.” And “Based on review of available data, the Company considers human amniotic membrane grafts available for ophthalmic use when criteria above are not met to be not medically necessary.”

10/01/2026 Coding update. PG 2 content updated.

Next Scheduled Review Date: 06/2027

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	15271, 15275, 17999, 65778, 65779, 65780, 66999
HCPCS	A2001, A2035, A4100, Q4132, Q4133, Q4137, Q4138, Q4139, Q4140, Q4145, Q4148, Q4150, Q4151, Q4153, Q4154, Q4155, Q4156, Q4157, Q4159, Q4160, Q4162, Q4163, Q4168, Q4169, Q4170, Q4171, Q4173, Q4174, Q4176, Q4177, Q4178, Q4180, Q4181, Q4183, Q4184, Q4185, Q4186, Q4187, Q4188, Q4189, Q4190, Q4191, Q4192, Q4194, Q4198, Q4199, Q4201, Q4204, Q4205, Q4206, Q4208, Q4209, Q4211, Q4212, Q4213, Q4214, Q4215, Q4216, Q4217, Q4218, Q4219, Q4221, Q4224, Q4225, Q4227, Q4229, Q4230, Q4232, Q4233, Q4234, Q4235, Q4236,

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	Q4237, Q4239, Q4240, Q4241, Q4242, Q4245, Q4246, Q4247, Q4248, Q4249, Q4250, Q4251, Q4252, Q4253, Q4254, Q4255, Q4256, Q4257, Q4258, Q4259, Q4260, Q4261, Q4262, Q4263, Q4264, Q4265, Q4266, Q4267, Q4268, Q4269, Q4270, Q4271, Q4272, Q4273, Q4274, Q4275, Q4276, Q4278, Q4279, Q4280, Q4281, Q4282, Q4283, Q4284, Q4285, Q4286, Q4287, Q4288, Q4289, Q4290, Q4291, Q4292, Q4293, Q4294, Q4295, Q4296, Q4297, Q4298, Q4299, Q4300, Q4301, Q4302, Q4303, Q4304, Q4305, Q4306, Q4307, Q4308, Q4309, Q4310, Q4311, Q4312, Q4313, Q4314, Q4315, Q4316, Q4317, Q4318, Q4319, Q4320, Q4321, Q4322, Q4323, Q4324, Q4325, Q4326, Q4327, Q4328, Q4329, Q4330, Q4331, Q4332, Q4333, Q4334, Q4335, Q4336, Q4337, Q4338, Q4339, Q4340, Q4341, Q4342, Q4343, Q4345, Q4346, Q4347, Q4348, Q4349, Q4350, Q4551, Q4352, Q4553, Q4354, Q4355, Q4356, Q4357, Q4358, Q4359, Q4360, Q4361, Q4362, Q4363, Q4364, Q4365, Q4366, Q4367, Q4368, Q4369, Q4370, Q4371, Q4372, Q4373, Q4375, Q4376, Q4377, Q4378, Q4379, Q4380, Q4382, Q4383, Q4384, Q4385, Q4386, Q4387, Q4388, Q4389, Q4390, Q4391, Q4392, Q4393, Q4394, Q4395, Q4396, Q4397, Q4398, Q4399, Q4400, Q4401, Q4402, Q4403, Q4404, Q4405, Q4406, Q4407, Q4408, Q4409, Q4410, Q4411, Q4412, Q4413, Q4414, Q4415, Q4416, Q4417, Q4418, Q4419, Q4420, Q4421, Q4422, Q4423, Q4424, Q4425, Q4426, Q4427, Q4428, Q4429, Q4431, Q4432, Q4433, Q4435, Q4436, Q4437, Q4438, Q4439, Q4440, V2790 Delete code effective 01/01/2026: Q4100 Add codes effective 10/01/2026: A2049, Q4207, Q4223, Q4243
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

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****Medically Necessary** (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan’s authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan’s pharmacy benefit.