Regence

Medical Policy Manual Medicine, Policy No. 170

Bioengineered Skin and Soft Tissue Substitutes and Amniotic Products

Effective: July 1, 2026

Next Review: February 2027
Last Review: June 2026

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Bioengineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman tissue, synthetic materials, or a composite of these materials. Amniotic products may be derived from amnion, chorion, amniotic fluid, and umbilical cord. There are many potential applications for these products, including breast reconstruction, chronic full-thickness diabetic lower-extremity ulcers, venous ulcers, severe burns, knee osteoarthritis, plantar fasciitis, and ophthalmic conditions.

MEDICAL POLICY CRITERIA

Notes:

- Product-specific HCPCS codes are listed below in brackets, where applicable.
- This policy does not apply to dural substitutes used during surgical procedures involving the central nervous system (brain and spinal cord) or to unprocessed cadaver skin allografts used as wound dressing.
- Clinical documentation to support criteria is required (See Required Documentation)

Medically Necessary

I. Breast reconstructive surgery using any of the following allogeneic acellular dermal matrix products may be considered **medically necessary**:

   A. AlloDerm® [Q4116]

   B. AlloMend®

   C. Cortiva® (AlloMax™)

   D. DermACELL® [Q4122]

   E. DermaMatrix™

   F. FlexHD® [Q4128]

   G. FlexHD® Pliable™

   H. GraftJacket® [Q4107]

II. Treatment of non-healing diabetic lower-extremity ulcers may be considered **medically necessary** when all of the following (A.-E.) are met:

   A. The ulcers have not adequately responded following a 1-month period of conventional ulcer therapy; and

   B. There is no wound infection; and

   C. HbA1c is less than 12% or has improved in the past 30 days; and

   D. There is adequate circulation to the affected extremity (e.g., by palpable pulses, ankle-brachial index [ABI], doppler); and

   E. One of the following products is used:

      1. Affinity® [Q4159]
      2. AlloPatch® [Q4128]
      3. AmnioBand® Membrane [Q4151]
      4. AmnioExcel® [Q4137]
      5. Apligraf® [Q4101]
      6. Biovance® [Q4154]
      7. EpiCord® [Q4187]
      8. EpiFix® [Q4186]
      9. Grafix® [Q4132, Q4133]
      10. Integra® Omnigraft™ Dermal Regeneration Matrix (also known as Omnigraft™) [Q4105]
      11. Integra® Flowable Wound Matrix [Q4114]
      12. Kerecis™ Omega3 [Q4158]
      13. mVASC®
      14. NuShield® [Q4160]

15. TheraSkin® [Q4121]

III. Treatment of chronic, lower-extremity skin ulcers due to venous insufficiency may be considered **medically necessary** when all of the following (A.-D.) are met:

A. The ulcers have not adequately responded following a 1-month period of conventional ulcer therapy; and

B. There is no wound infection; and

C. There is adequate circulation to the affected extremity (e.g., by palpable pulses, ankle-brachial index [ABI], doppler); and

D. One of the following products is used:

1. Apligraf® [Q4101]

2. Oasis®™ Wound Matrix [Q4102]

IV. Treatment of dystrophic epidermolysis bullosa using the following tissue-engineered skin substitutes may be considered **medically necessary**:

A. OrCel® (for the treatment of mitten-hand deformity when standard wound therapy has failed and when provided in accordance with the humanitarian device exemption [HDE] specifications of the U.S. Food and Drug Administration [FDA]).

V. Treatment of second- and third-degree burns using any of the following tissue-engineered skin substitutes may be considered **medically necessary**:

A. Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area ≥30% when provided in accordance with the HDE specifications of the FDA)

B. Integra® Dermal Regeneration Template [Q4105]

VI. Human amniotic membrane grafts not listed as investigational (see Policy Guidelines) may be considered **medically necessary** as a component of ophthalmologic surgery or repair, including but not limited to Prokera®, AmbioDisk™, AmnioGraft®, or AmnioPlast™.

Not Medically Necessary

VII. Treatment of lower-extremity ulcers due to diabetes or venous insufficiency is considered **not medically necessary** when Criterion II. or III. is not met.

VIII. The use of bioengineered skin and soft tissue substitutes for hernia repair or parastomal reinforcement is considered **not medically necessary**.

Investigational

IX. The use of amniotic membrane grafts or bioengineered skin and soft tissue substitutes for tendon repair is considered **investigational**.

X. For the specific amniotic membrane grafts and bioengineered skin and soft tissue substitutes listed above (Criteria I.-VI.), all other uses are considered **investigational**.

XI. All other amniotic products and bioengineered skin or soft tissue substitutes not listed above are considered **investigational (see Policy Guidelines)**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Amniotic fluid is considered an amniotic product.

INVESTIGATIONAL PRODUCTS

The following amniotic products, placental products, and skin and soft tissue substitutes are considered investigational. There are many products available, and this list is not all-inclusive.

- Abiomend Membrane/ Hydromembrane [Q4356]
- Abiomend Xplus Membrane/ Hydromembrane [Q4355]
- Absolv3 [Q4401]
- AC5® Advanced Wound System [A2020]
- ACApatch™ [Q4325]
- Acelagraft® [Q4395]
- ACell® UBM Hydrated/Lyophilized Wound Dressing
- Acesso [Q4311]
- Acesso AC [Q4312]
- Acesso DL [Q4293]
- Acesso TL [Q4300]
- Acesso TrifACA [Q4386]
- Activate™ Matrix [Q4301]
- A/C Wrap™ [Q4422]
- AdvoGraft Dual [Q4382]
- AéroGuard™ [Q4370]
- AlexiGuard DL-T [Q4417]
- AlexiGuard SL-T [Q4415]
- AlexiGuard TL-T [Q4416]
- Allacor P™ [A2035]
- AlloGen® [Q4212]
- AlloPly™ [Q4323]
- AlloSkin™ [Q4115]
- AlloSkin™ AC [Q4141]
- AlloSkin™ RT [Q4123]
- AlloWrap® [Q4150]
- Altiply™ [Q4235]
- AmchoPlast [Q4316]
- AmchoPlast Excel™ [Q4372]
- AmchoPlast FD™ [Q4360]
- AmchoThick™ [Q4368]
- American Amnion™ [Q4307]
- American Amnion AC™ [Q4306]
- American Amnion AC Tri-Layer™ [Q4305]
- AmnioAmp-MP™ [Q4250]
- Amnioarmor™ [Q4188]
- AmnioBand®, particulate [Q4168]
- AmnioBind™ [Q4225]
- Amnio Burgeon Membrane/Hydromembrane [Q4363]
- Amnio Burgeon Dual-Layer Membrane [Q4365]
- Amnio Burgeon Xplus Membrane/Hydromembrane [Q4364]
- AmnioCore™ [Q4227]
- AmniCore™ Pro [Q4298]
- AmniCore™ Pro+ [Q4299]
- AmniCore™ SL [Q4367]
- AmnioCyte™ Plus [Q4242]
- AmnioDefend™ FT Matrix [Q4379]
- AmnioMatrix® [Q4139]
- AmnioMatrix® DL [Q4410]
- AmnioMatrixF3X [Q4409]
- AmnioMatrixF4X [Q4411]
- Amnio-Maxx™ [Q4239]
- Amnio Quad-Core [Q4292]
- Amnio Tri-Core [Q4295]
- Amnion Bio/AxoBioMembrane™ [Q4211]
- Amniorepair® [Q4235]
- Amniotext™ [Q4245]
- Amniotext™ patch [Q4247]
- AmnioTX™ [Q4324]
- Amnio Wound [Q4181]
- AmnioWrap2™ [Q4221]
- Amniply™ [Q4249]
- Aongen™ Collagen Matrix
- APIS® [A2010]
- Apollo FT [Q4385]
- Architect® ECM, PX, FX [Q4147]
- ArdeoGraft [Q4333]
- Artacent® C [Q4336]
- Artacent® Cord [Q4216]

- Artacent® Trident [Q4337]
- Artacent® Velos [Q4338]
- Artacent® Vericlen [Q4339]
- Artacent® Wound [Q4169]
- Artacent® ac [Q4189, Q4190]
- ArthroFlex™ (Flex Graft) [Q4125]
- Ascendion™ [Q4390]
- Ascent™ [Q4213]
- AxoGuard® Nerve Protector (AxoGen)
- Axolotl Ambient™, Cryo™ [Q4215]
- Axolotl DualGraft™ [Q4332]
- Axolotl DualGraft™ Ultra [Q4384]
- Axolotl Graft™ [Q4331]
- Axolotl Graft™ Ultra [Q4383]
- Barrera™ sl or dl [Q4281]
- BellaCell HD [Q4220]
- Biobrane™ or Biobrane-L [A2043]
- Biobrane™ Glove [A2044]
- Bio-ConneKt® Wound Matrix [Q4161]
- BioDFence® [Q4140]
- BioDFence® Dryflex [Q4138]
- BioLab Membrane Wrap Flow™ [Q4418]
- BioLab Membrane Wrap-Lite Flow™ [Q4419]
- BioLab Membrane Wrap Solo™ [Q4421]
- BioLab Tri-Membrane Wrap Flow™ [Q4423]
- Biovance® tri-layer or 3L [Q4283]
- Biowound™, Plus, Xplus [Q4217]
- Caregraft™ [Q4322]
- Carepatch™ [Q4236]
- Cellesta™/Cellesta™ Duo [Q4184]
- Cellesta™ Cord [Q4214]
- Cellesta™ flowable amnion [Q4185]
- Choriofix™ [Q4412]
- ChoriPly [Q4359]
- CLARIX 100 [Q4156]
- CLARIX Flo [Q4155]
- Cocoon membrane [Q4264]
- Cogenex® amniotic membrane [Q4229]
- Cogenex® flowable amnion [Q4230]
- Cohealyx [A2036]
- CollaCare®
- CollaCare® Dental
- Collagen Wound Dressing (Oasis Research)
- CollaGUARD®
- CollaMend™
- CollaWound™
- Coll-e-Derm™ [Q4193]
- Collexa®
- Colliea®
- Complete™ AA [Q4303]
- Complete™ ACA [Q4302]
- Complete™ FT [Q4271]
- Complete™ SL [Q4270]
- Conexa™
- CoreCyte™ [Q4240]
- Coreleader Colla-Pad
- CorMatrix®
- Corplex™ [Q4232]
- Corplex P™ [A2035]
- CoreText™ or ProText™ [Q4246]
- Cryo-Cord™ [Q4237]
- CuraMatrix [Q4440]
- Cygnus™ [Q4170]
- Cygnus™ Disk [Q4362]]
- Cygnus™ Dual [Q4282]
- Cygnus™ Matrix [Q4199]
- Cygnus™ Solo [Q4413]
- Cymetra™ [Q4112]
- Cytal® (previously MatriStem®) [Q4118, Q4166]
- Dermadapt™ Wound Dressing
- Dermabind CH™ [Q4288]
- Dermabind CH N or CH X [Q4429]
- Dermabind DL™ [Q4287]
- DermaBind DL+ or DL N or DL X [Q4427]
- Dermabind FM™ [Q4313]
- Dermabind SL™ [Q4284]
- Dermabind SL+ or SL N or SL X [Q4428]
- Dermabind TL+, TL X [Q4426]
- Dermacyte® [Q4248]
- Dermacyte® AC [Q4343]
- Derma-Gide® [Q4203]
- DermaPure™ [Q4152]
- DermaSpan™ [Q4126]
- Dermavest® [Q4153]

- Derm-Maxx [Q4238]
- DressSkin
- Dual Layer Amnio Burgeon X-Membrane [Q4366]
- Dual Layer Impax™ Membrane [Q4262]
- DuoAmnion™ [Q4327]
- DuoGraft AA™ [Q4376]
- DuoGraft AC™ [Q4375]
- E-Graft [Q4318]
- Emerge Matrix [Q4297]
- Enclose™ TL [Q4351]
- Endoform Dermal Template™
- *ENDURA*Gen™
- Enverse™ [Q4258]
- Epieffect® [Q4278]
- EpiFix® Injectable [Q4145]
- EPIXPRESS [Q4361]
- Esano™ A [Q4272]
- Esano™ AAA [Q4273]
- Esano™ AC [Q4274]
- Esano™ ACA [Q4275]
- Excellagen [Q4149]
- ExpressGraft™
- E-Z Derm™ [Q4136]
- FlowerAmnioFlo™ [Q4177]
- Flower AmnioPatch™ [Q4178]
- FlowerDerm™ [Q4179]
- Fluid Flow™, Fluid GF™ [Q4206]
- Foundation DRS+ Duo [A2041]
- Foundation DRS Solo [A2034]
- Foundation DRS+ Solo [A2042]
- G4derm™ Plus [A2037]
- GalaFLEX™
- GammaGraft [Q4111]
- Genesis Amniotic Membrane [Q4198]
- Grafix Duo [Q4392]
- Grafix Plus [Q4304]
- Graftjacket® Xpress, injectable [Q4113]
- Helicoll™ [Q4164]
- Human Health Factor 10 Patch™ (HHF10P™) [Q4224]
- Hyalomatrix® [Q4117]
- Hyalomatrix® PA
- hMatrix® [Q4134]
- InnovaBurn® [A2022]
- InnovaMatrix® [A2001]
- InnovaMatrix® FD [A2039]
- InnovaMatrix® FS [A2013]
- InnovaMatrix® PD [A2023]
- InnovaMatrix® XL [A2022]
- InstaGraft [Q4439]
- Integra™ Matrix Wound Dressing [Q4108]
- Interfyl® [Q4171]
- Keramatrix® [Q4165]
- Kerecis® Omega3 MariGen® Shield [A2019]
- Keroxx® [Q4202]
- Lamellas [Q4292]
- Lamellas XT [Q4291]
- Mantle™ DL [Q4349]
- MariGen™ Pacto [A2038]
- MatriDerm® [A2027]
- Matrion™ [Q4201]
- Matrix HD™ [Q4345]
- Mediskin® [Q4135]
- Membrane Graft™/Membrane Wrap™ [Q4205]
- Membrane Wrap-Hydro™ [Q4290]
- Membrane Wrap-Lite™ [Q4373]
- MemoDerm™ [Q4126]
- Microlyte® Matrix [A2005]
- Microlyte® PainGuard™ [A2040]
- MicroMatrix Flex® [A2028]
- Miro3D Fibers [A2030]
- Miro3D Wound Matrix [A2025]
- Miroderm® biologic wound matrix [Q4175]
- MiroDry™ wound matrix [A2031]
- MiroTract® Wound Matrix [2029]
- Mirragen® [A2002]
- MLG Complete™ [Q4256]
- Most™ [Q4328]
- MyOwn Skin™ [Q4226]
- Myriad Matrix™ [A2032]
- Myriad Morcells™ [A2033]
- Natalin® [Q4396]
- NeoForm™
- NéoGuard™ [Q4371]
- NeoMatriX® [A2021]
- NeoPatch® [Q4176]
- NeoStim DL [Q4267]

