# Skin and Soft Tissue Substitutes

**Policy Number**: CS153.AA
**Effective Date**: April 1, 2026

➲ Instructions for Use

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**Commercial Policy**

- Skin and Soft Tissue Substitutes

## Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

| State | Policy/Guideline |
|---|---|
| Idaho | Skin and Soft Tissue Substitutes (for Idaho Only) |
| Indiana | None |
| Kansas | Skin and Soft Tissue Substitutes (for Kansas Only) |
| Kentucky | Skin and Soft Tissue Substitutes (for Kentucky Only) |
| Nebraska | Skin and Soft Tissue Substitutes (for Nebraska Only) |
| New Jersey | Skin and Soft Tissue Substitutes (for New Jersey Only) |
| New Mexico | Skin and Soft Tissue Substitutes (for New Mexico Only) |
| North Carolina | Skin and Soft Tissue Substitutes (for North Carolina Only) |
| Ohio | Skin and Soft Tissue Substitutes (for Ohio Only) |
| Pennsylvania | Skin and Soft Tissue Substitutes (for Pennsylvania Only) |
| Tennessee | Skin and Soft Tissue Substitutes (for Tennessee Only) |

## Coverage Rationale

### EPIFIX® or GRAFIX® (GRAFIX PL, GRAFIX PRIME, and GRAFIX PL PRIME) (Noninjectable)

**EPIFIX or GRAFIX is proven and medically necessary for treating a diabetic foot ulcer when all the following criteria are met:**

- Adequate circulation to the affected extremity, as indicated by one or more of the following:
  - Pedal pulses palpable or pulses confirmed with Doppler examination
  - Ankle-Brachial Index between 0.7 and 1.2
- Glycated hemoglobin test < 12% (within the last 90 days)
- Ulcer has failed to demonstrate adequate healing, with at least 4 weeks of standard wound care, which includes **all** of the following:
  - Application of dressings to maintain a moist wound environment

    - Debridement of necrotic tissue if present
    - Offloading
- No known contraindications, which may include but are not limited to the following:
    - Active Charcot deformity or major structural abnormalities of the affected foot
    - Chronic infection to the ulcer site
    - Known or suspected malignancy of the current ulcer being treated
    - Ulcer being treated does not extend to tendon, muscle, capsule, or bone

**Due to insufficient evidence of efficacy, EPIFIX and/or GRAFIX are unproven and not medically necessary for all other indications.**

## TransCyte®

**TransCyte is proven and medically necessary for treating surgically excised Full-Thickness Thermal Burn wounds and deep Partial-Thickness Thermal Burn wounds before autograft placement.**

**TransCyte is unproven and not medically necessary for all other indications due to insufficient evidence of efficacy.**

## Other Skin and Soft Tissue Substitutes

**The following skin and soft tissue substitutes are unproven and not medically necessary for any indication due to insufficient evidence of efficacy:**

- Abiomend Membrane and Abiomend Hydromembrane
- Abiomend Xplus Membrane and Abiomend Xplus Hydromembrane
- ACApatch™
- Acelagraft
- Acesso, Acesso AC, Acesso DL, and Acesso TL, or Acesso TrifACA
- Activate Matrix™
- AdvoGraft Dual™ and AdvoGraft One™
- AeroGuard and NeoGuard
- Affinity®
- AlloGen™
- alloPLY™
- AlloSkin™
- AlloWrap®
- Altiply®
- AmchoPlast™, AmchoPlast™ FD, and AmchoPlast™ EXCEL
- AmchoThick™
- American Amnion®, American Amnion AC®, and American Amnion AC Tri-Layer®
- AmniCore Pro
- AmniCore Pro+
- Amnio Burgeon® Dual-Layer Membrane
- Amnio Burgeon® Membrane and Hydromembrane
- Amnio Burgeon® Xplus Membrane and Xplus Hydromembrane
- AmnioCore SL
- AmnioPlast 1™, AmnioPlast 2™, and AmnioPlast Double
- AmnioTX
- Amnio Quad-Core
- Amnio Tri-Core Amniotic
- Amnio Wound™
- AmnioWrap2™
- AmnioAMP-MP™
- AmnioArmor™
- AmnioBand®
- AmnioBind™ or DermaBind TL™
- AmnioCore
- Amniocyte Plus™
- AmnioDefend™ FT Matrix
- AmnioExcel®, AmnioExcel® Plus, or BioDExcel™
- AMNIOFIX®
- AMNIOMATRIX® or BioDMatrix™
- Amnio-Maxx® or Amnio-Maxx® Lite
- AmnioRepair®
- AmnioPlast 1™, AmnioPlast 2™, and AmnioPlast 3™
- AmnioText™
- AmnioText™ Patch
- Amnion Bio™
- AMNIPLY™
- APIS®
- Apollo FT
- Architect®
- ArdeoGraft®
- Artacent® Cord
- Artacent® C, Artacent® AC, Artacent® Trident, Artacent® Velos, Artacent® Vericlen, and Artacent® Wound
- ArthroFLEX®
- Ascendion™
- Ascent™
- AxoBioMembrane™
- Axolotl Ambient™ or Axolotl Cryo™
- Axolotl Graft™, Axolotl DualGraft™, Axolotl DualGraft Ultra™, or Axolotl Graft Ultra™
- Barrera SL or Barrera DL
- BellaCell HD™
- bio-ConneKt®
- BioDFence® or BioDFence DryFlex®

- BioSkin®
- BioSkin Flow®
- BIOVANCE®, BIOVANCE® Tri-Layer, or BIOVANCE® 3L
- BioWound™, BioWound Plus, or BioWound Xplus
- CaregraFT™
- CarePATCH™
- Celera™ Dual Layer or Celera™ Dual Membrane
- Cellesta® or Cellesta® Duo
- Cellesta® Cord
- Cellesta® Flowable Amnion
- Choriply
- CLARIX®
- CLARIX FLO®
- Cocoon Membrane
- Cogenex® (amniotic membrane and flowable amnion)
- Cohealyx Collagen Dermal Matrix
- Coll-e-Derm™
- Complete™ AA
- Complete™ ACA
- Complete™ FT
- Complete™ SL
- Conexa™
- Corecyte™
- Coretext™ or Protext™
- CorMatrix®
- Corplex™
- Corplex P®, Theracor P, or Allacor P
- Cryo-Cord™
- CYGNUS®, CYGNUS® Dual, or CYGNUS® Matrix
- CYGNUS® Disk
- Cymetra™
- Cytal™
- DermaBind CH, DermaBind DL, DermaBind FM, or DermaBind SL
- DermACELL®, DermACELL® AWM, or DermACELL® AWM Porous *(*refer to the asterisked note below when DermACELL is used during breast reconstruction)*
- Dermacyte® AC Matrix Amniotic Membrane Allograft or Dermacyte® Amniotic Membrane Allograft
- Derma-Gide®
- DermaPure®
- DermaSpan™
- Dermavest® or Plurivest®
- Derm-Maxx®
- Dual Layer Amnio Burgeon X-Membrane
- Dual Layer Impax Membrane™
- DuoAmnion
- Duograft AA, duoGRAFT AC, and triGRAFT FT
- E-Graft™
- Emerge™ Matrix
- Enclose™ TL Matrix
- Enverse®
- EPICORD®
- EPIEFFECT®
- EPIFIX, injectable
- EPIXPRESS®
- Esano™ A, Esano™ AAA, Esano™ AC, or Esano™ ACA
- Excellagen®
- E-Z Derm®
- FlowerAmnioFlo™ or FlowerFlo™
- FlowerAmnioPatch™ or FlowerPatch™
- FlowerDerm™
- Fluid Flow™
- Fluid GF™
- Foundation Dermal Regeneration Scaffold (DRS) Solo
- G4Derm™ Plus
- GammaGraft™
- Genesis Amniotic Membrane
- GRAFIX® CORE
- GRAFIX® Duo
- GRAFIX® Plus
- Guardian
- Helicoll®
- hMatrix®
- Human Health Factor 10 Amniotic Patch (HHF10P™)
- Hyalomatrix®
- InnovaMatrix® AC, InnovaMatrix® FD, or InnovaMatrix® FS
- Integra® Flowable Wound Matrix
- InteguPly®
- Interfyl™
- Keramatrix®
- Kerasorb®
- Kerecis® Omega3 and Kerecis® Omega3 MariGen® Shield
- Keroxx™
- Lamellas and Lamellas XT
- Mantle DL Matrix
- MariGen® Pacto
- MatriDerm®
- Matrion®
- MatriStem® MicroMatrix®
- Matrix HD Allograft Dermis
- Mediskin™
- Membrane Graft™
- Membrane Wrap, Membrane Wrap-Hydro™, or Membrane Wrap-Lite™
- MemoDerm™
- Miro3D® Fibers
- MiroDry™ Wound Matrix
- Microlyte® Matrix
- MicroMatrix® Flex
- Mirragen® Advanced Wound Matrix
- MIRODERM™
- MiroTract™ Wound Matrix
- MLG-Complete™
- MOST
- MyOwn Skin™
- Myriad Matrix™

- Myriad Morcells™
- Natalin
- NeoMatriX®
- NeoPatch™
- NeoStim Membrane, NeoStim TL Membrane, and NeoStim DL
- NeoThelium FT, NeoThelium 4L, and NeoThelium 4L Plus
- NEOX®
- NEOX® FLO
- Novachor™
- Novafix™
- Novafix™ DL
- NovoSorb® SynPath™
- NuDYN™
- NuShield®
- Omeza Collagen Matrix
- Orion™
- Overlay SL Matrix
- PalinGen® Amniotic Tissue Allograft and PalinGen® Flow products
- PalinGen® Dual-Layer Membrane
- Palisade™ DM Matrix
- PelloGraft®
- PermeaDerm® B
- PermeaDerm® Glove
- PermeaDerm® C
- Phoenix™ Wound Matrix
- Polycyte™
- PriMatrix®
- Procenta®
- ProgenaMatrix®
- ProMatrX™
- PuraPly®, PuraPly® AM, or PuraPly® XT
- Rampart DL Matrix
- Rebound™ Matrix
- Reeva FT™
- RegeneLink® Amniotic Membrane Allograft
- REGUaRD™
- Relese®
- Renew FT Matrix
- RenoGraft®
- Repriza®
- Restorigin™
- Restrata® or Restrata® MiniMatrix
- Revita®
- Revitalon™
- RevoShield+® Amniotic Barrier
- SanoGraft®
- Sanopellis
- Sentry™ SL Matrix
- Shelter™ DM Matrix
- Signature APatch
- SimpliGraft™ or SimpliMax™
- Singlay
- SkinTE®
- STRATTICE™
- STRAVIX™ or STRAVIX PL™
- Summit AAA
- Supra SDRM®
- SUPRATHEL®
- SureDerm®
- Surfactor®
- SurGraft®, SurGraft AC, SurGraft ACA, SurGraft FT®, SurGraft TL®, or SurGraft XT®
- SurgiCORD™
- SurgiGRAFT™
- SurgiGRAFT™ Dual
- Symphony™
- TAG
- Talymed®
- TenSix®
- TheraGenesis
- TheraMend™
- TheraSkin®
- Therion™
- TOTAL
- TranZgraft®
- Tri-Membrane Wrap™
- TruSkin™
- VENDAJE®
- VENDAJE AC®
- VIA Matrix™
- Vim
- VitoGraft®
- WoundEx®
- WoundEx Flow
- WoundFix™, WoundFix Plus, or WoundFix Xplus
- WoundPlus™ Membrane
- Xceed TL Matrix™
- XCell Amnio Matrix™
- XCelliStem
- Xcellerate™
- XCM BIOLOGIC™ Tissue Matrix
- XWRAP®
- XWRAP Dual®
- XWRAP Plus®
- Zenith™ Amniotic Membrane

*Refer to the Medical Policy titled Breast Reconstruction for information about coverage for skin and soft tissue substitutes used during post mastectomy breast reconstruction procedures.

**Note**: Refer to the Clinical Evidence section for specific product information.

# Definitions

**Full-Thickness Thermal Burn (Third Degree Burn)**: A burn with destruction of all layers of the skin. These burns involve all the epidermal and dermal layers, with varying amounts of the sub-cutaneous layer involvement (Gomez and Cancio, 2007).

**Partial-Thickness Thermal Burn (Second Degree Burn)**: A burn that involves the epidermis and only part of the dermis. Deep Partial-Thickness Thermal Burns involve the epidermis and most parts of the dermis, leaving few intact skin appendages and nerve endings (Gomez and Cancio, 2007).

# Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

| HCPCS Code | Description |
|---|---|
| A2001 | InnovaMatrix AC, per sq cm |
| A2002 | Mirragen Advanced Wound Matrix, per sq cm |
| A2004 | XCelliStem, 1mg |
| A2005 | Microlyte Matrix, per sq cm |
| A2006 | NovoSorb SynPath dermal matrix, per sq cm |
| A2007 | Restrata, per sq cm |
| A2008 | TheraGenesis, per sq cm |
| A2009 | Symphony, per sq cm |
| A2010 | Apis, per sq cm |
| A2011 | Supra SDRM, per sq cm |
| A2012 | SUPRATHEL, per sq cm |
| A2013 | InnovaMatrix FS, per sq cm |
| A2014 | Omeza Collagen Matrix, per 100 mg |
| A2015 | Phoenix wound matrix, per sq cm |
| A2016 | PermeaDerm B, per sq cm |
| A2017 | PermeaDerm glove, each |
| A2018 | PermeaDerm C, per sq cm |
| A2019 | Kerecis Omega3 MariGen Shield, per sq cm |
| A2021 | NeoMatriX, per sq cm |
| A2026 | Restrata MiniMatrix, 5 mg |
| A2027 | MatriDerm, per sq cm |
| A2028 | MicroMatrix Flex, per mg |
| A2029 | MiroTract Wound Matrix sheet, per cc |
| A2030 | Miro3D fibers, per mg |
| A2031 | MiroDry Wound Matrix, per sq cm |
| A2032 | Myriad Matrix, per sq cm |
| A2033 | Myriad Morcells, 4 mg |
| A2034 | Foundation DRS Solo, per sq cm |
| A2035 | Corplex p or Theracor p or Allacor P, per mg |
| A2036 | Cohealyx Collagen Dermal Matrix, per sq cm |
| A2037 | G4Derm Plus, per ml |

| HCPCS Code | Description |
|---|---|
| A2038 | MariGen Pacto, per sq cm |
| A2039 | InnovaMatrix FD, per sq cm |
| A4100 | Skin substitute, FDA-cleared as a device, not otherwise specified |
| Q4100 | Skin substitute, not otherwise specified |
| Q4110 | PriMatrix, per sq cm |
| Q4111 | GammaGraft, per sq cm |
| Q4112 | Cymetra, injectable, 1 cc |
| Q4114 | Integra flowable wound matrix, injectable, 1 cc |
| Q4115 | AlloSkin, per sq cm |
| Q4117 | HYALOMATRIX, per sq cm |
| Q4118 | MatriStem micromatrix, 1 mg |
| Q4121 | TheraSkin, per sq cm |
| Q4122 | DermACELL, DermACELL AWM or DermACELL AWM Porous, per sq cm |
| Q4123 | AlloSkin RT, per sq cm |
| Q4125 | Arthroflex, per sq cm |
| Q4126 | MemoDerm, DermaSpan, TranZgraft or IntéguPly, per sq cm |
| Q4127 | Talymed, per sq cm |
| Q4130 | Strattice TM, per sq cm |
| Q4132 | Grafix Core and GrafixPL Core, per sq cm |
| Q4133 | Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq cm |
| Q4134 | HMatrix, per sq cm |
| Q4135 | Mediskin, per sq cm |
| Q4136 | E-Z derm, per sq cm |
| Q4137 | AmnioExcel, AmnioExcel Plus or BioDExcel, per sq cm |
| Q4138 | BioDFence DryFlex, per sq cm |
| Q4139 | AmnioMatrix or BioDMatrix, injectable, 1 cc |
| Q4140 | BioDFence, per sq cm |
| Q4141 | AlloSkin AC, per sq cm |
| Q4142 | Xcm biologic tissue matrix, per sq cm |
| Q4143 | Repriza, per sq cm |
| Q4145 | EpiFix, injectable, 1 mg |
| Q4146 | Tensix, per sq cm |
| Q4147 | Architect, Architect PX, or Architect FX, extracellular matrix, per sq cm |
| Q4148 | Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per sq cm |
| Q4149 | Excellagen, 0.1 cc |
| Q4150 | AlloWrap DS or dry, per sq cm |
| Q4151 | AmnioBand or Guardian, per sq cm |
| Q4152 | DermaPure, per sq cm |
| Q4153 | Dermavest and Plurivest, per sq cm |
| Q4154 | Biovance, per sq cm |
| Q4155 | Neox Flo or Clarix Flo 1 mg |
| Q4156 | Neox 100 or Clarix 100, per sq cm |
| Q4157 | Revitalon, per sq cm |
| Q4158 | Kerecis Omega3, per sq cm |
| Q4159 | Affinity, per sq cm |