- NeoStim Membrane [Q4266]
- NeoStim TL [Q4265]
- NeoThelium 4L [Q4388]
- NeoThelium 4L+ [Q4389]
- NeoThelium FT [Q4387]
- NEOX® 100 [Q4156]
- NEOX® Cord [Q4148]
- NEOX® Flo [Q4155]
- Novachor™ [Q4194]
- Novafix® [Q4208]
- Novafix® DL [Q4254]
- NovaShield or NovoGen Wound Matrix [A2045]
- NovoSorb™ [A2006]
- NuCel
- NuDYN® DL or DL Mesh [Q4285]
- NuDYN® SL or SLW [Q4286]
- NuForm™ [Q4420]
- Oasis® Burn Matrix [Q4103]
- Oasis® Ultra [Q4124]
- Ologen™ Collagen Matrix
- Omega3 Wound
- Omeza® Collagen Matrix or Complete Matrix [A2014]
- Orion [Q4276]
- Overlay™ SL [Q4352]
- PalinGen® or PalinGen® Xplus [Q4173]
- PalinGen® Dual-Layer Membrane [Q4354]
- PalinGen®/ProMatrX™, injectable [Q4174]
- Palisade™ DM [Q4350]
- PelloGraft [Q4320]
- Pelvicol®/PelviSoft®
- Permacol™
- PermeaDerm b [A2016]
- PermeaDerm c [A2018]
- PermeaDerm Glove [A2017]
- Phoenix Wound Matrix® [A2015]
- PolyCyte™ [Q4241]
- Polygon3 [Q4400]
- Pretect [Q4438]
- PriMatrix® [Q4110]
- PriMatrix® Dermal Repair Scaffold
- Procenta® [Q4310]
- ProgenaMatrix™ [Q4222]
- PuraPly™ Wound Matrix (previously FortaDerm™) [Q4172]
- PuraPly™ AM [Q4172, Q4196]
- PuraPly™ XT [Q4197]
- Puros® Dermis
- Rampart™ DL [Q4347]
- Rebound Matrix [Q4296]
- ReCell® [15011-15018, C1832, C8002]
- Reeva FT™ [Q4314]
- RegenePro™
- RegeneLink™ [Q4315]
- Reguard [Q4255]
- Relese™ [Q4257]
- Renati AC Membrane [Q4436]
- Renati Membrane [Q4435]
- Renew FT™ [Q4378]
- RenoGraft [Q4321]
- Repliform®
- Repriza [Q4143]
- Resolve Matrix™ [A2024]
- Restorigin™ [Q4191, Q4192]
- Restrata® [A2007]
- Restrata® MiniMatrix [A2026]
- Revita® [Q4180]
- Revitalon™ [Q4157]
- Revival™ AC [Q4437]
- Revive FT [Q4424]
- Revive TL [Q4425]
- Revoshield+® [Q4289]
- SanoGraft [Q4319]
- Sanopellis [Q4308]
- Sentry™ SL [Q4348]
- Shelter™ DM [Q4346]
- SimpliChor [Q4414]
- SimpliGraft™ [Q4340]
- SimpliMax™ [Q4341]
- Singlay™ [Q4329]
- SkinTE [Q4200. 1044T, 1045T, 1046T, 1047T, 1048T, 1049T]
- StrataGraft®
- Strattice™ (xenograft) [Q4130]
- Summit AAA [Q4397]
- Summit AC [Q4398]
- Summit FX [Q4399]
- Supra SDRM® [A2011]
- Suprathel® [A2012]

- Suprello™ [A2037]
- SureDerm® [Q4220]
- SurFactor®/Nudyn™ [Q4233]
- Surgicord [Q4218]
- SurgiGraft™ [Q4183]
- SurgiGraft™ dual [Q4219]
- SurgiMend®
- SurGraft® [Q4209]
- SurGraft® AC [Q4393]
- SurGraft® ACA [Q4394]
- SurGraft® FT [Q4268]
- SurGraft® TL [Q4263]
- SurGraft® XT [Q4269]
- Symphony [A2009]
- Talymed® [Q4127]
- TenoGlide™
- TenSIX™ Acellular Dermal Matrix [Q4146]
- TissueMend
- Theracor P [A2035]
- TheraForm™ Standard/Sheet
- TheraMend™ [Q4342]
- TheraGenesis® [A2008]
- Total™ [Q4330]
- TransCyte® [Q4182]
- TriGraft FT™ [Q4377]
- Tri-Membrane Wrap™ [Q4344]
- TruSkin™ [Q4167]
- Vendaje™ [Q4252]
- Vendaje™ AC [Q4279]
- Veritas® Collagen Matrix [C9354]
- VIA Matrix [Q4309]
- Vim® [Q4251]
- Vitograft [Q4317]
- WoundEx® Bioskin [Q4163]
- WoundEx® Flow [Q4162]
- Woundfix™, Plus, Xplus [Q4217]
- WoundPlus™ [Q4326]
- Xceed TL [Q4353]
- Xcellerate [Q4234]
- Xcell Amnio Matrix® [Q4280]
- XCelliStem® [A2004]
- XCM Biologic® Tissue Matrix [Q4142]
- XenMatrix™ AB
- XWRAP® [Q4204]
- XWRAP® 2.0 [Q4402]
- XWRAP Dual® [Q4358]
- XWRAP Dual Plus® [Q4403]
- XWRAP Hydro® [Q4408]
- XWRAP Hydro Plus® [Q4404]
- XWRAP Fenestra® [Q4406]
- XWRAP Fenestra Plus® [Q4405]
- XWRAP Plus® [Q4357]
- XWRAP Tribus® [Q4407]
- Zenith™ [Q4253]

REQUIRED DOCUMENTATION

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Medical history and physical examination notes
- A detailed description of the wound and treatment history, including
  - Size of wound and presence or absence of infection
  - Any underlying conditions or associated diagnoses
  - Specific types of conservative treatment and treatment response
  - Documentation of adequate circulation and/or HbA1c levels, when applicable
- A comprehensive wound care plan, including:
  - Name and quantity of product to be used
  - Concurrent conservative treatments (e.g., debridement, off-loading, compression, moist dressings, etc.)

CROSS REFERENCES

None

BACKGROUND

BIOENGINEERED SKIN AND SOFT TISSUE SUBSTITUTES

Bioengineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (e.g., dermis with cellular material removed, synthetic products) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. Acellular dermal matrix (ADM) products can differ in a number of ways, including as species source (human, bovine, porcine), tissue source (e.g., dermis, pericardium, intestinal mucosa), additives (e.g., antibiotics, surfactants), hydration (wet, freeze-dried), and required preparation (multiple rinses, rehydration).

Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species (e.g., bovine, porcine). Skin substitutes may also be composed of dermal cells, epidermal cells, or a combination of dermal and epidermal cells, and may provide growth factors to stimulate healing. Bioengineered skin substitutes can be used as either temporary or permanent wound coverings.

There are many potential applications for artificial skin and soft tissue products. One large category is nonhealing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, nonhealing lower-extremity wounds represent an ongoing risk for infection, sepsis, limb amputation, and death. Bioengineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

Other situations in which bioengineered skin products might substitute for living skin grafts include certain postsurgical states (e.g., breast reconstruction) in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Second- and third-degree burns are another indication in which artificial skin products may substitute for auto- or allografts. Certain primary dermatologic conditions that involve large areas of skin breakdown (e.g., bullous diseases) may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. ADM products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and other conditions.

AMNIOTIC PRODUCTS

Human Amniotic Membrane

Human amniotic membrane (HAM) consists of two conjoined layers, the amnion, and chorion, and forms the innermost lining of the amniotic sac 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 dehydrated HAM products, resulting in a readily available tissue with regenerative potential. In support, one dehydrated HAM product has been shown to elute growth factors into saline and stimulate the migration of mesenchymal stem cells, both in vitro and in vivo.[2]

Use of a HAM graft, which is 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.[1] The fluid contains proteins, carbohydrates, peptides, fats, amino acids, enzymes, hormones, pigments, and fetal cells. 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.

REGULATORY STATUS

There are many artificial skin and soft-tissue products that are commercially available or in development. Information on specific products is available in a 2020 Technical Brief on skin substitutes for treating chronic wounds that was commissioned by the Agency for Healthcare Research and Quality.[3]

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. ADM and amniotic products are classified as banked human tissue and therefore, not requiring FDA approval for homologous use. In 2017, the FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps).[4]

HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be

regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

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

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

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

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

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

AmnioClip (FORTECH GmbH) is a ring designed to hold the amniotic membrane in the eye

without sutures or glue fixation. A mounting device is used to secure the amniotic membrane within the AmnioClip. The AmnioClip currently has CE approval in Europe.

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of technology improves health outcomes for patients. Broadly defined, health outcomes are the length of life, quality of life, and ability to function – including benefits and harms. 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.

The following is a summary of key literature to date.

BREAST RECONSTRUCTION

Ng (2024) published a systematic review and meta-analysis comparing postoperative complications and patient-reported outcomes between patients who received ADM and those who did not.[6] Prospective cohort studies and RCTs were included (nine studies, n=3,161). There were no significant differences in postoperative outcomes between the ADM and non-ADM groups for key complications such as seroma (p=0.51), hematomas (p=0.20), infections (p=0.21), wound dehiscence (p=0.09), reoperations (p=0.70), implant loss (p=0.27), or skin necrosis (p=0.21).

A meta-analysis by Lee and Mun (2016) included 23 studies (total n=6,199 cases) on implant-based breast reconstruction that were published between February 2011 and December 2014.[7] The analysis included an RCT and three prospective comparative cohort studies; the remainder was retrospective comparative cohort studies. Use of ADM did not affect the total complication rate (see Table 1). ADM significantly increased the risk of major infection, seroma, and flap necrosis, but reduced risks of capsular contracture and implant malposition. Use of ADM allowed for significantly greater intraoperative expansion (mean difference 79.63, 95% confidence interval [CI], 41.99 to 117.26, p<0.001) and percentage of intraoperative filling (mean difference 13.30, 95% CI 9.95 to 16.65, p<0.001), and reduced the frequency of injections to complete expansion (mean difference -1.56, 95% CI -2.77 to -0.35, p=0.01).

Table 1. Meta-Analysis of Breast Reconstruction Outcomes with and without ADM

Outcome Measure	Relative Risk	95% Confidence Interval	p
Infection	1.42	1.02 to 1.99	0.04
Seroma	1.41	1.12 to 1.78	0.004
Mastectomy flap necrosis	1.44	1.11 to 1.87	0.006
Unplanned return to the operating room	1.09	0.63 to 1.90	NS
Implant loss	1.00	0.68 to 1.48	NS
Total complications	1.08	0.87 to 1.34	NS
Capsular contracture	0.26	0.15 to 0.47	<0.001
Implant malposition	0.21	0.07 to 0.59	0.003

Adapted from Lee and Mun (2016).[7]
ADM: acellular dermal matrix; *NS*: not significant.

A study by Davila (2013) used data from the American College of Surgeon's National Surgical

Quality Improvement Program to compare ADM-assisted tissue expander breast reconstruction (n=1,717) to submuscular tissue expander breast reconstruction (n=7,442) after mastectomy.[8] Complication rates did not differ significantly between the ADM-assisted (5.5%) and the submuscular tissue expander groups (5.3%, p=0.68). Rates of reconstruction-related complications, major complications, and 30-day reoperation did not differ significantly between cohorts.

ALLODERM®

Randomized Controlled Trials

McCarthy (2012) reported on a multicenter, blinded RCT of AlloDerm® in two-stage expander/implant reconstruction.[9] Seventy patients were randomized to AlloDerm® ADM-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. The trial was adequately powered to detect clinically significant differences in immediate postoperative pain but underpowered to detect the secondary endpoint of pain during tissue expansion. There were no significant differences between the groups in the primary outcomes of immediate postoperative pain (54.6 AlloDerm® vs. 42.8 controls on a 100-point visual analog scale) or pain during the expansion phase (17.0 AlloDerm® vs. 4.6 controls) or in the secondary outcome of rate of tissue expansion (91 days AlloDerm® vs. 108 days controls) and patient-reported physical well-being. There was no significant difference in adverse events, although the total number of adverse events was small.

Comparisons Between Products

AlloDerm® Versus AlloMax™

Hinchcliff (2017) conducted an RCT that compared AlloDerm® with AlloMax™ (n=15 each) for implant-based breast reconstruction.[10] Complications were assessed 7, 14, and 30 days postoperatively and biopsies of the ADMs were taken during implant exchange. Vessel density in the AlloMax™ biopsies was higher than in the AlloDerm® biopsies. Complications were reported in 26.1% of AlloMax™ cases and 8.0% of AlloDerm® cases; these complication rates did not differ statistically with the 30 patients in this trial.

AlloDerm® Versus DermaMatrix™

Mendenhall (2017) published an RCT that compared AlloDerm® with DermaMatrix™ in 111 patients (173 breasts).[11] There were no significant differences in overall rates of complications (AlloDerm® 15.4%, DermaMatrix™ 18.3%, p=0.8) or implant loss (AlloDerm® 2.2%, DermaMatrix™ 3.7%, p=0.5) between the two ADMs at three months. There were no statistically significant differences in the overall complication rates (6% vs. 13%, p=0.3), severity of complications, or patient satisfaction between the AlloDerm and DermaMatrix groups at two years after definitive reconstruction.[12]

AlloDerm Versus DermACELL

Davison (2024) conducted a prospective randomized trial comparing AlloDerm® with DermACELL® in 55 patients undergoing bilateral nipple and/or skin-sparing mastectomies.[13] Patients served as their own controls and were blinded to the random assignment of the two products to the left or right breast. The findings revealed no significant differences in drain removal time or average drain output between the two groups. However, a notable difference was observed in seroma rates, with 30.91% of AlloDerm® breasts

experiencing seromas compared to 14.55% in DermACELL® breasts (p<0.05). Additionally, incorporation rates were significantly higher for DermACELL® at 99.8% compared to AlloDerm® 's 93.4% (p<0.05). Both AlloDerm® and DermACELL® demonstrated a high success rate of 94.55% for reconstruction outcomes. Nonetheless, AlloDerm® was associated with a higher incidence of seromas and a trend towards lower incorporation rates.

AlloDerm Versus Cortiva

Keane (2024) conducted an RCT comparing Cortiva® with AlloDerm® in patients who underwent either direct-to-implant or tissue expander reconstruction (n=302).[14] The primary outcome measured was reconstructive failure, defined as premature explantation of tissue expanders or direct-to-implant reconstructions before three months postoperatively. 151 patients received AlloDerm® (280 breasts) and 151 received Cortiva® (277 breasts). The results showed no significant difference in reconstructive failure rates between the two ADMs, with AlloDerm® at 9.3% and Cortiva® at 8.3% (p=0.68). Additionally, there were no notable differences in other complications or patient-reported outcomes between the groups. Seroma formation was more prevalent in the AlloDerm® group (12%) compared to Cortiva® (7.6%, odds ratio [OR] 1.93, 95% CI 1.01 to 3.67, p=0.047).