| HCPCS Code | Description |
|---|---|
| Q4160 | Nushield, per sq cm |
| Q4161 | Bio-connekt wound matrix, per sq cm |
| Q4162 | WoundEx Flow, BioSkin Flow, 0.5 cc |
| Q4163 | WoundEx, BioSkin, per sq cm |
| Q4164 | Helicoll, per sq cm |
| Q4165 | Keramatrix or Kerasorb, per sq cm |
| Q4166 | Cytal, per sq cm |
| Q4167 | Truskin, per sq cm |
| Q4168 | Amnioband, 1 mg |
| Q4169 | Artacent wound, per sq cm |
| Q4170 | Cygnus, per sq cm |
| Q4171 | Interfyl, 1 mg |
| Q4173 | Palingen or palingen xplus, per sq cm |
| Q4174 | Palingen or promatrx, 0.36 mg per 0.25 cc |
| Q4175 | Miroderm, per sq cm |
| Q4176 | Neopatch, per sq cm |
| Q4177 | Floweramnioflo, 0.1 cc |
| Q4178 | Floweramniopatch, per sq cm |
| Q4179 | Flowerderm, per sq cm |
| Q4180 | Revita, per sq cm |
| Q4181 | Amnio wound, per sq cm |
| Q4182 | Transcyte, per sq cm |
| Q4183 | Surgigraft, per sq cm |
| Q4184 | Cellesta or Cellesta Duo, per sq cm |
| Q4185 | Cellesta Flowable Amnion (25 mg per cc); per 0.5 |
| Q4186 | Epifix, per sq cm |
| Q4187 | Epicord, per sq cm |
| Q4188 | AmnioArmor, per sq cm |
| Q4189 | Artacent AC, 1 mg |
| Q4190 | Artacent AC, per sq cm |
| Q4191 | Restorigin, per sq cm |
| Q4192 | Restorigin, 1 cc |
| Q4193 | Coll-e-Derm, per sq cm |
| Q4194 | Novachor, per sq cm |
| Q4195 | PuraPly, per sq cm |
| Q4196 | PuraPly AM, per sq cm |
| Q4197 | PuraPly XT, per sq cm |
| Q4198 | Genesis Amniotic Membrane, per sq cm |
| Q4199 | Cygnus matrix, per sq cm |
| Q4200 | SkinTE, per sq cm |
| Q4201 | Matrion, per sq cm |
| Q4202 | Keroxx (2.5 g/cc), 1 cc |
| Q4203 | Derma-Gide, per sq cm |
| Q4204 | XWRAP, per sq cm |
| Q4205 | Membrane graft or membrane wrap, per sq cm |

| HCPCS Code | Description |
|---|---|
| Q4206 | Fluid Flow or Fluid GF, 1 cc |
| Q4208 | Novafix, per sq cm |
| Q4209 | SurGraft, per sq cm |
| Q4211 | Amnion Bio or AxoBioMembrane, per sq cm |
| Q4212 | AlloGen, per cc |
| Q4213 | Ascent, 0.5 mg |
| Q4214 | Cellesta Cord, per sq cm |
| Q4215 | Axolotl Ambient or Axolotl Cryo, 0.1 mg |
| Q4216 | Artacent Cord, per sq cm |
| Q4217 | WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm |
| Q4218 | SurgiCORD, per sq cm |
| Q4219 | SurgiGRAFT-DUAL, per sq cm |
| Q4220 | BellaCell HD or Surederm, per sq cm |
| Q4221 | Amnio Wrap2, per sq cm |
| Q4222 | ProgenaMatrix, per sq cm |
| Q4224 | Human Health Factor 10 Amniotic Patch (HHF10-P), per sq cm |
| Q4225 | AmnioBind or DermaBind TL, per sq cm |
| Q4226 | MyOwn Skin, includes harvesting and preparation procedures, per sq cm |
| Q4227 | AmnioCore, per sq cm |
| Q4229 | Cogenex Amniotic Membrane, per sq cm |
| Q4230 | Cogenex flowable amnion, per 0.5 cc |
| Q4232 | Corplex, per sq cm |
| Q4233 | Surfactor or nudyn, per 0.5 cc |
| Q4234 | Xcellerate, per sq cm |
| Q4235 | AMNIOREPAIR or AltiPly, per sq cm |
| Q4236 | carePATCH, per sq cm |
| Q4237 | Cryo-Cord, per sq cm |
| Q4238 | Derm-Maxx, per sq cm |
| Q4239 | Amnio-Maxx or Amnio-Maxx Lite |
| 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 sq cm |
| Q4248 | Dermacyte Amniotic Membrane Allograft, per sq cm |
| Q4249 | AMNIPLY, for topical use only, per sq cm |
| Q4250 | AmnioAmp-MP, per sq cm |
| Q4251 | Vim, per sq cm |
| Q4252 | Vendaje, per sq cm |
| Q4253 | Zenith amniotic membrane, per sq cm |
| Q4254 | Novafix DL, per sq cm |
| Q4255 | REGUaRD, for topical use only, per sq cm |
| Q4256 | MLG-Complete, per sq cm |

| HCPCS Code | Description |
|---|---|
| Q4257 | Relese, per sq cm |
| Q4258 | Enverse, per sq cm |
| Q4259 | Celera Dual Layer or Celera Dual Membrane, per sq cm |
| Q4260 | Signature APatch, per sq cm |
| Q4261 | TAG, per sq cm |
| Q4262 | Dual Layer impax Membrane, per sq cm |
| Q4263 | SurGraft TL, per sq cm |
| Q4264 | Cocoon membrane, per sq cm |
| Q4265 | NeoStim TL, per sq cm |
| Q4266 | NeoStim Membrane, per sq cm |
| Q4267 | NeoStim DL, per sq cm |
| Q4268 | SurGraft FT, per sq cm |
| Q4269 | SurGraft XT, per sq cm |
| Q4270 | Complete SL, per sq cm |
| Q4271 | Complete FT, per sq cm |
| Q4272 | Esano A, per sq cm |
| Q4273 | Esano AAA, per sq cm |
| Q4274 | Esano AC, per sq cm |
| Q4275 | Esano ACA, per sq cm |
| Q4276 | ORION, per sq cm |
| Q4278 | EPIEFFECT, per sq cm |
| Q4279 | Vendaje AC, per sq cm |
| Q4280 | Xcell Amnio Matrix, per sq cm |
| Q4281 | Barrera SL or Barrera DL, per sq cm |
| Q4282 | Cygnus Dual, per sq cm |
| Q4283 | Biovance Tri-Layer or Biovance 3L, per sq cm |
| Q4284 | DermaBind SL, per sq cm |
| Q4287 | DermaBind DL, per sq cm |
| Q4288 | DermaBind CH, per sq cm |
| Q4289 | RevoShield+ Amniotic Barrier, per sq cm |
| Q4290 | Membrane Wrap-Hydro™, per sq cm |
| Q4291 | Lamellas XT, per sq cm |
| Q4292 | Lamellas, per sq cm |
| Q4293 | Acesso DL, per sq cm |
| Q4294 | Amnio Quad-Core, per sq cm |
| Q4295 | Amnio Tri-Core Amniotic, per sq cm |
| Q4296 | Rebound Matrix, per sq cm |
| Q4297 | Emerge Matrix, per sq cm |
| Q4298 | AmniCore Pro, per sq cm |
| Q4299 | AmniCore Pro+, per sq cm |
| Q4300 | Acesso TL, per sq cm |
| Q4301 | Activate Matrix, per sq cm |
| Q4302 | Complete ACA, per sq cm |
| Q4303 | Complete AA, per sq cm |
| Q4304 | GRAFIX PLUS, per sq cm |

| HCPCS Code | Description |
|---|---|
| Q4305 | American Amnion AC Tri-Layer, per sq cm |
| Q4306 | American Amnion AC, per sq cm |
| Q4307 | American Amnion, per sq cm |
| Q4308 | Sanopellis, per sq cm |
| Q4309 | VIA Matrix, per sq cm |
| Q4310 | Procenta, per 100 mg |
| Q4311 | Acesso, per sq cm |
| Q4312 | Acesso AC, per sq cm |
| Q4313 | DermaBind FM, per sq cm |
| Q4314 | Reeva FT, per sq cm |
| Q4315 | RegeneLink Amniotic Membrane Allograft, per sq cm |
| Q4316 | AmchoPlast, per sq cm |
| Q4317 | VitoGraft, per sq cm |
| Q4318 | E-Graft, per sq cm |
| Q4319 | SanoGraft, per sq cm |
| Q4320 | PelloGraft, per sq cm |
| Q4321 | RenoGraft, per sq cm |
| Q4322 | CaregraFT, per sq cm |
| Q4323 | alloPLY, per sq cm |
| Q4324 | AmnioTX, per sq cm |
| Q4325 | ACApatch, per sq cm |
| Q4326 | WoundPlus, per sq cm |
| Q4327 | DuoAmnion, per sq cm |
| Q4328 | MOST, per sq cm |
| Q4329 | Singlay, per sq cm |
| Q4330 | TOTAL, per sq cm |
| Q4331 | Axolotl Graft, per sq cm |
| Q4332 | Axolotl DualGraft, per sq cm |
| Q4333 | ArdeoGraft, per sq cm |
| Q4334 | AmnioPlast 1, per sq cm |
| Q4335 | AmnioPlast 2, per sq cm |
| Q4336 | Artacent C, per sq cm |
| Q4337 | Artacent Trident, per sq cm |
| Q4338 | Artacent Velos, per sq cm |
| Q4339 | Artacent Vericlen, per sq cm |
| Q4340 | SimpliGraft, per sq cm |
| Q4341 | SimpliMax, per sq cm |
| Q4342 | TheraMend, per sq cm |
| Q4343 | Dermacyte AC Matrix Amniotic Membrane Allograft, per sq cm |
| Q4344 | Tri-Membrane Wrap, per sq cm |
| Q4345 | Matrix HD Allograft Dermis, per sq cm |
| Q4346 | Shelter DM Matrix, per sq cm |
| Q4347 | Rampart DL Matrix, per sq cm |
| Q4348 | Sentry SL Matrix, per sq cm |
| Q4349 | Mantle DL Matrix, per sq cm |