Strattice™

Dikmans (2017) reported on early safety outcomes from an open-label multicenter RCT that compared porcine ADM-assisted one-stage expansion with two-stage implant-based breast reconstruction (see Table 2).[15] One-stage breast reconstruction with porcine ADM was associated with a higher risk of surgical complications, reoperation, and with removal of implant, ADM, or both (see Table 3). The trial was stopped early due to safety concerns, but it cannot be determined from this study design whether the increase in complications was due to the use of the xenogenic ADM or to the comparison between one-stage and two-stage reconstruction.

Table 2. Summary of Key RCT Characteristics

Author	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Dikmans (2017)[15]	EU	8	2013-2015	Women intending to undergo skin-sparing mastectomy and immediate IBBR	59 patients (91 breasts) undergoing 1-stage IBBR with ADM	62 women (92 breasts) undergoing 2-stage IBBR

ADM: acellular dermal matrix; IBBR: implant-based breast reconstruction; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Outcomes

Study	Surgical Complications	Severe Adverse Events	Reoperation	Removal of Implant ADM, or Both
Dikmans (2017)[15]				
1-stage with ADM, n (%)	27 (46)	26 (29)	22 (37)	24 (26)
2-stage with ADM, n (%)	11 (18)	5 (5)	9 (15)	4 (5)
OR (95% CI)	3.81 (2.67 to 5.43), p<0.001		3.38 (2.10 to 5.45), p<0.001	8.80 (8.24 to 9.40), p<0.001

ADM: acellular dermal matrix; CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial.

TENDON REPAIR

GraftJacket®

Barber (2012) reported an industry-sponsored multicenter RCT of augmentation with GraftJacket® human ADM for arthroscopic repair of large (>3 cm) rotator cuff tears involving two tendons.[16] Twenty-two patients were randomized to GraftJacket® augmentation and 20 patients to no augmentation. At a mean follow-up of 24 months (range 12-38 months), the American Shoulder and Elbow Surgeons score improved from 48.5 to 98.9 in the GraftJacket® group and from 46.0 to 94.8 in the control group (p=0.035). The Constant score improved from 41 to 91.9 in the GraftJacket® group and from 45.8 to 85.3 in the control group (p=0.008). The University of California, Los Angeles score did not differ significantly between groups. Gadolinium-enhanced MRI scans showed intact cuffs in 85% of repairs in the GraftJacket® group and 40% of repairs in the control group. However, no correlation was found between MRI findings and clinical outcomes. Rotator cuff retears occurred in three (14%) patients in the GraftJacket® group and nine (45%) patients in the control group.

Rashid (2020) reported disruption of the native extracellular matrix with either GraftJacket® or Permacol™ (porcine acellular dermis) as a patch overlay for rotator cuff repair in a small controlled study with 13 patients.[17] The disruption was greater in the Permacol™ group and there was an immune response in one of three patients following use of the xenograft.

SURGICAL REPAIR OF HERNIAS OR PARASTOMAL REINFORCEMENT

A systematic review by Bellows (2013) evaluated the clinical effectiveness of acellular collagen-based scaffolds for the repair of incisional hernias.[18] The bioprosthetic materials could be harvested from bovine pericardium, human cadaveric dermis, porcine small intestine mucosa, porcine dermal collagen, or bovine dermal collagen. Products included in the search were Surgisis®, Tutomesh®, Veritas®, AlloDerm®, FlexHD®, AlloMax™, CollaMend™, Permacol™, Strattice™, FortaGen®, ACell, DermaMatrix™, XenMatrix™, and SurgiMend®. Sixty publications with 1,212 repairs were identified and included in the review, although meta-analysis could not be performed. There were four level III studies (two AlloDerm®, two Permacol™); the remainder was level IV or V. The largest number of publications were on AlloDerm® (n=27) and Permacol™ (n=18). No publications on incisional hernia repair were identified for AlloMax™, FortaGen®, DermaMatrix™, or ACell. The overall incidence of a surgical site occurrence (e.g., postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, mechanical failure) was 82.6% for porcine small intestine mucosa, 50.7% for xenogenic dermis, 48.3% for human dermis, and 6.3% for xenogenic pericardium. No comparative data were identified that could establish superiority to permanent synthetic meshes.

AlloDerm® as an Overlay

Espinosa-de-los-Monteros (2007) retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm® performed in 37 patients and compared them with 39 randomly selected cases.[19] They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

Comparisons Between Products

AlloDerm® Versus Surgisis® Gold

Gupta (2006) compared the efficacy and complications associated with use of AlloDerm® and Surgisis® bioactive mesh in 74 patients who underwent ventral hernia repair.[20] The first 41 procedures were performed using Surgisis® Gold 8-ply mesh formed from porcine small intestine submucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm®. Patients were seen 7 to 10 days after discharge from the hospital and at six weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm® mesh resulted in eight (24%) hernia recurrences. Fifteen (45%) of the AlloDerm® patients developed a diastasis or bulging at the repair site. Seroma formation was only a problem in two patients.

AlloDerm® Versus FlexHD®

A study by Bochicchio (2013) compared AlloDerm® with FlexHD® for complicated hernia surgery.[21] From 2005 to 2007, AlloDerm® was used to repair large (>200 cm^2), symptomatic, complicated ventral hernias that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD® was used to repair large, complicated ventral hernias in patients meeting the same criteria (n=40). The two groups were comparable at baseline. At one-year follow-up, all AlloDerm® patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, true recurrence) requiring a second repair. Eleven (31%) patients in the FlexHD® group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

FlexHD® Versus Strattice™

Roth (2017) reported on a prospective study assessing clinical and quality-of-life outcomes following complex hernia repair with a human (FlexHD®) or porcine (Strattice™) ADM.[22] The study was funded by the Musculoskeletal Transplant Foundation, which prepares and supplies FlexHD®. Patients were enrolled if they had a hernia at least 6 cm in the transverse dimension, active or prior infection of the abdominal wall, and/or enterocutaneous fistula requiring mesh removal. Eighteen (51%) of the 35 patients had undergone a previous hernia repair. After abdominal wall repair with the ADM, 20 (57%) patients had a surgical site occurrence, and nearly one-third had hospital readmission. The type of biologic material did not impact hernia outcomes. There was no comparison with synthetic mesh in this study, limiting interpretation.

Strattice™ Versus Synthetic Mesh

Remulla (2026) reported on the 5-to-10-year follow-up of a multicenter RCT comparing biologic mesh (Strattice™ Reconstructive Tissue Matrix, a non-cross-linked porcine ADM) with synthetic mesh (Bard Soft Mesh, medium-weight polypropylene) for single-stage retromuscular repair of clean-contaminated and contaminated ventral hernias.[23] Of 253 patients originally randomized, 203 (80.2%) achieved minimum five-year follow-up (median 5.4 years). Synthetic mesh was associated with a significant reduction in midline hernia recurrence risk (hazard ratio [HR] 0.46, 95% CI 0.25 to 0.86, p=0.015). The overall 5-to-10-year midline recurrence rate was 17.8% across both groups: 23.6% in the biologic group versus 11.8% in the synthetic group, corresponding to an absolute risk reduction of 11.8% (95% CI 2.1 to 21.4) with synthetic mesh.

This advantage was primarily observed within the first two years; the difference in recurrence rates beyond two years was not statistically significant. No new mesh infections or mesh excisions occurred in either group beyond two years postoperatively. Three patients (1.2%) required intervention for ongoing wound-related issues.

Dhanani (2025) reported three-year outcomes of a single-center pilot RCT comparing biologic mesh (non-cross-linked porcine acellular dermal matrix) with synthetic mesh (medium-density, macroporous polypropylene) for complex open ventral hernia repair.[24] Of the 87 patients randomized (44 biologic, 43 synthetic), 61 (70%) completed the study through the three-year follow-up. No significant differences were observed between biologic and synthetic mesh for major complications (50% vs 30%, RR 2.34, 95% CI 0.80 to 6.90, p=0.123), hernia recurrence (39% vs 24%, p=0.214), mesh infection (14% vs 3%, p=0.144), or reoperation (18% vs 12%, p=0.531). Both groups demonstrated clinically meaningful improvements in functional status and pain scores at three years. The study was limited by its small sample size and 30% loss to follow-up, and it was underpowered to detect significant differences in complication rates.

Seefeldt (2025) reported the BIOLAP multicenter, randomized, self-controlled clinical trial comparing biological versus synthetic mesh in laparoendoscopic inguinal hernia repair.[25] A total of 491 patients with primary bilateral inguinal hernias were enrolled across 21 certified German hernia centers; each patient received a non–cross-linked, acellular, collagenous biological mesh on one side and a lightweight synthetic mesh on the other, with randomization determining side assignment. The biological meshes came from three different manufacturers, and both patients and follow-up clinicians were blinded to mesh allocation. At six months, there was no significant difference in pain between biological and synthetic mesh (mean VAS score at rest 0.3 for both, p=0.76). At two years, the recurrence rate was significantly higher for biological meshes (11.2%) than for synthetic meshes (2.5%, p<0.001), and seroma rates were also significantly higher with biological mesh (33.4% vs 21.6%, p<0.001). On multivariate analysis, biological mesh was the strongest predictor of recurrence (OR 4.53, 95% CI 2.42 to 8.49, p<0.001).

Bellows (2014) reported early results of an industry-sponsored multicenter RCT that compared Strattice™ (non-cross-linked porcine ADM, n=84) with a standard synthetic mesh (n=88) for the repair of inguinal hernias.[26] The trial was designed by the surgeons and was patient- and assessor-blinded to reduce risk of bias. Blinding continued through two years of follow-up. The primary outcome was resumption of activities of daily living at one year. Secondary outcomes included complications, recurrences, or chronic pain (i.e., pain that did not disappear by three months postsurgery). At three-month follow-up, there were no significant differences in either the occurrence or type of wound events (relative risk [RR] 0.98, 95% CI 0.52 to 1.86). Pain was reduced from one to three days postoperative in the group treated with Strattice™, but at three-month follow-up pain scores did not differ significantly between groups.

A double-blind RCT by Brunbjerg (2020) compared Strattice™ to synthetic mesh (Prolene®) to prevent hernia or bulging in 29 patients admitted to a single center in Denmark for pedicled transverse rectus abdominis musculocutaneous flap surgery.[27] At two-years post-surgery, bulging frequency was higher in the Strattice™ group (35.7%) than in the synthetic mesh group (6.7%), but the difference was not statistically significant (p = 0.11). Two Strattice™ patients developed a hernia, while none of the mesh patients did. No differences were found for abdominal muscle strength between baseline and two-year measurements.

Strattice™ Versus No Reinforcement

Also in 2014, the Parastomal Reinforcement With Strattice™ (PRISM) Study Group reported a multicenter, double-blinded, randomized trial of Strattice™ for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies.[28] Patients were randomized to standard stoma construction with no reinforcement (n=58) or stoma construction with Strattice™ as parastomal reinforcement (n=55). At 24-month follow-up (n=75), the incidence of parastomal hernias was similar for the two groups (13.2% of controls, 12.2% of study group).

Adverse Events

Permacol™ (porcine acellular dermal matrix) was reported in a case series of 13 patients to result in recurrent intestinal fistulation and intestinal failure when used for abdominal reconstructive surgery.[29]

DIABETIC LOWER-EXTREMITY ULCERS

Systematic Reviews

A 2016 Cochrane review evaluated skin substitutes for the treatment of diabetic foot ulcers.[30] Seventeen trials (total n=1,655 participants) were included in the meta-analysis. Most trials identified were industry-sponsored, and an asymmetric funnel plot indicated publication bias. Pooled results of published trials found that skin substitutes increased the likelihood of achieving complete ulcer closure compared with standard of care (SOC) alone (RR 1.55, 95% CI 1.30 to 1.85). Use of skin substitutes also led to a statistically significant reduction in amputations (RR 0.43, 95% CI 0.23 to 0.81), although the absolute risk difference was small. Analysis by individual products found a statistically significant benefit on ulcer closure for Apligraf®, EpiFix®, and Hyalograft-3D™. The products that did not show a statistically significant benefit for ulcer closure were Dermagraft®, GraftJacket®, Kaloderm®, and OrCel®.

A systematic review by Lakmal (2021) included eight RCTs, two prospective studies and two retrospective studies that evaluated the use of amniotic membrane allografts for the treatment of diabetic foot ulcers.[31] Generally, the studies reported that better wound closure rates were seen with the amniotic membrane products than with standard care, but a meta-analysis was not possible due to study heterogeneity.

Amniotic Membranes

At least seven RCTs have evaluated rates of healing with amniotic membrane grafts or placental membrane grafts compared to SOC or an advanced wound therapy in patients with chronic diabetic foot ulcers (see Table 4). 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 5). In a 2018 trial, the cryopreserved placental membrane Grafix® was found to be non-inferior to an advanced fibroblast-derived wound therapy (Dermagraft®).[32]

Table 4. Summary of Key RCT Characteristics

Study	Participants	Intervention	Comparator
Cazell (2024)[33]	218 patients with diabetic foot ulcers	n=109, NuShield®	N=109, SOC
Serena (2020)[34]	76 patients with chronic (>4 weeks) non-healing diabetic foot ulcers	n=38, Affinity	n=38, SOC

Study	Participants	Intervention	Comparator
	unresponsive to SOC and extending into dermis, subcutaneous tissue, muscle, or tendon		
Ananian (2018)[32]	75 patients with chronic (>4 weeks) non-healing diabetic foot ulcers between 1 cm^2 and 15 cm^2	n=38, Grafix® weekly for up to 8 weeks	n=37, Dermagraft® (fibroblast-derived) weekly for up to 8 weeks
Tettelbach (2019)[35]	155 patients with chronic (> 4 weeks) non-healing diabetic foot ulcers	n=101 EpiCord® plus SOC	n=54 SOC with alginate dressing
DiDomenico (2018)[36]	80 patients with non-healing (4 weeks) diabetic foot ulcers	AmnioBand® Membrane plus SOC	SOC
Snyder (2016)[37]	29 patients with non-healing diabetic foot ulcers	AmnioExcel® plus SOC	SOC
Zelen (2015, 2016)[38, 39]	60 patients with less than 20% wound healing in a 2-week run-in period	EpiFix®	Apligraf® or SOC with collagen-alginate dressing
Tettelbach (2019)[40]	110 patients with non-healing (4 weeks) lower extremity ulcers	EpiFix®	SOC with alginate dressing
Lavery (2014)[41]	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 5. Summary of Key RCT Results

Study	Wounds Healed	Time to Complete Healing	Adverse Events
Cazelle (2024)[33]	12 weeks (ITT)	Median	None reported
N	218	218	
NuShield®	50%	84 days	
SOC	35%	Not attained by 12 weeks	
p-value	0.04		
Serena (2020)[34]	16 weeks (ITT)	Median	
N	76	76	
Affinity	58%	11 weeks	
SOC	29%	not attained by 16 weeks	
HR (95% CI), p-value	1.75 (1.16 to 2.70), p=0.01		
Ananian (2018)[32]	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), Lower bound for non-inferiority	9.68% (−10.7 to 28.9), -15%		
Tettelbach (2018)[35]	12 Weeks (ITT) n (%)		Patients with Adverse Events (% of total)

Study	Wounds Healed	Time to Complete Healing	Adverse Events
N	155		155
EpiCord®	71 (70%)		42 (42%)
SOC	26 (48%)		33 (61%)
p-value	0.009		
DiDomenico (2018)[36]	12 weeks (ITT) n (%)	Mean Days (95% CI)	
N	80	80	
Amnioband®	34 (85)	37.0 (29.5 to 44.4)	
SOC	13 (33)	67.3 (59.0 to 79.6)	
HR (95% CI)		4.25 (0.44 to 0.79), p<0.001	
Snyder (2016)[37]	6 Weeks (PP) Mean (95% CI)		
N	21		
AmnioExcel®	45.5% (32.9% to 58.0%)		
SOC	0%		
p-value	0.014		
Zelen (2015, 2016)[38, 39]	Wounds Healed at 12 Weeks		
N	100		
EpiFix®	NR		
Apligraf®	NR		
SOC	NR		
HR (95% CI)	5.66; (3.03 to 10.57), p<0.001 vs. SOC		
Tettelbach (2019)[40]	Wounds Healed at 12 Weeks (ITT)		
N	110		
EpiFix®	70%		
SOC	50%		
p-value	0.034		
Lavery (2014)[41]	Wounds Healed at 12 Weeks		Patients with Adverse Events
N	97	97	97
Grafix®	62.0%	42.0	44.0%
SOC	21.3%	69.5	66.0%
p-value	<0.001	0.019	0.031

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.

Many of these studies had methodologic limitations, including a lack of blinding and loss of patients to follow up.

Smiell (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.[42] Of those treated, 28 ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of eight weeks and a mean of 2.4 amniotic membrane applications.

Frykberg (2017) reported treatment of complex chronic wounds (exposed tendon or bone) with Grafix®.[43] With the cryopreserved placental membrane applied weekly for up to 16 weeks, 59% of wounds closed with a mean time to closure of nine weeks.

Apligraf®

Veves (2001) reported on a randomized prospective trial on the effectiveness of Apligraf® (previously called Graftskin), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers.[44] The trial involved 24 centers in the United States; 208 patients were randomized to ulcer treatment with Apligraf® (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical debridement and adequate foot off-loading, was provided in both groups. Apligraf® was applied at the beginning of the study and weekly thereafter for a maximum of four weeks (maximum of five applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Apligraf®-treated patients achieved complete wound healing compared with 36 (38%) in the control group (p=0.004). The Kaplan-Meier method median time to complete closure was 65 days for Apligraf®, which was significantly lower than the 90 days observed in the control group (p=0.003). The rates of adverse reactions were similar between groups, except osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf® group. Trialists concluded that application of Apligraf® for a maximum of four weeks resulted in higher healing rates than state-of-the-art treatment and was not associated with any significant adverse events. This trial was reviewed in a 2001 TEC Assessment, which concluded that Apligraf®, in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.[45]

Dermagraft®

A 2003 pivotal multicenter FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft® (human-derived fibroblasts cultured on mesh) or control.[46] Over the 12-week study, patients received up to eight applications of Dermagraft®. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft® group was 91% compared with 78% for the control group. Ulcers treated with Dermagraft® closed significantly faster than ulcers treated with conventional therapy. No serious adverse events were attributed to Dermagraft®. Ulcer infections developed in 10.4% of the Dermagraft® patients compared with 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft®-treated group (19% vs. 32.5%). A 2015 retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft® (5.5% vs. 12.6%, p=0.031).[47] Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

AlloPatch®

AlloPatch® Pliable human reticular acellular dermis was compared with SOC in an industry-sponsored multicenter trial by Zelen (2017, 2018).[48, 49] The initial trial with 20 patients per group was extended to determine the percent healing at six weeks with 40 patients per group. Healing was evaluated by the site investigator and confirmed by an independent panel. At six weeks, 68% (27/40) of wounds treated using AlloPatch® had healed compared with 15% (6/40) in the SOC-alone group (p<0.001). At 12 weeks, 80% (32/40) of patients in the AlloPatch® group had healed compared to 30% (12/40) in the control group. Mean time to heal

within 12 weeks was 38 days (95% CI 29 to 47 days) for the HR-ADM group and 72 days (95% CI 66 to 78 days) for the SOC group (p<0.001).

Integra® Omnigraft Dermal Regeneration Template or Integra® Flowable Wound Matrix

Integra® Dermal Regeneration Template is a biosynthetic skin substitute that is FDA-approved for life-threatening thermal injury. The FOUNDER (Foot Ulcer New Dermal Replacement) multicenter study (32 sites) assessed Integra® Dermal Regeneration Template (marketed as Omnigraft™) for chronic nonhealing diabetic foot ulcers under an FDA-regulated investigational device exemption.[50] A total of 307 patients with at least one chronic diabetic foot ulcer were randomized to treatment with the Integra® Template or a control condition (sodium chloride gel 0.9%). Treatment was given for 16 weeks or until wound closure. There was a modest increase in wound closure with the Integra® Template (51% vs. 32%, p=0.001) and a shorter median time to closure (43 days vs. 78 days, p=0.001). There was a strong correlation between investigator-assessed and computerized planimetry assessment of wound healing (*r*=0.97). Kaplan-Meier analysis showed the greatest difference between groups in wound closure up to 10 weeks, with diminishing differences after 10 weeks. Trial strengths included adequate power to detect an increase in wound healing of 18%, which was considered to be clinically significant, secondary outcomes of wound closure and time to wound closure by computerized planimetry, and intention-to-treat (ITT) analysis.

Integra® Flowable Wound Matrix is composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. It is supplied as a granular product that is mixed with saline. Campitiello (2017) published an RCT that compared the flowable matrix with wet dressing in 46 patients who had Wagner grade 3 diabetic foot ulcers.[51] The ulcers had developed over 39 weeks. Complete healing at six weeks was achieved in significantly more patients in the Integra® Flowable Wound Matrix group than in the control group, while the risk of rehospitalization and major amputation was reduced with Integra® Flowable Wound Matrix (see Table 6).

Table 6. Probability of Wound Healing with IFWM Versus SOC

Study	Complete Wound Healing	Rehospitalization	Major Amputation
Campitiello (2017)[51]			
IFWM, n (%)	20 (86.95)	2 (6.69)	1 (4.34)
SOC, n (%)	12 (52.17)	10 (43.47)	7 (30.43)
RR (95% CI)	1.67 (1.09 to 2.54)	0.10 (0.01 to 0.72)	0.16 (0.02 to 1.17)
p	0.010	0.001	0.028

CI: confidence interval; IFWM: Integra® Flowable Wound Matrix; RR: relative risk; SOC: standard of care.

GraftJacket® Regenerative Tissue Matrix

Brigido (2004) reported a small (n=40) randomized pilot study comparing GraftJacket® with conventional treatment for chronic nonhealing diabetic foot ulcers.[52] Control patients received conventional therapy with débridement, wound gel with gauze dressing, and off-loading. GraftJacket® patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the GraftJacket® group. Preliminary one-month results showed that, after a single treatment, ulcers treated with GraftJacket® healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs. 15%), width (50% vs. 23%), area (73% vs. 34%), and depth (89% vs. 25%), respectively. With

follow-up to four weeks, no data were reported on the proportion with complete closure or the mean time to heal. All grafts were incorporated into the host tissue.

Reyzelman (2009) reported an industry-sponsored multicenter randomized study that compared a single application of GraftJacket® with SOC in 86 patients with diabetic foot ulcers.[53] Eight patients, six in the study group and two in the control group, did not complete the trial. At 12 weeks, complete healing was observed in 69.6% of the GraftJacket® group and 46.2% of controls. After adjusting for ulcer size at presentation, a statistically significant difference in nonhealing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks for the GraftJacket® group versus 6.8 weeks for the control group. The authors did not report whether this difference was statistically significant. Median time to healing was 4.5 weeks for GraftJacket® (range 1-12 weeks) and 7.0 weeks for control (range 2-12 weeks). Kaplan-Meier method survivorship analysis for time to complete healing at 12 weeks showed a significantly lower nonhealing rate for the study group (30.4%) than for the control group (53.9%). The authors commented that a single application of GraftJacket®, as used in this study, was often sufficient for complete healing. Conclusions drawn from this study are limited by the small study population and differences in ulcer size at baseline. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant.

Reyzelman and Bazarov (2015)[54] reported the results of an industry-sponsored meta-analysis of GraftJacket® for diabetic foot ulcers, which included the two studies described above and a third RCT by Brigido (2006)[55] (total n=154 patients). The time to heal was estimated for the Brigido (2004) study,[52] based on the average wound reduction per week. The estimated difference in time to heal was larger for Brigido's (2004) study (-4.30 weeks) than for the other two studies that measured the difference in time to heal (-1.58 weeks and -1.10 weeks). Analysis of the proportion of wounds that healed included Brigido (2006) and Reyzelman (2009). The OR in the smaller study by Brigido (2006) was considerably larger, with a lack of precision in the estimate (OR 15.0, 95% CI 2.26 to 99.64), and the combined odds (3.75, 95% CI 1.72 to 8.19) was not significant when analyzed using a random-effects model. Potential sources of bias included publication and reporting biases, study selection biases, incomplete data selection, post hoc manipulation of data, and subjective choice of analytic methods.

DermACELL® Versus GraftJacket® Regenerative Tissue Matrix or Standard of Care

DermACELL® and GraftJacket® are both composed of human ADM. Walters (2016) reported on a multicenter randomized comparison of DermACELL®, GraftJacket®, or SOC (2:1:2 ratio) in 168 patients with diabetic foot ulcers.[56] The study was sponsored by LifeNet Health, a nonprofit organ procurement association and processor for DermACELL®. At 16 weeks, the proportion of completely healed ulcers was 67.9% for DermACELL®, 47.8% for GraftJacket®, and 48.1% for SOC. The 20% difference in completely healed ulcers was statistically significant for DermACELL® versus SOC (p=0.039). The mean time to complete wound closure did not differ significantly for DermACELL® (8.6 weeks), GraftJacket® (8.6 weeks), and SOC (8.7 weeks).

A second report from this study was published by Cazzell (2017).[57] This analysis compared DermACELL® with SOC and did not include the GraftJacket® arm. The authors reported that either one or two applications DermACELL® led to a greater proportion of wounds healed compared with SOC in per-protocol analysis, but there was no significant difference between DermACELL® (one or two applications) and SOC when analyzed by ITT. For the group of

patients who received only a single application, the percentage of patients who achieved complete wound healing was significantly higher than SOC at 16 and 24 weeks, but not at 12 weeks. Although reported as ITT analysis, results were analyzed only for the group who received a single application of DermACELL®. This would not typically be considered ITT.

mVASC®

Gould (2022) reported results of the HIFLO (Healing in Diabetic Foot Ulcers with Microvascular Tissue) Trial.[58] This was a multicenter RCT comparing weekly application of the processed microvascular tissue (PMVT) allograft, mVASC®, in addition to a standardized diabetic foot ulcer protocol versus standard wound care with a collagen alginate dressing control in 100 adults with Wagner Grade 1 and 2 diabetic foot ulcers of at least four weeks and less than 52 weeks duration. Wound and local peripheral neuropathy assessment were performed weekly. The primary outcome of the study was complete wound closure at 12 weeks. The investigator and a blinded physician made the initial determination of wound closure, followed by adjudication and confirmation by an independent, blinded panel of plastic surgeons. All participants who attended at least one treatment visit were included in the analysis. There was missing data for 15 participants at week 12 (three in mVASC® vs. 12 in control) and 14 of these were missing due to adverse events related to the wound. These were included in the primary analysis and counted as wound healing failures. The mean age of participants was 60 years, 90% of participants were White and 10% were Black, and 66% of participants were men. At randomization, the mean size of the wound area was 3.3 cm^2 and the mean duration of the wound was 15 weeks. The proportion of participants with complete wound closure at week 12 was 74% (37/50) for mVASC versus 38% (19/50) for control ($p<0.001$). Of the wounds that healed, the mean time to healing was also statistically significantly faster for the mVASC® group (54 days, 95% CI 46 to 61 vs. 64 days, 95% CI 57 to 72, $p=0.009$). The 10-point Semmes-Weinstein monofilament test of peripheral neuropathy also favored mVASC® (118% vs. 11%, $p=0.028$). No adverse events or serious adverse events related to the study treatment or the procedure were reported. There were 11 adverse events reported, three for mVASC® and eight for controls, that were related to the wound.

Theraskin®

Armstrong (2022) reported results of an RCT including 100 adults with non-healing Wagner 1 diabetic foot ulcers comparing Theraskin (n=50) to SOC (n=50).[59] The index ulcer had to have been present for greater than four weeks and less than one year with a minimum size of 1.0 cm^2 and a maximum size of 25 cm^2. Standard of care included glucose monitoring, weekly debridement as appropriate, and an offloading device. The dressing in the SOC group was calcium alginate. The primary outcome was the proportion of full-thickness wounds healed at 12 weeks. Wound healing was assessed initially by the investigator and confirmed by blinded adjudication panel. Wounds were closed when there was 100% re-epithelization and no drainage. The mean age of participants was 60 years; 53% of participants were male, 70% were White, and 15% were Black. The mean wound area at baseline was 4.1 cm^2. Participants who did not have healing of at least 50% by 6 weeks were allowed to seek alternative rescue wound care (TheraSkin® n=1, SOC n=11). In addition, three participants in the TheraSkin® group and eight in the SOC group had worsening of the wound or an adverse event before week 12. All enrolled participants were included in analysis and missing data were imputed using last observation carried forward. The percent of participants with complete wound healing at week 12 was 76% (38/50) in the intervention group compared with 36% (18/50) in the SOC group ($p<0.01$). The mean percent area reduction at 12 weeks was 77.8% in the

TheraSkin® group compared with 49.6% in the SOC group (p<0.01). There were no statistically significant differences between groups in QOL or pain score measures.