| HCPCS Code | Description |
|---|---|
| Q4350 | Palisade DM Matrix, per sq cm |
| Q4351 | Enclose TL Matrix, per sq cm |
| Q4352 | Overlay SL Matrix, per sq cm |
| Q4353 | Xceed TL Matrix, per sq cm |
| Q4354 | PalinGen Dual-Layer Membrane, per sq cm |
| Q4355 | Abiomend Xplus Membrane and Abiomend Xplus Hydromembrane, per sq cm |
| Q4356 | Abiomend Membrane and Abiomend Hydromembrane, per sq cm |
| Q4357 | XWRAP Plus, per sq cm |
| Q4358 | XWRAP Dual, per sq cm |
| Q4359 | ChoriPly, per sq cm |
| Q4360 | AmchoPlast FD, per sq cm |
| Q4361 | EPIXPRESS, per sq cm |
| Q4362 | CYGNUS Disk, per sq cm |
| Q4363 | Amnio Burgeon Membrane and Hydromembrane, per sq cm |
| Q4364 | Amnio Burgeon Xplus Membrane and Xplus Hydromembrane, per sq cm |
| Q4365 | Amnio Burgeon Dual-Layer Membrane, per sq cm |
| Q4366 | Dual Layer Amnio Burgeon X-Membrane, per sq cm |
| Q4367 | AmnioCore SL, per sq cm |
| Q4368 | AmchoThick, per sq cm |
| Q4369 | AmnioPlast 3, per sq cm |
| Q4370 | AeroGuard, per sq cm |
| Q4371 | NeoGuard, per sq cm |
| Q4372 | AmchoPlast EXCEL, per sq cm |
| Q4373 | Membrane Wrap-Lite, per sq cm |
| Q4375 | duoGRAFT AC, per sq cm |
| Q4376 | Duograft AA, per sq cm |
| Q4377 | triGRAFT FT, per sq cm |
| Q4378 | Renew FT Matrix, per sq cm |
| Q4379 | AmnioDefend FT Matrix, per sq cm |
| Q4380 | AdvoGraft One, per sq cm |
| Q4382 | AdvoGraft Dual, per sq cm |
| Q4383 | Axolotl Graft Ultra, per sq cm |
| Q4384 | Axolotl DualGraft Ultra, per sq cm |
| Q4385 | Apollo FT, per sq cm |
| Q4386 | Acesso TrifACA, per sq cm |
| Q4387 | NeoThelium FT, per sq cm |
| Q4388 | NeoThelium 4L, per sq cm |
| Q4389 | NeoThelium 4L Plus, per sq cm |
| Q4390 | Ascendion, per sq cm |
| Q4391 | AmnioPlast Double, per sq cm |
| Q4392 | GRAFIX Duo, per sq cm |
| Q4393 | SurGraft AC, per sq cm |
| Q4394 | SurGraft ACA, per sq cm |
| Q4395 | Acelagraft, per sq cm |
| Q4396 | Natalin, per sq cm |

| HCPCS Code | Description |
|---|---|
| Q4397 | Summit AAA, per sq cm |

# Description of Services

Skin substitutes, also known as bioengineered, tissue-engineered, or artificial skin, are a mixed group of biological, synthetic, or biosynthetic materials that can provide temporary or permanent coverage of wounds of various etiologies. Their goal is to mimic the properties of normal skin to create an environment to promote healing. Skin substitutes are an important adjunctive treatment in the management of acute or uninfected chronic wounds, in addition to other soft tissue indications.

No universal classification system exists that allows for simple categorization of all the products that are currently commercially available. The most recent system by Davison-Kotler et al. (2018) organized skin substitutes according to the following factors:

- Cellularity (cellular or acellular)
- Layering (single layer or bilayer)
- Replaced region (epidermis, dermis, or both)
- Materials used (biological, synthetic, or both)
- Permanence (temporary or permanent)

Kumar and Gupta (2008; updated 2023) developed the most commonly used classification system, in which three classes were proposed:

- Class 1 skin substitute:
  - Temporary impervious dressing materials without negative pressure
    - Single-layer material:
      - Naturally occurring membrane/cover as a biological dressing substitute; for example, amniotic membrane or potato peel
      - Single-layer synthetic skin dressing material substitute; for example, a synthetic polymer sheet
    - Bilayered tissue-engineered material
  - Temporary impervious dressing materials with negative pressure; for example, a limited access dressing without interface material like a sponge used in vacuum-assisted closure therapy. Under limited access dressing collection will be removed by negative pressure, and it will prevent/clear an infection, leading to healing or requiring further surgical intervention for healing
- Class 2 skin substitute – single-layer durable substitutes:
  - Epidermal substitutes
  - Dermal substitutes (bovine collagen sheet, porcine collagen sheet, and bovine collagen matrix)
- Class 3 skin substitute – composite skin substitutes:
  - Skin graft (allograft-cadaver skin, xenograft-pig)
  - Bioengineered skin

The most common commercially available skin substitute products are acellular dermal substitutes made from natural biological materials from which the living cells have been removed; these are used to treat and manage chronic wounds and include decellularized donated human dermis, human placental membranes, and animal tissue. Regardless of the source, the skin substitute provides a matrix into which cells can migrate to induce tissue regeneration and begin wound healing.

## Chronic Wounds

Wounds are disturbances of the skin's structural and functional integrity and generally move through separate phases of healing until the skin's structure and function are restored. Individuals with chronic wounds, such as diabetic foot ulcers, pressure ulcers, and venous leg ulcers, experience loss of function, pain, wound recurrence, and significant morbidity. The standard of care for all chronic wound types includes performing debridement of necrotic tissue; maintaining moisture balance; preventing and treating infection; correcting ischemia; and using compression (for venous leg ulcers) and offloading (for diabetic foot ulcers). Four weeks of standard treatments without a 50% reduction in wound size may require a change of or additional therapies.

## Burns

For burn injuries, historically, autologous skin grafts have been the only way to provide skin coverage following debridement. However, this can result in disfigurement and scarring of the donor site as well as the potential lack of donor

sites in severe cases. Dermal substitutes are an acceptable option for acute partial- or full-thickness burns as well as partial-thickness hypertrophic scars and contractures.

### Other Soft Tissue Indications

Skin and soft tissue substitutes can also be used for repair, reconstruction, and reinforcement of tendons; injection laryngoplasty; various cardiac applications, including pericardial reconstruction, valve reconstruction, and acquired vascular defects; and trauma that results in skin avulsions and degloving injuries.

The number of products and the rate at which they are being developed and becoming available for use clinically make it a challenge to perform high-quality studies to compare the effectiveness of one product with that of another. Many skin and tissue substitutes are included in ongoing clinical trials. Refer to ClinicalTrials.gov for more information (Accessed September 30, 2025).