Theraskin® Versus Dermagraft®

Sanders (2014) reported on a small (n=23) industry-funded randomized comparison of Theraskin® (cryopreserved human skin allograft with living fibroblasts and keratinocytes) and Dermagraft® for diabetic foot ulcers.[60] Wound size at baseline ranged from 0.5 to 18.02 cm^2; the average wound size was about 5 cm^2 and was similar for the two groups (p=0.51). Grafts were applied according to manufacturers' instructions over the first 12 weeks of the study until healing, with an average of 4.4 Theraskin® grafts (every two weeks) compared with 8.9 Dermagraft® applications (every week). At week 12, complete wound healing was observed in 63.6% of ulcers treated with Theraskin® and 33.3% of ulcers treated with Dermagraft® (p<0.049). At 20 weeks, complete wound healing was observed in 90.9% of the Theraskin®-treated ulcers compared with 66.7% of the Dermagraft® group (p=0.428).

Theraskin® Versus Apligraf®

DiDomenico (2011) compared Theraskin® with Apligraf® for the treatment of diabetic foot ulcers in a small (n=29) RCT.[61] The risk of bias in this study is uncertain because reporting did not include a description of power analysis, statistical analysis, method of randomization, or blinding. The percentage of wounds closed at 12 weeks was 41.3% in the Apligraf® group and 66.7% in the Theraskin® group. Results at 20 weeks were not substantially changed from those at 12 weeks, with 47.1% of wounds closed in the Apligraf® group and 66.7% closed in the Theraskin® group. The percentage healed in the Apligraf® group was lower than expected based on prior studies. The average number of grafts applied was similar for both groups (1.53 for Apligraf®, 1.38 for Theraskin®). The low number of dressing changes may have influenced results, with little change in the percentage of wounds closed between 12 and 20 weeks. An adequately powered trial with blinded evaluation of wound healing and a standard treatment regimen would permit greater certainty on the efficacy of this product.

Cytal® (MatriStem) Versus Dermagraft®

Frykberg (2016) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cytal® (a porcine urinary bladder-derived extracellular matrix) versus Dermagraft® in 56 patients with diabetic foot ulcers.[62] The mean duration of ulcers before treatment was 263 days (range, 30-1095 days). The primary outcome was the percent wound closure with up to eight weeks of treatment using blinded evaluation of photographs. ITT analysis found complete wound closure in five (18.5%) wounds treated with Cytal® compared with two (6.9%) wounds treated with Dermagraft® (not statistically significant). Quality of life, measured by the Diabetic Foot Ulcer Scale, improved from 181.56 to 151.11 in the Cytal® group and from 184.46 to 195.73 in the Dermagraft® group (p=0.074). It should be noted that this scale is a subjective measure and patients were not blinded to treatment.

PriMatrix®

Lantis (2021) reported on a multicenter RCT comparing PriMatrix® plus standard of care to PriMatrix® alone in 226 patients with diabetic foot ulcers.[63] Study subjects underwent a two-week run-in period of SOC treatment and were excluded if they had a wound reduction of 30% or more. Patients randomized to the SOC group received weekly treatment at the study site identical to the SOC treatment applied during the screening period. In addition, control group

patients performed daily dressing changes, which consisted of wound cleaning, application of saline gel and secondary dressings. The primary endpoint was the percentage of subjects with complete wound closure, defined as 100% re-epithelialization without drainage during the 12-week treatment phase. Significantly more patients in the PriMatrix® group experienced complete wound closure at 12 weeks (45.6% vs. 27.9%, p=0.008). It is unclear if this difference (17.7%) is clinically significant; the study was powered to detect a 20% difference between groups. The time to complete healing did not differ between groups for the wounds that healed. Major study limitations include lack of blinding, limited generalizability, and insufficient duration of follow-up to assess wound recurrence.

Oasis® Wound Matrix Versus Regranex Gel

Niezgoda (2005) compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS® Wound Matrix (a porcine acellular wound care product) to Regranex Gel.[64] This industry-sponsored, multicenter RCT was conducted at nine outpatient wound care clinics and involved 73 patients with at least one diabetic foot ulcer. Patients were randomized to receive either Oasis® Wound Matrix (n=37) or Regranex Gel (n=36) and secondary dressing. Wounds were cleaned and débrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks, 18 (49%) Oasis®-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients. Oasis® treatment met the noninferiority margin but did not demonstrate that healing in the Oasis® group was statistically superior (p=0.055). Post hoc subgroup analysis showed no significant difference in incidence of healing in patients with type 1 diabetes (33% vs. 25%) but showed a significant improvement in patients with type 2 diabetes (63% vs. 29%). There was also increased healing of plantar ulcers in the Oasis® group (52% vs. 14%). These post hoc findings are considered hypothesis-generating. Additional study with a larger number of subjects is needed to compare the effect of Oasis® treatment to current SOC.

Autologous Grafting on HYAFF Scaffolds

Uccioli (2011) reported a multicenter RCT of cultured expanded fibroblasts and keratinocytes grown on an HYAFF scaffold (benzyl ester of hyaluronic acid) compared with paraffin gauze for difficult diabetic foot ulcers.[65] A total of 180 patients were randomized. At 12 weeks, complete ulcer healing was similar for the two groups (24% treated vs. 21% controls). At 20 weeks, complete ulcer healing was achieved in a similar proportion of the treatment group (50%) and the control group (43%, log-rank test = 0.344). Subgroup analysis, adjusted for baseline factors and possibly post-hoc, found a statistically significant benefit of treatment on dorsal ulcers but not plantar ulcers.

Mirragen® Advanced Wound Matrix

Armstrong (2022) reported a multi-center, single-blinded RCT (n=40, five sites) comparing Mirragen® Advanced Wound Matrix. a borate-based bioactive glass fiber matrix (BBGFM), with SOC in subjects with chronic, full-thickness, non-infected, non-ischemic diabetic foot ulcers (University of Texas 1A/Wagner 1).[66] Both groups received SOC including weekly debridement as needed and offloading; the BBGFM group received weekly application of the matrix in addition to SOC. At 12 weeks, complete wound closure was achieved in 70% (14/20) of BBGFM-treated subjects compared with 25% (5/20) of SOC subjects (adjusted p=0.006); the corresponding number needed to treat was 2.0 (95% CI 1.4 to 5.8). Mean percent area reduction at 12 weeks was 79% in the BBGFM group compared with 37% in the SOC group (adjusted p=0.027). The authors noted that investigator blinding was not possible given the

absence of a sham product, and that withdrawal of non-responding subjects at six weeks resulted in censoring of outcomes.

Armstrong (2025) reported a multi-center, single-blind RCT (n=148, 14 sites) comparing BBGFM plus SOC with SOC alone in subjects with chronic, full-thickness, non-infected, non-ischemic diabetic foot ulcers (University of Texas 1A/Wagner Grade 1).[67] The trial was stopped early following a pre-specified interim analysis. In the modified intention-to-treat (mITT) analysis, 48% (32/67) of BBGFM-treated subjects achieved complete wound closure at 12 weeks compared with 24% (16/66) of SOC subjects (p=0.007); mean time to healing was 9.1 weeks (95% CI 8.1 to 10.0) versus 10.4 weeks (95% CI 9.6 to 11.1) for SOC (adjusted p=0.042). In the per-protocol analysis, 73% (32/44) of BBGFM subjects healed compared with 42% (16/38) of SOC subjects (p=0.007); mean time to healing was not significantly different between groups. The authors identified investigator non-blinding and early withdrawal of non-responding subjects as study limitations, noting that it is unknown how many of the 36 withdrawn subjects (24% of the mITT population) might have healed within 12 weeks had they not been withdrawn.

Kerecis™ Omega3 Wound

Systematic Reviews

Ruiz-Muñoz (2024) conducted a systematic review and meta-analysis of RCTs comparing fish skin grafts (Kerecis™ Omega3 Wound) with standard care for diabetic foot ulcer healing. Five RCTs with a total of 411 patients were included. Pooled analysis showed a significantly higher rate of complete ulcer healing in the fish skin graft groups compared with standard care (OR 3.34, 95% CI 2.14 to 5.20, p<0.01), with no heterogeneity between studies (I^2=0%). Sensitivity analysis confirmed the robustness of findings, and publication bias testing did not indicate asymmetry. The authors noted that blinding of participants and personnel was compromised in three of the five included trials.

Randomized Controlled Trials

Dardari (2024) reported the Odinn trial, an international, open-label, multicenter RCT comparing Kerecis™ Omega3 Wound with standard wound care in patients with deep diabetic foot ulcers penetrating to bone, joint, or tendon (University of Texas [UT] grade 2 or 3).[68] A total of 255 patients were randomized (129 fish skin graft, 126 standard care) across 15 tertiary care centers in France, Italy, Germany, and Sweden. Treatment was applied weekly for six weeks, then biweekly through week 14, with healing assessed at 16 weeks by a blinded adjudication committee. At 16 weeks, 44.0% of wounds healed in the fish skin graft group compared with 26.4% in the standard care group (p<0.001, OR 2.55, 95% CI 1.43 to 4.63), with continued healing observed at 20 weeks (45.7% vs 32.4%) and 24 weeks (55.2% vs 37.8%). Cox regression analysis showed fish skin graft was associated with faster time to healing (HR 1.59, 95% CI 1.07 to 2.36). Primary wound infection rates were similar between groups (30.2% vs 29.3%). The study was limited by its open-label design; however, wound closure was confirmed by a blinded adjudication committee.

Lullove (2021, 2022) reported interim results and Lantis (2023) reported the final results of a RCT of the Kerecis™ Omega3 Wound plus standard wound care compared to standard care alone in 49 patients with diabetic lower extremity skin ulcers.[69-71]. The primary outcome was healing at 12 weeks. Complete ulcer healing was based on the site investigator's assessment, as evidenced by complete (100%) re-epithelialization without drainage and need of dressing.

An independent panel of wound care experts who were blinded to the patient allocation process and the principal investigator's assessment reviewed all study-related decisions made by the site investigators and confirmed healing status. Secondary outcomes were time to heal and wound area reduction by percentage at 12 weeks. Patients underwent a two-week run-in period prior to randomization. If the ulcer reduced in area by 20% or more after 14 days of standard care, the patient was excluded as a screening failure. If the wound area was reduced by less than 20%, the patient was randomized and enrolled in the study. At 12 weeks, the complete healing rate was significantly higher in the intervention arm (57% vs. 31%), but time to healing did not differ between groups for wounds that healed completely. Among the subset of wounds that did not heal completely by 12 weeks (n=65), there was a larger percent wound reduction in the intervention group (86% vs. 64%, p=0.03). Of the 45 participants whose wound healed during the 12 weeks of the trial, 42 were available for follow-up 6 to 12 months after healing. Three (11%) ulcer recurrences were reported in the intervention arm compared to one (7%) in the control arm.

LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

EpiFix®

Two RCTs evaluated the use of EpiFix® for venous leg ulcers. Serena (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.[72] The primary outcome in this trial was the proportion of patients with 40% wound closure at four weeks, which was achieved by about twice as many patients in the combined EpiFix® group compared with the control group. However, a similar percentage of patients in the combined EpiFix® group and the control group achieved complete wound closure during the four-week study. There was no significant difference in healing for wounds given one versus two applications of amniotic membrane (62% vs. 63%, respectively). Strengths of this trial included adequate power and ITT analysis with last observation carried forward. Limitations included the lack of blinding for wound evaluation and use of 40% closure rather than complete closure. A 2015 retrospective study of 44 patients from this RCT (31 treated with amniotic membrane) found that wounds with at least 40% closure at four weeks (n=®20) had a closure rate of 80% by 24 weeks; however, this analysis did not account for additional treatments after the four-week randomized trial period.

A second industry-sponsored multicenter open-label RCT, reported by Bianchi (2018, 2019), evaluated the time to complete ulcer healing following weekly treatment with EpiFix® d-HAM plus compression therapy or compression wound therapy alone.[73, 74] Patients treated with EpiFix® had a higher probability of complete healing by 12 weeks, as adjudicated by blinded outcome assessors (hazard ratio 2.26, 95% CI 1.25 to 4.10, p=0.01), and improved time to complete healing, as assessed by Kaplan-Meier analysis. In per-protocol analysis, healing within 12 weeks was reported for 60% of patients in the EpiFix® group and 35% of patients in the control group (p<0.013). Intent-to-treat analysis found complete healing in 50% of patients in the EpiFix® group compared to 31% of patients in the control group (p=0.0473). There were several limitations of this trial. 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 eight weeks were handled. Patients in the control group who did not have a 40% decrease in wound area at eight weeks were considered study failures and treated with advanced wound therapies. The ITT analysis used last-observation-

carried-forward for these patients and sensitivity analysis was not performed to determine how alternative methods of handling the missing data would affect results. Kaplan-Meier analysis suggested a modest improvement in the time to heal when measured by ITT analysis, but may be subject to the same methodological limitations.

Biovance

As described above, Smiell (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.[42] 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 eight 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.

AmnioBand

Serena (2022) reported an industry-sponsored, multicenter, open-label RCT comparing once- or twice-weekly applications of AmnioBand® Membrane plus compression bandaging with compression bandaging alone in patients with chronic venous leg ulcers.[75] 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 four 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=0.001). Receiving HAM was independently associated with odds of complete healing at 12 weeks after adjusting for baseline wound area (OR 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=0.012). 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.

Apligraf®

Falanga (1998) reported on a multicenter randomized trial of Apligraf® living cell therapy.[76] A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or to compression therapy and treatment with Apligraf®. Apligraf® was applied up to a maximum of five (mean, 3.3) times per patient during the initial three weeks. The primary endpoints were the percentage of patients with complete healing by six months after initiation of treatment and the time required for complete healing. At six-month follow-up, the percentage of patients healed was higher with Apligraf® (63% vs. 49%), and the median time to complete wound closure was shorter (61 days vs. 181 days). Treatment with Apligraf® was superior to compression therapy in healing larger (>1000 mm^2) and deeper ulcers and ulcers of more than six months in duration. There were no symptoms or signs of rejection, and the occurrence of adverse events was similar in both groups. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf® (Graftskin), in conjunction with good local wound care, met TEC criteria for the treatment of venous ulcers that fail to respond to conservative management.[45]

Oasis® Wound Matrix

Mostow (2005) reported on an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment using Oasis® Wound Matrix (xenogenic collagen scaffold from porcine small intestinal mucosa) with SOC in 120 patients who had chronic ulcers due to venous insufficiency that had not adequately responded to conventional therapy.[77] Healing was assessed weekly for up to 12 weeks, with follow-up performed after six months to assess recurrence. After 12 weeks of treatment, there was a significant improvement in the percentage of wounds healed in the Oasis® group (55% vs. 34%). After adjusting for baseline ulcer size, patients in the Oasis® group were 3 times more likely to heal than those in the group receiving SOC. Patients in the SOC group whose wounds did not heal by week 12 were allowed to cross over to Oasis® treatment. None of the healed patients treated with Oasis® wound matrix who was seen for the 6-month follow-up experienced ulcer recurrence.

A research group in Europe has described two comparative studies of the Oasis® matrix for mixed arteriovenous ulcers. In a quasi-randomized study, Romanelli (2007) compared the efficacy of two extracellular matrix-based products, Oasis® and Hyaloskin® (extracellular matrix with hyaluronic acid).[78] Fifty-four patients with mixed arteriovenous leg ulcers were assigned to the two arms based on order of entry into the study; 50 patients completed the study. Patients were followed twice weekly, and dressings changed more than once a week, only when necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis®-treated ulcers compared with 46.2% of Hyaloskin®-treated ulcers. Oasis® treatment significantly increased the time to dressing change (mean, 6.4 days vs. 2.4 days), reduced pain on a 10-point scale (3.7 vs. 6.2), and improved patient comfort (2.5 vs. 6.7).

Romanelli (2010) compared Oasis® with a moist wound dressing (SOC) in 23 patients with mixed arteriovenous ulcers and 27 patients with venous ulcers.[79] The trial was described as randomized, but the method of randomization was not described. After the eight-week study period, patients were followed monthly for six months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis®-treated ulcers at eight weeks compared with 65% of the SOC group. On average, Oasis®-treated ulcers achieved complete healing in 5.4 weeks compared with 8.3 weeks for the SOC group. Treatment with Oasis® also increased the time to dressing change (5.2 days vs. 2.1 days) and the percentage of granulation tissue formed (65% vs. 38%).

Dermagraft®

Dermagraft® living cell therapy has been approved by the FDA for repair of diabetic foot ulcers. Use of Dermagraft® for venous ulcers is an off-label indication. Harding (2013) reported an open-label multicenter RCT that compared Dermagraft® plus compression therapy (n=186) with compression therapy alone (n=180).[80] The trial had numerous inclusion and exclusion criteria that restricted the population to patients who had nonhealing ulcers with compression therapy but had the capacity to heal. ITT analysis revealed no significant difference between the two groups in the primary outcome measure, the proportion of patients with completely healed ulcers by 12 weeks (34% Dermagraft® vs. 31% control). Prespecified subgroup analysis revealed a significant improvement in the percentage of wounds healed for ulcers of 12 months or less in duration (52% vs. 37%) and for ulcers of 10 cm or less in diameter (47% vs. 39%). There were no significant differences in the secondary outcomes of time to healing, complete healing by week 24, and percent reduction in ulcer area.

PriMatrix®

Karr (2011) published a retrospective comparison of PriMatrix® (xenogenic ADM) and Apligraf® in 28 venous stasis ulcers.[81] The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Criteria were venous stasis ulcers of four weeks in duration, at least 1 cm^2 in diameter, and to a depth of subcutaneous tissue, with healthy tissue at the ulcer edge, adequate arterial perfusion to heal, and ability to tolerate compression therapy. The time to complete healing for PriMatrix® was 32 days with 1.3 applications compared with 63 days with 1.7 applications for Apligraf®. Although promising, additional study with a larger number of subjects is needed to assess the effect of PriMatrix® treatment in compared with current SOC.

DermACELL®

Cazzell (2019) published an RCT on DermACELL® ADM for venous leg ulcers in 18 patients.[82] This was part of a larger study of the acellular dermal matrix for chronic wounds of the lower extremity in 202 patients; the component on diabetic lower extremity ulcers was previously reported by Cazzell (2017) and is described above.[57] When including patients who required more than one application of the ADM, the percent of wounds closed at 24 weeks was 29.4% with DermACELL® and 33.3% with SOC, suggesting no benefit DermACELL® for the treatment of venous ulcers in this small substudy.

Theraskin® Versus Standard of Care

In the propensity-matched study by Gurtner (2020) described above, Theraskin® did not improve the healing rate of venous ulcers (66.1%) compared to SOC (70.1%).[83]

DEEP DERMAL BURNS

Epicel®

One case series from 2000 has described the treatment of 30 severely burned patients with Epicel®.[84] The cultured epithelial autografts were applied to a mean of 37% of total body surface area (TBSA). Epicel® achieved permanent coverage of a mean of 26% of TBSA, an area similar to that covered by conventional autografts (mean 25%). Survival was 90% in these severely burned patients.

Integra® Dermal Regeneration Template

A 2013 study compared Integra® with split-thickness skin graft and with viscose cellulose sponge (Cellonex), using three, 10 x 5 cm test sites on each of 10 burn patients.[85] The surrounding burn area was covered with meshed autograft. Biopsies were taken from each site on days 3, 7, 14, and 21, and at months 3 and 12. The tissue samples were stained and examined for markers of inflammation and proliferation. The Vancouver Scar Scale was used to assess scars. At 12-month follow-up, the three methods resulted in similar clinical appearance, along with similar histologic and immunohistochemical findings.

Branski (2007) reported on a randomized trial that compared Integra® with a standard autograft-allograft technique in 20 children with an average burn size of 73% TBSA (71% full-thickness burns).[86] Once vascularized (about 14-21 days), the Silastic epidermis was stripped and replaced with thin (0.05-0.13 mm) epidermal autograft. There were no significant differences between the Integra® group and controls in burn size (70% vs. 74% TBSA), mortality (40% vs. 30%), and hospital length of stay (41 vs. 39 days), all respectively. Long-term follow-up revealed a significant increase in bone mineral content and density (24 months)

and improved scarring in terms of height, thickness, vascularity, and pigmentation (at 12 months and 18-24 months) in the Integra® group. No differences were observed between groups in the time to first reconstructive procedure, cumulative reconstructive procedures required during two years, and cumulative operating room time required for these procedures. The authors concluded that Integra® can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

Heimbach (2003) reported on a multicenter (13 U.S. burn care facilities) post-approval study involving 222 burn injury patients (36.5% TBSA, range 1%-95%) who were treated with Integra® Dermal Regeneration Template.[87] Within two to three weeks, the dermal layer regenerated, and a thin epidermal autograft was placed over the wound. The incidence of infection was 16.3%. Mean take rate (absence of graft failure) of Integra® was 76.2%; the median take rate was 98%. The mean take rate of epidermal autograft placed over Integra® was 87.7%; the median take rate was 95%.

Hicks (2019) conducted a systematic review of Integra® dermal regeneration template for the treatment of acute full thickness burns and burn reconstruction.[88] A total of 72 studies with 1,084 patients (four RCTs, four comparative studies, five cohort studies, two case control studies, 24 case series, and 33 case reports) were included in the review. The majority of patients (74%) were treated with Integra® for acute burns, and the remainder (26%) for burn reconstruction. The take of the skin substitute was 86% (range 0-100%) for acute burn injuries and 95% (range 0-100%) for reconstruction. The take of the split-thickness skin graft over the template was 90% for acute burn injuries and 93% for reconstruction. There was high variability in reporting of outcomes, but studies generally supported satisfactory cosmetic results in patients who have insufficient autograft and improvement in range of motion in patients who were treated with Integra® for burn reconstruction. There was an overall complication rate of 13%, primarily due to infection, graft loss, hematoma formation, and contracture.

An infection rate of 18% was noted in a systematic review of complication rates in 10 studies that used Integra® dermal regeneration template for burns.[89]

ReCell® Autologous Cell Harvesting Device

Two RCTs have evaluated ReCell® for deep dermal burns.[90, 91] In both studies, two similar areas with a burn injury in the same individual were randomized to the control or treatment intervention (i.e., all participants received both treatments). The studies differed in their populations, interventions, and outcome measures. Holmes (2018)[90] was a head-to-head comparison of ReCell® alone versus skin grafting alone, and Holmes (2019)[91] compared ReCell® in combination with skin grafting. In the earlier study, participants all had deep partial thickness burns, while in the 2019 study the population included individuals with mixed-depth, full thickness burns. In the 2018 study, the primary effectiveness endpoints were the incidence of wound closure at four weeks and the incidence of complete donor site healing at one week. In the 2019 trial, the co-primary effectiveness endpoints were non-inferiority of the incidence of ReCell®-treated site closure by week eight when compared to the control, and the superiority of the 37% relative reduction in donor skin for the ReCell® treatment when compared with the control. Although the ReCell® treatment was comparable to standard care on outcomes such as complete wound closure; confidence in the strength of the overall body of evidence is limited by individual study limitations and heterogeneity of populations, interventions, and outcome measures across studies.

DYSTROPHIC EPIDERMOLYSIS BULLOSA

OrCel® was approved under a humanitarian device exemption (HDE) for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. HDE status has been withdrawn for Dermagraft® for this indication.

Fivenson (2003) reported the off-label use of Apligraf® in five patients with recessive dystrophic epidermolysis bullosa who underwent syndactyly release.[92]

HUMAN AMNIOTIC MEMBRANE FOR OPHTHALMOLOGIC 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.

Liu (2019) conducted a systematic review of 17 studies (390 eyes) of amniotic membrane for corneal ulcers.[93] All but one of the studies was conducted outside of the U.S. There was one RCT with 30 patients, the remainder of the studies were prospective or retrospective case series. Corneal healing was obtained in 97% (95% CI 0.94 to 0.99, p=0.089) of patients evaluated. In the 12 studies (222 eyes) that reported on vision, the vision improvement rate was improved in 113 eyes (53%, 95% CI 0.42 to 0.65, p<0.001).

Khokhar (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.[94] At the three-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 (2013) published a series of 35 eyes of 33 patients who were treated with the self-retained Prokera® HAM for a variety of ocular surface disorders.[95] Nine of the eyes had non-healing corneal ulcers. Complete or partial success was seen in two of nine (22%) patients with this indication. This study also reported on 11 eyes of 11 patients with neurotrophic keratopathy that had not responded to conventional treatment. 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.

Dos Santos Paris (2013) published an RCT that compared fresh HAM with stromal puncture for the management of pain in patients with bullous keratopathy.[96] 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 two treatments. Symptoms had been present for approximately two years. HAM resulted in a more regular epithelial surface at up to 180 days follow-up, but there was no difference between the treatments related to the presence of bullae or the severity or duration of pain. Because of the similar effects on pain, the authors recommended initial use of the simpler stromal puncture procedure, with use of HAM only if the pain did not resolve.

John (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.[97] 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 one-month and three-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 one month and 1.0 at three 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 three 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 DRy Eye Amniotic Membrane (DREAM) study, reported by McDonald (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.[98] 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 2-11) resulted in an improved ocular surface and reduction in the DEWS score from 3.25 at baseline to 1.44 at one week, 1.45 at one month and 1.47 at three months (p=0.001). Ten percent of eyes required repeated treatment. There was no significant difference in the number of topical medications following c-HAM treatment.

PERIPHERAL NERVE INJURIES

The Cochrane Collaboration published a meta-analysis of bioengineered nerve conduits and wraps for repairs of peripheral nerves of the upper extremity in 2022.[99] The authors included only RCTs or quasi-RCT experimental studies and found five that included the desired interventions and had follow-up periods of at least 12 months. A total of 213 participants were included in the studies, which compared nerve reconstruction with artificial wraps or conduits to standard repair either with direct end-to-end epineural repair or with autologous nerve grafting. Sensory recovery assessed with the British Medical Research Council (BMRC) grading scale was higher in the wrap or conduit group than in standard repair with very low certainty of evidence on Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) at 12 months (mean difference 0.03, range -0.43 to 0.49) and 24 months follow-up (MD 0.01, 95% CI -0.06 to 0.08). Rosen model instrument comparisons between conduit or wrap versus standard repair revealed no between-group differences through 24 months (MD -0.17, 95% CI -0.38 to 0.05, p=0.13) and was determined to have low certainty of evidence; findings at 5 years follow-up in a single study found a greater improvement in the conduit or wrap group, but the estimate also had low certainty of evidence (mean difference 0.23, 95% CI 0.07 to 0.38). The rate of adverse event occurrence may be greater in patients treated with nerve wraps or conduits than with standard techniques, but the evidence had a GRADE rating reflected a very low certainty of evidence (risk ratio 7.15, 95% CI 1.74 to 29.42). The authors also sought BMRC muscle strength scores, which were not reported in the included studies. The authors concluded that based on the currently available high-quality evidence, the use of currently available nerve repair devices is not supported over the standard of care due to heterogeneity in included participants, the pattern of injury, timing of repair, timing of outcome assessment, and choice of outcome measurement scales. A limitation of this systematic review is that they did not explicitly separate studies by the use of nerve conduits versus wraps for further analysis.

MISCELLANEOUS

Punch Biopsy Wounds

Baldursson (2015) reported a double-blinded RCT with 81 patients (162 punch biopsy wounds) that compared Kerecis™ Omega3 Wound (derived from fish skin) with Oasis® SIS ECM (porcine small intestinal submucosa extracellular matrix).[100] The primary outcome (the percentage of wounds healed at 28 days) was similar for the fish skin ADM (95%) and the porcine SIS ECM (96.3%). The rate of healing was faster with Kerecis™ Omega3 (p=0.041). At 21 days, 72.5% of the fish skin ADM group had healed compared with 56% of the porcine SIS ECM group.

A similar RCT by Kirsner (2020) included 85 patients and compared the Kerecis™ Omega3 to a dehydrated human amnion/chorion membrane product.[101] This study also reported faster healing in the Kerecis™ Omega3 group (hazard ratio 2.37, 95% CI 1.75 to 3.21, p=0.0014). Interpretation of these studies is limited because they did not include an accepted control condition for this indication.

Split-Thickness Donor Sites

There is limited evidence to support the efficacy of OrCel® compared with SOC for the treatment of split-thickness donor sites in burn patients. Still (2003) (examined the safety and efficacy of bilayered OrCel® to facilitate wound closure of split-thickness donor sites in 82 severely burned patients.[102] Each patient had two designated donor sites that were randomized to a single treatment of OrCel® or standard dressing (Biobrane-L). The healing time for OrCel® sites was significantly shorter than for sites treated with a standard dressing, enabling earlier recropping. OrCel® sites also exhibited a nonsignificant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

Pressure Ulcers

Brown-Etris (2019) reported an RCT of 130 patients with stage 3 or stage 4 pressure ulcers who were treated with Oasis® Wound Matrix (extracellular collagen matrix derived from porcine small intestinal submucosa) plus SOC or SOC alone.[103] At 12 weeks, the proportion of wounds healed in the collagen matrix group was 40% compared to 29% in the SOC group. This was not statistically significant (p=0.111). There was a statistical difference in the proportion of patients who achieved 90% wound healing (55% vs. 38% p=0.037), but complete wound healing is the preferred and most reliable measure. It is possible that longer follow-up may have identified a significant improvement in the percent of wounds healed. The study did include six-month follow-up, but there was high loss to follow-up and an insufficient number of patients at this time point for statistical comparison.

In the propensity matched study by Gurtner (2020) described above, Theraskin® improved the healing rate of pressure ulcers by 20% (66.7% vs 46.8%).[83]

Plantar Fasciitis

A 2016 network meta-analysis of 22 RCTs (total n=1,216 patients) compared injection therapies for plantar fasciitis.[104] 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 two to six months (seven RCTs) favored botulinum toxin for pain and patient recovery plan for composite outcomes.