## Clinical Evidence

### Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes

Sui et al. (2024) conducted a systematic review of 15 randomized controlled trials (RCTs) to evaluate the effectiveness and safety of the application of dermal matrix therapy as an adjuvant treatment to standard of care (SOC). Diabetic foot ulcers (DFUs) can lead to diabetic foot infection, lower leg amputation, and even mortality. While SOC practices have been known as the gold standard for DFU care, SOC alone may not be enough to heal all DFUs and prevent recurrence. This study included a total of 1,524 individuals. Of them, 689 were treated with SOC alone, while 835 received SOC plus dermal matrix. Compared with the SOC group, a significantly shorter time [mean difference (MD), 2.84; 95% CI, 1.37-4.32; $p < 0.001$] was required to achieve complete healing in the dermal matrix group. A significantly higher complete healing rate [odds ratio (OR), 0.40; 95% CI, 0.33-0.49; $p < 0.001$] and lower overall [risk ratio (RR), (1.83; 95% CI, 1.15-2.93; $p = 0.011$*) and major (RR, 2.64; 95% CI, 1.30-5.36; $p = 0.007$)] amputation risks were achieved in the dermal matrix group compared with the SOC group. No significant difference in the wound area, ulcer recurrence rate, and complication risk between the two groups was observed. Study limitations include that (1) a small sample size was included; (2) products among the manufacturers varied, which may have resulted in bias; (3) the trials were not blinded; (4) there was a lack of concealment to the investigator; and (5) follow-up times varied. The authors concluded that dermal matrix used as an adjuvant therapy in conjunction with SOC effectively improved the healing process of DFUs and reduced the amputation risk compared with SOC alone. This use of dermal matrix was also well tolerated by the individuals, with no additional risk of complications. (Cazzell et al., 2017, 2019b, and Zelen et al., 2016, are included in this study.)

Alomairi et al. (2024) conducted a systematic review and meta-analysis to assess the application and effectiveness of human amniotic membrane (HAM) in the treatment of diabetic and venous leg ulcers to improve the management of chronic wounds. This review included 10 RCTs involving 633 individuals who were randomly assigned to either a treatment group receiving amniotic membrane (n = 323) or a control group receiving SOC (n = 310). HAM was used in all studies rather than synthetic types. Diabetes was the primary cause of the ulcer. The ulcers had a mean size of 4.3 $cm^2$ in the standard care group and 3.6 $cm^2$ in the amniotic membrane group. Findings revealed that HAM treatment significantly accelerated ulcer closure, with over 90% complete healing compared with standard care. The authors noted that a number of complications occurred during treatment. The follow-up was limited to 12 to 16 weeks, proving only short-term efficacy and exposing possible complications from the treatment itself. Study limitations include a limited number of RCTs, small sample sizes in some studies, and large population of older male individuals, which may have affected healing times. In addition, no standardized protocol for HAM preparation was followed, which possibly affected product quality. The majority of the studies focused on individuals with diabetes with leg ulcers. Also, short-term follow-up across trials varied between 6 and 16 weeks, emphasizing the need to evaluate HAM's long-term efficacy and safety. Added research is needed, particularly focusing on a diverse array of cutaneous ulcers, given that the majority of the studies primarily addressed diabetic ulcers and often had small sample sizes. (Serena et al., 2022, Serena et al., 2020, Snyder et al., 2016, Bianchi et al., 2018, DiDomenico et al., 2016, Lavery et al., 2014, Zelen et al., 2014, Tettelbach et al., 2019, Zelen et al., 2013, and Zelen et al., 2016, are all included in this review.)

A Hayes Health Technology Assessment for Skin Substitutes for Venous Leg Ulcers in Adults concluded that a low-quality body of evidence provided consistent evidence, which suggests that acellular and cellular skin substitutes may improve healing of chronic venous leg ulcers when used in conjunction with standard wound care (SWC). The Hayes report gives a “C” rating for the use of acellular or cellular skin substitutes as an adjunct to SWC to treat adults with chronic, uninfected venous leg ulcers that have not healed with SWC alone. Evidence directly comparing different cellular skin substitutes with SWC alone and for skin substitute products or types is extremely limited and of very low quality. Skin substitutes

appear to be safe, and no major safety concerns were reported. Additional large, well-designed clinical trials are needed to better evaluate the comparative effectiveness and safety of skin substitutes as adjuncts to SWC and as alternatives to other skin substitutes. The skin substitutes that were a part of the evidence base for this report included EPIFIX, TheraSkin, Talymed, and PriMatrix (Hayes, Skin Substitutes for Venous Leg Ulcers in Adults, 2020; updated 2023).

A Hayes report (2020; updated 2023) for acellular skin substitutes for chronic foot ulcers in adults with diabetes indicates that there is an overall low-quality body of evidence that suggests that acellular skin substitutes appear to heal more chronic DFUs than SWC alone and in a shorter period of time. While acellular skin substitutes appear to have some benefits over cellular skin substitutes, in terms of the incidence, time to healing, and possibly quality of life, no definitive conclusions can be drawn regarding comparative effectiveness and safety of these products due to the limited number of studies overall; this also includes the individual skin substitutes. Questions remain about the effect of acellular skin substitutes on the incidence of amputation and ulcer recurrence due to the limited number of studies on these outcomes. Evidence that directly compares different acellular skin substitutes or compares acellular with cellular skin substitutes is extremely limited and of very low quality, resulting in an inability determine whether any one product or product type is superior. The acellular skin substitutes that were part of the evidence base for this report include EPIFIX, EPICORD, AmnioBand, AmnioExcel, MatriStem MicroMatrix, and DermACELL (Hayes, Acellular Skin Substitutes for Chronic Foot Ulcers in Adults with Diabetes Mellitus, 2020; updated 2023).

A Hayes report (2020; updated 2023) for Cellular Skin Substitutes for Chronic Foot Ulcers in Adults with Diabetes indicates that there is an overall low-quality body of evidence that assesses the comparative effectiveness and safety of cellular skin substitutes incremental to SWC alone for the treatment of DFUs in individuals with diabetes. The overall quality of the bodies of evidence comparing cellular skin substitutes with other cellular skin substitutes and cellular skin substitutes with acellular skin substitutes as adjuncts to SWC are very low. While cellular skin substitutes appear to benefit DFU healing over SWC alone, evidence on individual products to assess whether any particular cellular skin substitute is more effective than the others is insufficient. Large, well-designed clinical trials are needed to better evaluate the comparative effectiveness and safety of cellular skin substitutes as adjuncts to SWC and as alternatives to acellular skin substitutes. The cellular skin substitutes that were a part of the evidence base for this report include Affinity, GRAFIX, Matristem MicroMatrix, and TheraSkin (Hayes, Cellular Skin Substitutes for Chronic Foot Ulcers in Adults with Diabetes Mellitus, 2020; updated 2023).

In a technical brief prepared for the Agency for Healthcare Research and Quality (AHRQ), Snyder et al. (2020) evaluated skin substitutes for treating chronic wounds. Systematic reviews/meta-analyses, RCTs, and prospective, nonrandomized comparative studies that examined commercially available skin substitutes in individuals with DFUs, venous leg ulcers, pressure ulcers, and arterial leg ulcers were included in the review. Overall, 76 commercially available skin substitutes were identified and categorized based on the Davison-Kotler classification system. In total, 68 (89%) were categorized as acellular dermal substitutes, mostly replacements from human placental membranes and animal tissue sources. Three systematic reviews and 22 RCTs examined the use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in DFUs, pressure ulcers, and venous leg ulcers. Overall, 21 ongoing clinical trials (all RCTs) examined an additional nine skin substitutes with comparable classifications. EPIFIX was reviewed in five studies. GRAFIX/GRAFIX PRIME, MatriStem Wound Matrix/MatriStem MicroMatrix, TheraSkin, and DermACELL were all reviewed in two studies each. The findings of the review included the following:

- While 85% of studies examining acellular dermal substitutes described the experimental intervention as favorable over SOC for wound healing and shorter healing time, insufficient data are available to determine whether wound recurrence or other sequela are less frequent with acellular dermal substitutes. Only three studies compared cellular dermal substitutes with SOC. Clinical evidence for cellular dermal substitutes may be limited by the lack of robust, well-controlled clinical trials of these products in this category.
- Of the six head-to-head, comparative studies, findings from five studies did not indicate significant differences between skin substitutes in outcomes measured at the latest follow-up (> 12 weeks). The investigators concluded that the current evidence base may be insufficient to determine whether one skin substitute product is superior to another.
- The investigators found little information on the long-term effects of using skin substitutes. Wound recurrence was seldom reported, and potential toxic and carcinogenic effects are not known. Information on amputations and hospitalizations due to infections is also missing. Before findings can be relied on, more data are needed on hospitalization, pain reduction, need for amputation, exudate, odor control, and return to baseline activities of daily living and function.
- The investigators indicated that variation in study designs reduces the ability to compare outcomes across studies. For example, the investigators identified 20 different criteria in 38 (published and ongoing) studies that reported a wound size inclusion criterion. Sizes ranged from as small as 0.5 to 100 $cm^2$. Overall, 1 to 25 $cm^2$ was the most common range used as a wound size inclusion criterion. More than 4 weeks was the most common wound duration inclusion criterion (25 studies), while a few studies allowed up to 52 weeks. Only six published studies reported on

wound recurrence after 12 weeks. Given the variation in these and other study design features, the investigators indicated that research in this field may benefit from a more standardized study design.
- The investigators found that the industry funded 20 of 22 RCTs included in this report, which raises significant concerns about possible publication bias and selective outcome reporting; results unfavorable to the industry may not be reported or published.

According to the investigators, this technical brief's clearest implications are the lack of studies examining the efficacy of most skin substitute products and need for better-designed studies that provide more clinically relevant data. The investigators indicated that future studies may be improved by using a 4-week run-in period before study enrollment and at least a 12-week study period. Future studies should also report whether wounds recur during the 6-month follow-up.

Alvaro-Afonso et al. (2020) reviewed the recent advances in dermo-epidermal skin substitutes (DSSs) for the treatment of DFUs. The PubMed and Cochrane databases were systematically searched for systematic reviews published after 2013 and for RCTs. A retrospective evaluation of 28 RCTs was performed, without meta-analysis. Four of these used EPIFIX, including three that compared it with SOC, with two also reviewed in the Su systematic review reported above. Rates of complete wound closure and time to healing were examined for 17 commonly available DSSs. Healing rates after 12 weeks and time to complete closure of DFUs were heterogeneous among the 28 RCTs. The best healing rates at 12 weeks were accomplished with dermal cellular substitutes (EPIFIX, 100%; AmnioBand, 85%). The authors concluded that based on these studies, DSSs used in conjunction with standard care appear to improve the healing rates of DFUs compared with standard care alone. The authors indicated that new studies with more homogeneous samples are needed to ascertain the role of ulcer size, duration, depth, and/or type in the efficacy of DSSs. According to the authors, future RCTs should include individuals with severe comorbidities to be more representative of clinical reality.

Gordon et al. (2019) conducted a systematic review to determine the efficacy of biological skin substitutes for healing DFUs. Some products included in this review were AmnioExcel, DermACELL, EPICORD, EPIFIX, GRAFIX, MatriStem, and TheraSkin. The main objective was to calculate a pooled risk ratio for the proportion of wounds completely closed by 12 weeks. Secondary objectives included a pooled risk ratio for the proportion of wounds completely closed by 6 weeks and the mean time to healing. Biological skin substitutes were organized both very specifically into product brand and more broadly by four main groups based on product composition: allografts/xenografts, cultured skin grafts, dermal substitutes, and biosynthetic dressings. Overall, 25 studies were identified that assessed the proportion of complete wound closure by 12 weeks. Wounds treated with biological dressings were 1.67 times more likely to heal by 12 weeks than those treated with SOC dressings ($p < 0.00001$). Five studies assessed the proportion of complete wound closure by 6 weeks. Wounds treated with biological dressings were 2.81 times more likely to heal by 6 weeks than those treated with SOC dressings ($p = 0.0001$). Descriptively, 29 of 31 studies that assessed time to healing favored biological dressings over SOC dressings. Cultured skin grafts did not show a statistical difference over SOC. The authors concluded that this systematic review provides supporting evidence that biological skin substitutes are more effective than SOC dressings at healing DFUs by 12 weeks. This review has several study limitations, one being that the individual products were assessed in only one or two studies. Complete wound healing was assessed at 12 weeks, but the mean time to healing in that time periods was not assessed. Finally, adverse effects of the skin products were not mentioned. Future studies must address the relative benefits with different skin substitutes as well as the long-term implications of these products.

## Skin and Soft Tissue Substitutes

### *Abiomend Membrane and Abiomend Hydromembrane*

Studies are lacking regarding the use of Abiomend Membrane and Abiomend Hydromembrane for wound treatment. Therefore, it is not possible to determine whether Abiomend Membrane or Abiomend Hydromembrane has a beneficial effect on health outcomes.

Abiomend Membrane and Abiomend Hydromembrane (Amnio Technology) are amniotic membrane products that are used as a wound covering and act as a barrier for full- and partial-thickness, chronic, and acute wounds.

### *Abiomend Xplus Membrane and Abiomend Xplus Hydromembrane*

Studies are lacking regarding the use of Abiomend Xplus Membrane and Abiomend Xplus Hydromembrane for wound treatment. Therefore, it is not possible to determine whether Abiomend Membrane or Abiomend Xplus Hydromembrane has a beneficial effect on health outcomes.

Abiomend Xplus Membrane and Abiomend Xplus Hydromembrane (Amnio Technology) are amniotic membrane products that are used as a wound covering and act as a barrier for full- and partial-thickness, chronic, and acute wounds.

## *ACApatch*

Studies are lacking regarding the use of ACApatch for wound treatment. Therefore, it is not possible to determine whether ACApatch has a beneficial effect on health outcomes.

ACApatch (RegenTX Partners, LLC) is a dehydrated allograft composed of three layers: two amnion layers and one chorion layer intended to act as a barrier, providing protective coverage from the surrounding environment for acute and chronic wounds.

## *Acelagraft*

Due to a lack of sufficient studies on Acelagraft for wound treatment, it is currently not possible to determine whether Acelagraft has a beneficial effect on health outcomes.

Acelagraft (RMBB Health) is a bilayered, decellularized, dehydrated HAM allograft. Acelagraft acts as a protective barrier against external elements and is used to cover both acute and chronic wounds. It is indicated for surgical sites; partial- and full-thickness wounds; traumatic injuries; burns; diabetic, venous, arterial, and pressure ulcers; and wounds with exposed tendon, muscle, or bone.

## *Acesso, Acesso AC, Acesso DL, Acesso TL, and Acesso TrifACA*

Studies are lacking regarding the use of Acesso, Acesso AC, Acesso DL, Acesso TL, and Acesso TrifACA for wound treatment. Therefore, it is not possible to determine whether Acesso, Acesso AC, Acesso DL, Acesso TL, or Acesso TrifACA has a beneficial effect on health outcomes.

Acesso (Dynamic Medical Services, LLC) is a sterile, single-layered HAM that is intended to serve as a wound barrier or protective covering for acute and chronic wounds.

Acesso AC (Dynamic Medical Services, LLC) is a dual-layer human amnion/chorion membrane that is intended to serve as a protective covering or barrier for acute and chronic wounds.

Acesso DL (Dynamic Medical Services, LLC; Surgenex®) is a dehydrated, dual-layered HAM allograft that is intended to serve as a barrier or cover for acute and chronic wounds.

Acesso TL (Dynamic Medical Services, LLC; Surgenex) is a dehydrated allograft that is derived from donated human placental birth tissue. Acesso TL membrane is a triple-layer amniotic membrane that is intended for use “over the wound” and “as a barrier” or “protective coverage…to acute and chronic wounds.”

Acesso TrifACA (Dynamic Medical Services, LLC) is a full-thickness amnion/chorion/amnion membrane that is provided as a sterile, single-use, dehydrated, resorbable allograft derived from donated human placental tissue. It is intended for use as a protective barrier for acute and chronic wounds.

## *Activate Matrix*

Studies are lacking regarding the use of Activate Matrix for wound treatment. Therefore, it is not possible to determine whether Activate Matrix has a beneficial effect on health outcomes.

Activate Matrix consists of all three layers of the placental membranes, including the amnion, intermediate layer, and chorion. It is a minimally manipulated human placental membrane product that is derived from donated placental tissues that retain the structural and functional characteristics of the tissues. The final product is dehydrated and composed of extracellular matrix proteins; it serves as a natural, biological barrier or wound cover.

## *AdvoGraft Dual and AdvoGraft One*

Studies are lacking regarding the use of AdvoGraft Dual and AdvoGraft One for wound treatment. Therefore, it is not possible to determine whether AdvoGraft Dual or AdvoGraft One has a beneficial effect on health outcomes.

AdvoGraft Dual (RMBB Health) is a dual-layer amniotic membrane that is derived from processed human placental tissue and intended for use as a barrier and cover for acute and chronic wounds.

AdvoGraft One (RMBB Health) is a single-layer amniotic membrane that is intended for use as a barrier and cover for acute and chronic wounds.

## *AeroGuard and NeoGuard*

Studies are lacking regarding the use of AeroGuard and NeoGuard for wound treatment. Therefore, it is not possible to determine whether AeroGuard or NeoGuard has a beneficial effect on health outcomes.

AeroGuard (C5 Biomedical, LLC), a dehydrated, single-layer HAM allograft product that is derived from donated, healthy human birth tissue, is intended for homologous use as a protective wound covering or barrier for acute and chronic wounds.

NeoGuard (C5 Biomedical, LLC), a dehydrated, double-layer HAM allograft product that is derived from donated, healthy human birth tissue, is intended for homologous use as a protective wound covering or barrier for acute and chronic wounds.

## *Affinity*

There are few published studies that address the use of Affinity. Therefore, it is not possible to determine whether Affinity has a beneficial effect on health outcomes.

Affinity (Organogenesis Inc.) is a fluid membrane allograft that is intended for clinical use in wound repair and healing.

Refer to the above section titled Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes for additional articles/reports that evaluate Affinity.