An RCT by Cazzell (2018) enrolled 145 patients and reported three-month follow-up.[105] In this trial, amniotic membrane injection led to greater improvements in the Visual Analog Scale (VAS) for pain and the Foot Functional Index between baseline and three months compared to controls. VAS at three 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. The major limitation of the study is the short-term follow-up.

Osteoarthritis

In 2016, a feasibility study (n=6) was reported of ReNu™ cryopreserved human amniotic membrane (c-HAM) suspension with amniotic fluid-derived cells for the treatment of knee osteoarthritis.[106] A single intra-articular injection of the suspension was used, with follow-up at one and two 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.

Pill (2025) conducted a double-blind, randomized, prospective study comparing the effectiveness of amniotic tissue injections versus corticosteroid injections for pain relief and function in patients with severe knee osteoarthritis (n=81).[107] Patients with severe knee osteoarthritis were randomized to receive either a single injection of BioDRestore™ (amniotic tissue) or triamcinolone acetonide (corticosteroid). Outcome measures included the Knee Injury and Osteoarthritis Outcome Score (KOOS), Single Alpha Numeric Evaluation, pain (VAS), Lysholm Rating, and Veterans-Rand-12 scales collected at baseline, 6 weeks, and 3, 6, and 12 months postinjection. The study found no overall difference in function or pain relief between amniotic tissue and corticosteroid injections for patients with knee osteoarthritis. Integra LifeSciences, the maker of the product used in this study, was issued an FDA warning letter in 2024.

Repair Following Mohs Micrographic Surgery

Lu (2022) published a systematic review of skin substitutes for management of Mohs micrographic surgery wounds.[108] Of the 40 studies that met inclusion criteria, there were 23 case series, 14 case reports, two cohort studies, and one RCT. The most frequently used substitutes were porcine collagen (57.5%), bovine collagen (11.3%), Integra (7.7%), hyaluronic acid-derived products (6.2%), amnion/chorion-derived products (5.8%), and allogeneic epidermal-dermal composite grafts (5.8%). Follow-up in these studies ranged from one week to 21 months. The authors noted a lack of high-quality evidence and a need for blinded RCTs comparing the performance of skin substitutes with traditional methods.

Toman (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.[109] 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 nine months or later and included documentation of

suboptimal scarring, scar revision, treatment, and patient satisfaction. A greater proportion of patients who received EpiFix® repair experienced zero complications (97.9% vs. 71.3%, p<0.0001, RR 13.67, 95% CI 4.33 to 43.12). Placental allograft reconstructions developed less infection (p=0.004) and were less likely to experience poor scar cosmesis (p<0.0001). 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.

Other Indications

In addition to indications previously reviewed, off-label uses of bioengineered skin substitutes have included inflammatory ulcers (e.g., pyoderma gangrenosum, vasculitis), scleroderma digital ulcers, post-keloid removal wounds, genetic conditions, and variety of other conditions.[110] Products that have been FDA-approved or -cleared for one indication (e.g., lower-extremity ulcers) have also been used off-label in place of other FDA-approved or -cleared products (e.g., for burns).[111] No controlled trials were identified for these indications.

PRACTICE GUIDELINE SUMMARY

Wound Healing Society

In 2016, the Wound Healing Society updated their guidelines on diabetic foot ulcer treatment.[112] 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 two randomized controlled trials on dehydrated amniotic membrane were included with references on living and acellular bioengineered skin substitutes.

Society for Vascular Surgery

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:[113] "For DFUs [diabetic foot ulcers] that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (platelet-derived growth factor [PDGF], living cellular therapy, extracellular matrix products, amnionic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice."

SUMMARY

BREAST RECONSTRUCTION

There is enough evidence to show that some allogeneic acellular dermal matrix (ADM) products can improve health outcomes for individuals who are undergoing medically necessary breast reconstruction. A systematic review found no difference in overall complication rates with ADM allograft compared with standard procedures for breast

reconstruction. Reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM, however, capsular contracture and malposition of implants may be reduced. Therefore, the use of AlloDerm®, AlloMend®, Cortiva® (AlloMax™), DermACELL®, DermaMatrix™, FlexHD®, FlexHD® Pliable™, or GraftJacket® may be considered medically necessary for breast reconstruction.

There is not enough evidence to show that other amniotic products or bioengineered skin or soft tissue substitutes can improve health outcomes for patients undergoing breast reconstruction. Therefore, the use of products other than AlloDerm®, AlloMend®, Cortiva® (AlloMax™), DermACELL®, DermaMatrix™, FlexHD®, FlexHD® Pliable™, or GraftJacket® is considered investigational for this indication.

DIABETIC LOWER-EXTREMITY ULCERS

There is enough research to show that certain skin substitutes can improve health outcomes for certain patients who have diabetic lower-extremity ulcers that have not responded to conventional treatment. Randomized controlled trials have demonstrated that these products may improve ulcer healing compared with the standard of care. In addition, clinical practice guidelines for diabetic wound care recommend the use of skin substitutes in some cases. Therefore, the use of Affinity®, AlloPatch®, AmnioBand® Membrane, AmnioExcel®, Apligraf®, Biovance®, Dermagraft®, EpiCord®, EpiFix®, Grafix®, Integra® Omnigraft™, Integra® Flowable Wound Matrix, mVASC®, or TheraSkin® may be considered medically necessary for the treatment of non-healing diabetic lower-extremity ulcers that have not responded to a 1-month period of conventional ulcer therapy. Treatment of diabetic lower-extremity ulcers with skin substitutes prior to 1-month of conventional ulcer therapy is considered not medically necessary.

There is not enough evidence to show that other amniotic products or bioengineered skin or soft tissue substitutes can improve health outcomes for patients with nonhealing diabetic lower-extremity ulcers. Therefore, the use of products other than Affinity®, AlloPatch®, AmnioBand® Membrane, AmnioExcel®, Apligraf®, Biovance®, Dermagraft®, EpiCord®, EpiFix®, Grafix®, Integra® Omnigraft™, Integra® Flowable Wound Matrix, mVASC®, or TheraSkin® is considered investigational for this indication.

LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

There is enough evidence to show that the use of Apligraf® or Oasis® Wound Matrix can improve health outcomes for individuals who have nonhealing lower-extremity ulcers due to venous insufficiency. Randomized controlled trials have demonstrated that these products can improve the healing of these wounds compared with the standard of care. Therefore, Apligraf® or Oasis® Wound Matrix may be considered medically necessary for the treatment of ulcers that have not responded to 1-month period of conventional ulcer therapy. Treatment of lower-extremity ulcers due to venous insufficiency with skin substitutes prior to 1-month of conventional ulcer therapy is considered not medically necessary.

There is not enough evidence to show that other amniotic products or bioengineered skin or soft tissue substitutes can improve health outcomes for patients with lower-extremity ulcers due to venous insufficiency. Therefore, the use of products other than Apligraf® or Oasis® Wound Matrix is considered investigational for this indication.

DYSTROPHIC EPIDERMOLYSIS BULLOSA

OrCel® was approved by the FDA under a humanitarian drug exemption for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. Therefore, OrCel® may be considered medically necessary for this indication.

There is not enough evidence to show that other amniotic products or bioengineered skin or soft tissue substitutes can improve health outcomes for patients with dystrophic epidermolysis bullosa, and only OrCel® has received a humanitarian drug exemption for this condition. Therefore, the use of products other than OrCel® is considered investigational for dystrophic epidermolysis bullosa.

DEEP DERMAL BURNS

There is enough evidence to show that Epicel® and Integra® Dermal Regeneration Template may improve health outcomes for individuals who have deep dermal burns. Epicel® has received FDA approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. Comparative studies have demonstrated improved outcomes for Integra® Dermal Regeneration Template for the treatment of burns. Therefore, Epicel® or Integra® Dermal Regeneration Template may be considered medically necessary for the treatment of second- or third-degree burns.

There is not enough evidence to show that products other than Epicel® or Integra® Dermal Regeneration Template can improve health outcomes for patients with second- or third-degree burns. Therefore, the use of other amniotic products or bioengineered skin substitutes is considered investigational for this indication.

OPHTHALMIC INDICATIONS

There is limited evidence to show that human amniotic membrane products can improve health outcomes for patients with ophthalmologic indications, however these disorders are rare, and randomized controlled trials are unlikely. The use of certain amniotic products has become standard of care for the treatment of corneal injuries or as a component of corneal or conjunctival surgical repair, and therefore human amniotic membranes for ocular use, including but not limited to Prokera®, AmbioDisk™, or AmnioGraft® may be considered medically necessary for these indications.

SURGICAL REPAIR OF HERNIAS OR PARASTOMAL REINFORCEMENT

There is enough evidence to show that bioengineered skin substitutes do not improve health outcomes for individuals who are undergoing surgical repair of hernias or parastomal reinforcement. Several comparative studies including RCTs have shown no difference in outcomes between tissue-engineered skin substitutes and either standard synthetic mesh or no reinforcement. Therefore, the use of bioengineered skin substitutes is considered not medically necessary for these indications.

TENDON REPAIR

There is not enough research to show that skin substitutes or amniotic products can improve health outcomes for individuals who are undergoing tendon repair. A single trial found

improved outcomes with the GraftJacket® allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of patients is needed to evaluate the consistency of the effect. Therefore, the use of skin substitutes or amniotic products for tendon repair is considered investigational.

OTHER INDICATIONS

There is not enough research to show that skin substitutes or amniotic products can improve health outcomes for patients with disorders other than those listed in the medical necessity criteria. Off-label uses of bioengineered skin substitutes have included inflammatory ulcers, scleroderma digital ulcers, post-keloid removal wounds, genetic conditions, and variety of other conditions, however there is a lack of controlled trials for these uses. Therefore, the use of skin substitutes or amniotic products for other indications is considered investigational.

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CODES

NOTE: While codes for skin substitute application (e.g., 15271-15278, 15777) do not have pre-authorization requirements, they may be denied when used for the application of a product that does not meet medical necessity criteria.

Codes	Number	Description
CPT	1044T	Harvest of full-thickness skin for autologous heterogeneous skin-construct graft, including direct closure of donor site; first 5 sq cm or less
	1045T	Harvest of full-thickness skin for autologous heterogeneous skin-construct graft, including direct closure of donor site; each additional 5 sq cm, or part thereof (List separately in addition to code for primary procedure)
	1046T	Autologous heterogeneous skin-construct graft application, trunk, arms, legs; first 50 sq cm or less, or 0.5% of body area of infants and children
	1047T	Autologous heterogeneous skin-construct graft application, trunk, arms, legs; each additional 50 sq cm, or each additional 0.5% of body area of infants and

Codes	Number	Description
		children, or part thereof (List separately in addition to code for primary procedure)
	1048T	Autologous heterogeneous skin-construct graft application, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 50 sq cm or less, or 0.5% of body area of infants and children
	1049T	Autologous heterogeneous skin-construct graft application, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 50 sq cm, or each additional 0.5% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15011	Harvest of skin for autograft; first
	15012	; each additional 25 sq cm
	15013	Preparation of skin autograft, requiring enzymatic processing; first 25 sq cm or less
	15014	; each additional 25 sq cm
	15015	Application of skin autograft; first 480 sq cm or less
	15016	; each additional 480 sq cm
	15017	Application of skin autograft; first 480 sq cm or less
	15018	; each additional 480 sq cm
	15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
	15272	; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
	15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
	15274	; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
	15276	; total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
	15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
	15278	; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15777	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (ie, breast, trunk) (List separately in addition to code for primary procedure)
HCPCS	A2001	Innovamatrix ac, per square centimeter
	A2002	Mirragen advanced wound matrix, per square centimeter
	A2004	Xcellistem, 1 mg
	A2005	Microlyte matrix, per square centimeter
	A2006	Novosorb synpath dermal matrix, per square centimeter
	A2007	Restrata, per square centimeter
	A2008	Theragenesis, per square centimeter

Codes	Number	Description
	A2009	Symphony, per square centimeter
	A2010	Apis, per square centimeter
	A2011	Supra sdrm, per square centimeter
	A2012	Suprathel, per square centimeter
	A2013	Innovamatrix fs, per square centimeter
	A2014	Omeza collagen matrix or omeza complete matrix, per 100 mg
	A2015	Phoenix wound matrix, per square centimeter
	A2016	Permeaderm b, per square centimeter
	A2017	Permeaderm glove, each
	A2018	Permeaderm c, per square centimeter
	A2019	Kerecis omega3 marigen shield, per square centimeter
	A2020	Ac5 advanced wound system (ac5)
	A2021	Neomatrix, per square centimeter
	A2022	Innovaburn or innovamatrix xl, per square centimeter
	A2023	Innovamatrix pd, 1 mg
	A2024	Resolve matrix or xenopatch, per square centimeter
	A2025	Miro3d, per cubic centimeter
	A2026	Restrata minimatrix, 5 mg
	A2027	Matriderm, per square centimeter
	A2028	Micromatrix flex, per mg
	A2029	Mirotract wound matrix sheet, per cubic centimeter
	A2030	Miro3d fibers, per milligram
	A2031	Mirodry wound matrix, per square centimeter
	A2032	Myriad matrix, per square centimeter
	A2033	Myriad morcells, 4 milligrams
	A2034	Foundation drs solo, per square centimeter
	A2035	Corplex p or theracor p or allacor p, per milligram
	A2036	Cohealyx collagen dermal matrix, per square centimeter
	A2037	G4derm plus/suprello, per milliliter
	A2038	Marigen pacto, per square centimeter
	A2039	Innovamatrix fd, per square centimeter
	A2040	Microlyte painguard, per square centimeter
	A2041	Foundation drs+ duo, per square centimeter
	A2042	Foundation drs+ solo, per square centimeter
	A2043	Biobrane, per square centimeter
	A2044	Biobrane glove, each
	A2045	Novashield or novogen wound matrix, per square centimeter
	A4100	Skin substitute, fda cleared as a device, not otherwise specified
	A6460	Synthetic resorbable wound dressing, sterile, pad size 16 sq in or less, without adhesive border, each dressing
	A6461	Synthetic resorbable wound dressing, sterile, pad size more than 16 sq in but less than or equal to 48 sq in, without adhesive border, each dressing
	C1832	Autograft suspension, including cell processing and application, and all system components
	C8002	Preparation of skin cell suspension autograft, automated, including all enzymatic processing and device components (do not report with manual suspension preparation)
	C9354	Acellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm
	C9356	Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per sq cm
	C9358	Dermal substitute, native, non-denatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters

Codes	Number	Description
	C9360	Dermal substitute, native, nondenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters
	C9363	Skin substitute, Integra Meshed Bilayer Wound Matrix, per square centimeter
	C9364	Porcine implant, Permacol, per square centimeter
	G0681	Application of a premarket approval (pma), 510(k), 361 human cells, tissues or cellular and tissue-based products (hct/p) non-sheet form skin substitute for a wound surface area up to 100 sq cm; first 25 sq cm or less of wound surface area
	G0682	Application of a premarket approval (pma), 510(k), 361 human cells, tissues or cellular and tissue-based products (hct/p) non-sheet form skin substitute for a wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
	G0683	Application of a premarket approval (pma), 510(k), 361 human cells, tissues or cellular and tissue-based products (hct/p) non-sheet form skin substitute graft for a wound surface greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
	G0684	Application of a premarket approval (pma), 510(k), 361 human cells, tissues or cellular and tissue-based products (hct/p) non-sheet form skin substitute graft for a wound surface greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
	~~Q4100~~	~~Skin substitute, not otherwise specified~~ (Deleted 1/1/2026)
	Q4101	Apligraf, per square centimeter
	Q4102	Oasis Wound Matrix, per square centimeter
	Q4103	Oasis Burn Matrix, per square centimeter
	Q4104	Integra Bilayer Matrix Wound Dressing (BMWD), per square centimeter
	Q4105	Integra Dermal Regeneration Template (DRT) or Integra Omnigraft dermal regeneration matrix, per square centimeter
	~~Q4106~~	~~Dermagraft, per square centimeter~~ (Deleted 1/1/2026)
	Q4107	Graftjacket, per square centimeter
	Q4108	Integra Matrix, per square centimeter
	Q4110	PriMatrix, per square centimeter
	Q4111	GammaGraft, per square centimeter
	Q4112	Cymetra, injectable, 1 cc
	Q4113	Graftjacket Xpress, injectable, 1 cc
	Q4114	Integra Flowable Wound Matrix, injectable, 1 cc
	Q4115	AlloSkin, per square centimeter
	Q4116	AlloDerm, per square centimeter
	Q4117	Hyalomatrix, per square centimeter
	Q4118	MatriStem micromatrix, 1 mg
	Q4121	TheraSkin, per square centimeter
	Q4122	Dermacell, dermacell awm or dermacell awm porous, per square centimeter (revised description 10/01/19)
	Q4123	AlloSkin RT, per square centimeter
	Q4124	Oasis Ultra Tri-Layer Wound Matrix, per square centimeter
	Q4125	Arthroflex, per square centimeter
	Q4126	Memoderm, Dermaspan, Transgraft or Integuply, per square centimeter
	Q4127	Talymed, per square centimeter
	Q4128	Flexhd, or allopatchhd, per square centimeter
	Q4130	Strattice TM, per square centimeter
	Q4132	"Grafix CORE and GrafixPL CORE, per square centimeter

Codes	Number	Description
	Q4133	Grafix prime, grafixpl prime, stravix and stravixpl, per square centimeter
	Q4134	hMatrix, per square centimeter
	Q4135	Mediskin, per square centimeter
	Q4136	EZ-derm, per square centimeter
	Q4137	Amnioexcel, amnioexcel plus or biodexcel, per square centimeter
	Q4138	BioDFence dryflex, per square centimeter
	Q4139	AmnioMatrix or biodmatrix, injectable, 1 cc
	Q4140	Biodfence, per square centimeter
	Q4141	Alloskin AC, per square centimeter
	Q4142	Xcm biologic tissue matrix, per square centimeter
	Q4143	Repriza, per square centimeter
	Q4145	Epifix, injectable, 1 mg
	Q4146	TenSIX, per square centimeter
	Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per square centimeter
	Q4148	NEOX CORD 1K, NEOX CORD RT, or CLARIX CORD 1K, per square centimeter
	Q4149	Excellagen, 0.1 cc
	Q4150	AlloWrap DS or dry, per square centimeter
	Q4151	AmnioBand or Guardian, per square centimeter
	Q4152	DermaPure per square centimeter
	Q4153	Dermavest and Plurivest, per square centimeter
	Q4154	Biovance, per square centimeter
	Q4155	Neoxflo or Clarixflo, 1 mg
	Q4156	NEOX 100 or CLARIX 100, per square centimeter
	Q4157	Revitalon, per square centimeter
	Q4158	Kerecis Omega3, per square centimeter
	Q4159	Affinity, per square centimeter
	Q4160	NuShield, per square centimeter
	Q4161	Bio-ConneKt Wound Matrix, per square centimeter
	Q4162	WoundEx Flow, BioSkin Flow, 0.5 cc
	Q4163	WoundEx, BioSkin, per square centimeter
	Q4164	Helicoll, per square centimeter
	Q4165	Keramatrix, per square centimeter
	Q4166	Cytal, per square centimeter
	Q4167	Truskin, per square centimeter
	Q4168	Amnioband, 1 mg
	Q4169	Artacent wound, per square centimeter
	Q4170	Cygnus, per square centimeter
	Q4171	Interfyl, 1 mg
	Q4172	Puraply or puraply am, per square centimeter
	Q4173	Palingen or palingen xplus, per square centimeter
	Q4174	Palingen or promatrx, 0.36 mg per 0.25 cc
	Q4175	Miroderm, per square centimeter
	Q4176	Neopatch, per square centimeter
	Q4177	Floweramnioflo, 0.1 cc
	Q4178	Floweramniopatch, per square centimeter
	Q4179	Flowerderm, per square centimeter
	Q4180	Revita, per square centimeter
	Q4181	Amnio wound, per square centimeter
	Q4182	Transcyte, per square centimeter
	Q4183	Surgigraft, per square centimeter

Codes	Number	Description
	Q4184	Cellesta or cellesta duo, per square centimeter
	Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
	Q4186	Epifix, per square centimeter
	Q4187	Epicord, per square centimeter
	Q4188	Amnioarmor, per square centimeter
	Q4189	Artacent ac, 1 mg
	Q4190	Artacent ac, per square centimeter
	Q4191	Restorigin, per square centimeter
	Q4192	Restorigin, 1 cc
	Q4193	Coll-e-derm, per square centimete
	Q4194	Novachor, per square centimeter
	Q4195	Puraply, per square centimeter
	Q4196	Puraply am, per square centimeter
	Q4197	Puraply xt, per square centimeter
	Q4198	Genesis amniotic membrane, per square centimeter
	Q4199	Cygnus matrix, per square centimeter
	Q4200	Skin te, per square centimeter
	Q4201	Matrion, per square centimeter
	Q4202	Keroxx (2.5g/cc), 1cc
	Q4203	Derma-gide, per square centimeter
	Q4204	Xwrap, per square centimeter
	Q4205	Membrane graft or membrane wrap, per square centimeter
	Q4206	Fluid flow or fluid GF, 1 cc
	Q4208	Novafix, per square cenitmeter
	Q4209	Surgraft, 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
	Q4222	Progenamatrix, per square centimeter
	Q4224	Human health factor 10 amniotic patch (hhf10-p), per square centimeter
	Q4225	Amniobind or dermabindtl, per square centimeter
	Q4226	MyOwn skin, includes harvesting and preparation procedures, per square centimeter
	Q4227	Amniocore, per square centimeter
	Q4229	Cogenex amniotic membrane, per square centimeter
	Q4230	Cogenex flowable amnion, per 0.5 cc
	Q4232	Corplex, per square centimeter
	Q4233	Surfactor or Nudyn, per 0.5 cc
	Q4234	Xcellerate, per square centimeter
	Q4235	Amniorepair or altiply, per square centimeter
	Q4236	Carepatch, per square centimeter
	Q4237	Cryo-cord, per square centimeter
	Q4238	Derm-maxx, per square centimeter

Codes	Number	Description
	Q4239	Amnio-maxx or Amnio-maxx lite, per square centimeter
	Q4240	Corecyte, for topical use only, per 0.5 cc
	Q4241	Polycyte, for topical use only, per 0.5 cc
	Q4242	Amniocyte plus, per 0.5 cc
	Q4245	Amniotext, per cc
	Q4246	Coretext or Protext, per cc
	Q4247	Amniotext patch, per square centimeter
	Q4248	Dermacyte Amniotic Membrane Allograft, per square centimeter
	Q4249	AMNIPLY, for topical use only, per sq cm
	Q4250	AmnioAmp-MP, per sq cm
	Q4251	Vim, per square centimeter
	Q4252	Vendaje, per square centimeter
	Q4253	Zenith amniotic membrane, per square centimeter
	Q4254	Novafix DL, per sq cm
	Q4255	REGUaRD, for topical use only, per sq cm
	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
	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
	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

Codes	Number	Description
	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	Amnicore 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
	Q4311	Acesso, per square centimeter
	Q4312	Acesso ac, per square centimeter
	Q4313	Dermabind fm, per square centimeter
	Q4314	Reeva ft, per square cenitmeter
	Q4315	Regenelink amniotic membrane allograft, per square centimeter
	Q4316	Amchoplast, per square centimeter
	Q4317	Vitograft, per square centimeter
	Q4318	E-graft, per square centimeter
	Q4319	Sanograft, per square centimeter
	Q4320	Pellograft, per square centimeter
	Q4321	Renograft, per square centimeter
	Q4322	Caregraft, per square centimeter
	Q4323	Alloply, per square centimeter
	Q4324	Amniotx, per square centimeter
	Q4325	Acapatch, per square centimeter
	Q4326	Woundplus, per square centimeter
	Q4327	Duoamnion, per square centimeter
	Q4328	Most, per square centimeter
	Q4329	Singlay, per square centimeter
	Q4330	Total, per square centimeter
	Q4331	Axolotl graft, per square centimeter
	Q4332	Axolotl dualgraft, per square centimeter
	Q4333	Ardeograft, per square centimeter
	Q4334	Amnioplast 1, per square centimeter
	Q4335	Amnioplast 2, per square centimeter
	Q4336	Artacent c, per square centimeter
	Q4337	Artacent trident, per square centimeter
	Q4338	Artacent velos, per square centimeter
	Q4339	Artacent vericlen, per square centimeter
	Q4340	Simpligraft, per square centimeter
	Q4341	Simplimax, per square centimeter
	Q4342	Theramend, per square centimeter
	Q4343	Dermacyte ac matrix amniotic membrane allograft, per square centimeter
	Q4344	Tri-membrane wrap, per square centimeter
	Q4345	Matrix hd allograft dermis, per square centimeter

Codes	Number	Description
	Q4346	Shelter dm matrix, per square centimeter
	Q4347	Rampart dl matrix, per square centimeter
	Q4348	Sentry sl matrix, per square centimeter
	Q4349	Mantle dl matrix, per square centimeter
	Q4350	Palisade dm matrix, per square centimeter
	Q4351	Enclose tl matrix, per square centimeter
	Q4352	Overlay sl matrix, per square centimeter
	Q4353	Xceed tl matrix, per square centimeter
	Q4354	Palingen dual-layer membrane, per square centimeter
	Q4355	Abiomend xplus membrane and abiomend xplus hydromembrane, per square centimeter
	Q4356	Abiomend membrane and abiomend hydromembrane, per square centimeter
	Q4357	Xwrap plus, per square centimeter
	Q4358	Xwrap dual, per square centimeter
	Q4359	Choriply, per square centimeter
	Q4360	Amchoplast fd, per square centimeter
	Q4361	Epixpress, per square centimeter
	Q4362	Cygnus disk, per square centimeter
	Q4363	Amnio burgeon membrane and hydromembrane, per square centimeter
	Q4364	Amnio burgeon xplus membrane and xplus hydromembrane, per square centimeter
	Q4365	Amnio burgeon dual-layer membrane, per square centimeter
	Q4366	Dual layer amnio burgeon x-membrane, per square centimeter
	Q4367	Amniocore sl, per square centimeter
	Q4368	Amchothick, per square centimeter
	Q4369	Amnioplast 3, per square centimeter
	Q4370	Aeroguard, per square centimeter
	Q4371	Neoguard, per square centimeter
	Q4372	Amchoplast excel, per square centimeter
	Q4373	Membrane wrap lite, per square centimeter
	Q4375	Duograft ac, per square centimeter
	Q4376	Duograft aa, per square centimeter
	Q4377	Trigraft ft, per square centimeter
	Q4378	Renew ft matrix, per square centimeter
	Q4379	Amniodefend ft matrix, per square centimeter
	Q4380	Advograft one, per square centimeter
	Q4382	Advograft dual, per square centimeter
	Q4383	Axolotl graft ultra, per square centimeter
	Q4384	Axolotl dualgraft ultra, per square centimeter
	Q4385	Apollo ft, per square centimeter
	Q4386	Acesso trifaca, per square centimeter
	Q4387	Neothelium ft, per square centimeter
	Q4388	Neothelium 4l, per square centimeter
	Q4389	Neothelium 4l+, per square centimeter
	Q4390	Ascendion, per square centimeter
	Q4391	Amnioplast double, per square centimeter
	Q4392	Grafix duo, per square centimeter
	Q4393	Surgraft ac, per square centimeter
	Q4394	Surgraft aca, per square centimeter
	Q4395	Acelagraft, per square centimeter
	Q4396	Natalin, per square centimeter
	Q4397	Summit aaa, per square centimeter

Codes	Number	Description
	Q4398	Summit ac, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4399	Summit fx, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4400	Polygon3 membrane, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4401	Absolv3 membrane, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4402	Xwrap 2.0, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4403	Xwrap dual plus, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4404	Xwrap hydro plus, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4405	Xwrap fenestra plus, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4406	Xwrap fenestra, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4407	Xwrap tribus, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4408	Xwrap hydro, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4409	Amniomatrixf3x, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4410	Amchomatrixdl, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4411	Amniomatrixf4x, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4412	Choriofix, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4413	Cygnus solo, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4414	Simplichor, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4415	Alexiguard sl-t, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4416	Alexiguard tl-t, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4417	Alexiguard dl-t, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4418	Biolab membrane wrap flow, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4419	Biolab membrane wrap lite flow, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4420	Nuform, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4421	
	Q4422	Biolab membrane wrap solo, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4423	A/c wrap, per square centimeter (add-on, list separately in addition to primary procedure)

Codes	Number	Description
	Q4424	Biolab tri-membrane wrap flow, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4425	Revive ft, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4426	Revive tl, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4427	Dermabind tl + or dermabind tl x, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4428	Dermabind dl n or dermabind dl + or dermabind dl x, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4429	Dermabind sl n or dermabind sl + or dermabind sl x, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4431	Pma skin substitute product, not otherwise specified (list in addition to primary procedure)
	Q4432	510(k) skin substitute product, not otherwise specified (list in addition to primary procedure)
	Q4433	361 hct/p skin substitute product, not otherwise specified (list in addition to primary procedure)
	Q4435	Renati membrane, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4436	Renati ac membrane, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4437	Revival ac, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4438	Pretect, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4439	Instagraft, per square centimeter (add-on, list separately in addition to primary procedure)
	Q4440	Curamatrix, per square centimeter (add-on, list separately in addition to primary procedure)

Date of Origin: *December 2018*