An ECRI Clinical Evidence Assessment for Affinity Amniotic Allograft for Treating Diabetic Foot Ulcers indicates that evidence from one RCT (Serena et al., 2020, as seen below) and one retrospective case series indicates that Affinity is safe and promotes healing of DFUs more than standard care alone. However, the RCT enrolled few individuals, and additional RCTs are needed to verify findings and enable conclusions. Large RCTs that compare Affinity with standard care and other tissue-based wound care products are needed to warrant comparative-effectiveness conclusions. (Updated June 20, 2024.)

Serena et al. (2020) conducted a multicenter, prospective RCT across 14 centers to assess clinical outcomes associated with the use of hypothermically stored amniotic membrane plus SOC compared with SOC alone in the treatment of DFUs over a 16-week study period (12-week treatment phase and a 4-week follow-up phase). Overall, 76 participants with DFUs were treated with either Affinity plus standard care (n = 38) or standard care alone (n = 38). Wound closure in the Affinity group was significantly greater than that in the control group at both 12 weeks (55% vs. 29%; p = 0.02) and 16 weeks (58% vs. 29%; p = 0.01). At 16 weeks, wound closure was reported in 60% of Affinity participants vs. 48% of control participants (p = 0.04). The authors reported that the probability of wound closure with Affinity vs. standard care increased by 75% (hazard ratio, 1.75). Limitations include that the study lacked blinding and that it was conducted under carefully controlled conditions. The authors concluded that the use of Affinity increased the frequency and probability of DFU wound closure. When used as an adjunct to SOC, hypothermically stored amniotic membrane significantly reduced baseline ulcer area, depth, and volume. Additional data from well-designed trials are needed to support these conclusions. (Included in ECRI above.)

## *AlloGen*

There are few published studies that address the use of AlloGen. Therefore, it is not possible to determine whether AlloGen has a beneficial effect on health outcomes.

AlloGen (VIVEX Biologics, Inc.) is a liquid matrix that is derived from amniotic fluid. AlloGen is intended to act as a cushion to support joint capsules and other injured or traumatized tissues for the treatment of nonhealing wounds and burn injuries.

## *alloPLY*

Studies are lacking regarding the use of alloPLY for wound treatment. Therefore, it is not possible to determine whether alloPLY has a beneficial effect on health outcomes.

alloPLY (RegenTX Partners, LLC) is a dehydrated, dual-layer epithelium/basement membrane allograft that retains the amniotic membrane's key structural components related to its utility to serve as a barrier. alloPLY is intended to be used as a wound cover and barrier.

## *AlloSkin*

There are few published studies that address the use of AlloSkin. Therefore, it is not possible to determine whether AlloSkin has a beneficial effect on health outcomes.

AlloSkin (AlloSource) is a meshed human allograft skin for acute and chronic wound therapy. It comprises cadaveric epidermis and dermis.

Moravvej et al. (2016) evaluated allogeneic fibroblasts on meshed split-thickness skin grafts (STSGs) in 14 participants. After debridement and wound excision, a meshed STSG was used to cover the entire wound. AlloSkin (all fibroblasts cultured on a combination of silicone and glycosaminoglycan) was applied on one side, and petroleum jelly-impregnated gauze (Iran Polymer and Petrochemical Institute) was applied on the other. The healing time, scar formation, and pigmentation score were assessed for the participants. AlloSkin demonstrated good properties compared with petroleum jelly-impregnated gauze. The average healing time (8.8 days), compared with that in the petroleum jelly group (13.6 days), and hypertrophic scar formation were significantly different between the two groups. The difference in scar formation became insignificant after 12 months. In addition, the skin pigmentation score in the AlloSkin group was closer to normal. The authors concluded that AlloSkin grafting, including fibroblasts on meshed STSGs, may be a useful method to reduce healing time and scar size and may require less autologous STSGs in extensive burns, in which a high percentage of skin is burned and for which available donor sites are lacking. Larger prospective, controlled clinical studies are needed to compare the effectiveness of human skin allograft with that of standard care.

## *AlloWrap*

There are few published studies that address the use of AlloWrap. Therefore, it is not possible to determine whether AlloWrap has a beneficial effect on health outcomes.

AlloWrap (AlloSource) is a HAM that is designed to provide a biological barrier following surgical repair.

## *AmchoPlast, AmchoPlast EXCEL, and AmchoPlast FD*

Studies are lacking regarding the use of AmchoPlast, AmchoPlast EXCEL, or AmchoPlast FD for wound treatment. Therefore, it is not possible to determine whether AmchoPlast, AmchoPlast EXCEL, or AmchoPlast FD has a beneficial effect on health outcomes.

AmchoPlast (LifeCell) is a minimally manipulated, dehydrated human amnion/chorion membrane (dHACM) allograft that is intended for use as a protective barrier and cover that offers protection from the surrounding environment in repair and reconstruction procedures.

AmchoPlast EXCEL (Cellution Biologics/LifeCell) is a minimally manipulated, dehydrated human amnion-chorion membrane allograft for homologous use. It acts as a barrier and provides protective coverage for acute and chronic wounds from the surrounding environment.

AmchoPlast FD (LifeCell) is a sterile, lyophilized allograft derived from donated human amnion-chorion membrane. It consists of a basement membrane and stromal matrix collagen layer.

## *AmchoThick*

Studies are lacking regarding the use of AmchoThick for wound treatment. Therefore, it is not possible to determine whether AmchoThick has a beneficial effect on health outcomes.

AmchoThick (Cellution Biologics) is a dehydrated human amnion-chorion amnion membrane allograft that acts as a barrier and provides protective coverage for acute and chronic wounds from the surrounding environment.

## *American Amnion, American Amnion AC, and American Amnion AC Tri-Layer*

Studies that address the use of American Amnion, American Amnion AC, and American Amnion AC Tri-Layer are lacking. Therefore, it is not possible to determine whether American Amnion, American Amnion AC, and/or American Amnion AC Tri-Layer have a beneficial effect on health outcomes.

American Amnion (BioStem Technologies) is a decellularized human amniotic allograft product that is derived from placental tissues, which are sterilized by e-beam irradiation. American Amnion is intended for use as a protective covering for soft tissue wounds.

American Amnion AC (BioStem Technologies) is a decellularized human amniotic and chorionic allograft product that is derived from placental tissues, which are sterilized by e-beam irradiation. American Amnion AC is intended for use as a protective covering for soft tissue wounds.

American Amnion AC Tri-Layer (BioStem Technologies) is a decellularized human amniotic, intermediate, and chorionic allograft product that is derived from placental tissues, which are sterilized by e-beam irradiation. American Amnion AC Tri-Layer is intended for use as a protective covering for soft tissue wounds.

### *AmniCore Pro*

Studies are lacking regarding the use of AmniCore Pro for wound treatment. Therefore, it is not possible to determine whether AmniCore Pro has a beneficial effect on health outcomes.

AmniCore Pro (Stability Biologics) comprises donated amniotic membrane and chorionic membrane, whereas all other AmnioCore brands comprise only amnionic membranes. The AmnioCore Pro is a dual-layer allograft with an amnion inferior surface and a chorion superior surface.

### *AmniCore Pro+*

Studies are lacking regarding the use of AmniCore Pro+ for wound treatment. Therefore, it is not possible to determine whether AmniCore Pro+ has a beneficial effect on health outcomes.

AmniCore Pro+ (Stability Biologics) is a three-layer allograft that comprises amniotic membrane and chorionic membrane, whereas AmnioCore Pro is a dual-layer amnion/chorion graft; all the other AmnioCore brands comprise only amnionic membranes. The AmnioCore Pro+ is a three-layer allograft with an amnion inferior surface, chorion inner layer, and amnion superior surface.

### *Amnio Burgeon Dual-Layer Membrane*

Studies are lacking regarding the use of Amnio Burgeon Dual-Layer Membrane for wound treatment. Therefore, it is not possible to determine whether Amnio Burgeon Dual-Layer Membrane has a beneficial effect on health outcomes.

Amnio Burgeon Dual-Layer Membrane (OneBioTech) is an amniotic membrane product that is used as a wound covering and acts as a barrier for full- and partial-thickness, chronic, and acute wounds.

### *Amnio Burgeon Membrane and Hydromembrane*

Studies are lacking regarding the use of Amnio Burgeon Membrane and Hydromembrane for wound treatment. Therefore, it is not possible to determine whether Amnio Burgeon Membrane and Hydromembrane has a beneficial effect on health outcomes.

Amnio Burgeon Membrane and Hydromembrane (OneBioTech) is an amniotic membrane product that is used as a wound covering and acts as a barrier for full- and partial-thickness, chronic, and acute wounds.

### *Amnio Burgeon Xplus Membrane and Xplus Hydromembrane*

Studies are lacking regarding the use of Amnio Burgeon Xplus Membrane and Xplus Hydromembrane for wound treatment. Therefore, it is not possible to determine whether Amnio Burgeon Xplus Membrane and Xplus Hydromembrane has a beneficial effect on health outcomes.

Amnio Burgeon Xplus Membrane and Xplus Hydromembrane (OneBioTech) is an amniotic membrane product used as a wound covering and acts as a barrier for full- and partial-thickness, chronic, and acute wounds.

### *AmnioCore SL*

Studies are lacking regarding the use of AmnioCore SL for wound treatment. Therefore, it is not possible to determine whether AmnioCore SL has a beneficial effect on health outcomes.

AmnioCore SL (Stability Biologics) is a single-layer, allogeneic amniotic membrane allograft for use as a barrier and is applied as a single-use covering.

### *AmnioTX*

Studies are lacking regarding the use of AmnioTX for wound treatment. Therefore, it is not possible to determine whether AmnioTX has a beneficial effect on health outcomes.

AmnioTX (RegenTX Partners, LLC) is a dehydrated, dual-layer amniotic membrane protective wound covering that is intended to be used as a barrier that protects wounds.

### *Amnio Quad-Core*

Studies are lacking regarding the use of Amnio Quad-Core for wound treatment. Therefore, it is not possible to determine whether Amnio Quad-Core has a beneficial effect on health outcomes.

Amnio Quad-Core (Stability Biologics) comprises donated human tissue that has been screened, recovered, and serologically/microbiologically tested at Clinical Laboratory Improvement Amendments-certified laboratories in adherence to U.S. Food and Drug Administration, state, and American Association of Tissue Banks requirements. Amnio Quad-Core is a four-layer, allogeneic amniotic membrane allograft for use as a barrier and is applied as a single-use covering.

### *Amnio Tri-Core Amniotic*

Studies are lacking regarding the use of Amnio Tri-Core Amniotic for wound treatment. Therefore, it is not possible to determine whether Amnio Tri-Core Amniotic has a beneficial effect on health outcomes.

Amnio Tri-Core Amniotic (Stability Biologics) is a three-layer, allogeneic amniotic membrane allograft for use as a barrier and is applied as a covering.

### *AmnioAMP-MP*

There are few published studies that address the use of AmnioAMP-MP. Therefore, it is not possible to determine whether AmnioAMP-MP has a beneficial effect on health outcomes.

AmnioAMP-MP (CellGenuity Regenerative Science) amniotic membrane is a sterile human tissue allograft membrane patch that is intended for homologous use to cover and protect a recipient's tissue; it is used for acute and chronic wounds and as a barrier to enhance soft tissue healing after a primary surgical repair or general reconstructive surgery to reduce scar tissue formation and enhance soft tissue healing.

### *Amnio Wound*

There are few published studies that address the use of Amnio Wound. Therefore, it is not possible to determine whether Amnio Wound has a beneficial effect on health outcomes.

Amnio Wound (Alpha Tissue, LLC) is a lyophilized HAM allograft that comprises an epithelial layer and two fibrous connective tissue layers; it is specifically processed to be used for the repair and replacement of lost or damaged dermal tissue.

### *AmnioWrap2*

There are few published studies that address the use of AmnioWrap2. Therefore, it is not possible to determine whether AmnioWrap2 has a beneficial effect on health outcomes.

AmnioWrap2 (Direct Biologics LLC) is a placental-based allograft that comprises unseparated amnion and chorion membranes, including the intact intermediate layer. It is indicated as a protective covering when placed over a wound bed or surgical site and provides the key components found in human placental tissues, including an intact extracellular matrix, growth factors, and cytokines.

### *AmnioArmor*

There are few published studies that address the use of AmnioArmor. Therefore, it is not possible to determine whether AmnioArmor has a beneficial effect on health outcomes.

AmnioArmor (Bone Bank Allografts, a subsidiary of Globus Medical, Inc.) is a dehydrated HAM allograft that is derived from placental tissue submucosa. It is intended as a wound covering for acute and chronic wounds.

### *AmnioBand Viable Membrane and Guardian*

There is insufficient evidence to support the use of AmnioBand Viable Membrane and Guardian due to study limitations. Larger studies are needed to establish safety, efficacy, and long-term outcomes.

AmnioBand and Guardian (MTF Biologics) are human tissue allografts that are made of donated placental membrane. Although marketed under two different brand names, the products are identical.

Refer to the above section titled Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes for additional articles/reports that evaluate AmnioBand.

A 2020 ECRI Clinical Evidence Assessment concluded that while the evidence from two small RCTs and one case series suggests that AmnioBand may improve wound healing compared with Apligraf® and when added to standard care in individuals with DFUs, the studies include too few individuals to be conclusive; additionally, the studies do not validate each other because each one addressed a different comparison. Larger, double-blinded RCTs are needed to validate findings, compare AmnioBand with other skin grafts, assess AmnioBand's use in different chronic wound types, and report on longer-term outcomes.

In a multicenter RCT, Serena et al. (2022) evaluated the safety and effectiveness of weekly and biweekly applications of AmnioBand, a dehydrated human amnion and chorion allograft (dHACA), plus SOC compared with SOC alone for chronic venous leg ulcers. This study included participants with chronic venous leg ulcers at eight wound care centers across the United States. The main end point was the number of healed ulcers at 12 weeks. Secondary endpoints included the number of ulcers that achieved 40% closure at 4 weeks, along with any adverse effects. SOC included cleaning and debriding of the ulcer, application of multilayer compression bandaging, and instructions to keep the leg elevated and the bandage dry. Inclusion criteria included age ≥ 18 years; Ankle-Brachial Index of > 0.75, skin perfusion pressure of > 30 mmHg, or transcutaneous oximetry measurement of > 30 mmHg; venous leg ulcer wound area of ≥ 2 $cm^2$ but < 20 $cm^2$; duration of longer than 1 month; extension of the venous leg ulcer through the full thickness of the skin but not down to the muscle, tendon, or bone; and a study ulcer with a clean, granulating base, with minimal adherent slough, that was treated with compression therapy for a minimum of 14 days prior to randomization. Participants were excluded if the ulcer was infected, was suspicious for cancer, was caused by a condition other than venous insufficiency, required treatment with negative-pressure wound therapy or hyperbaric oxygen therapy, or had previously been treated with cellular and/or tissue-based products. Participants were also excluded if they had a history of HIV/AIDS or drug or alcohol abuse; radiation therapy at the ulcer site; ulcers on the dorsum of the foot or with ≥ 50% of the ulcer below the malleolus; current pregnancy or currently breastfeeding; diabetes, with an hemoglobin $A_{1c}$ ($HbA_{1c}$) of > 12.0 in the past 90 days; renal dysfunction, with a serum creatinine level of ≥ 3.0 mg/dl in the last 90 days; tobacco use in the last 30 days; and a history of liver disease, with active cirrhosis. Of 101 participants screened, 60 participants were eligible and enrolled, with 20 participants randomized to each group. At 12 weeks, significantly more venous leg ulcers healed in the two dHACA-treated groups (75%) than in the SOC group (30%) ($p = 0.001$), even after adjustment for wound area ($p = 0.002$), with an OR of 8.7 (95% CI, 2.2-33.6). There were no significant differences in the proportion of wounds with percentage area reduction (PAR) of ≥ 40% at 4 weeks among all groups. The adverse event rate was 63.5%. Among the 38 adverse events, none were graft or procedure related, and all were resolved with appropriate treatment. Limitations include the lack of blinding and short-term follow-up. The manufacturer assisted with the funding of this study. In conclusion, dHACA and SOC, regardless of frequency (weekly or biweekly), healed approximately 45% more venous leg ulcers than SOC alone. The authors indicated that the use of dHACA should be considered as an adjunct to SOC for nonhealing venous leg ulcers.

Glat et al. (2019; reviewed in the ECRI report above) conducted an RCT, in which dHACA (AmnioBand) was compared with one of the earliest and most commonly accepted tissue-engineered skin substitutes (TESSs) (Apligraf) in the treatment of nonhealing DFUs over a period of 12 weeks, to assess the superiority of healing. Following a 2-week screening period during which participants with DFUs were treated with collagen alginate dressing, 60 participants were randomized at five sites to receive either dHACA or TESSs applied weekly, with weekly follow-up for up to 12 weeks. The mean time to heal in the 6-week time period in the dHACA group was 24 days (95% CI, 18.9-29.2 days) vs. 39 days (95% CI, 36.4-41.9 days) in the TESS group; the mean time to heal at 12 weeks was 32 days (95% CI, 22.3-41.0 days) for dHACA-treated wounds vs. 63 days (95% CI, 54.1-72.6 days) for TESS-treated wounds. The proportion of wounds healed at study completion (12 weeks) was 90% (27/30) in the dHACA group vs. 40% (12/30) in the TESS group. It was concluded that aseptically processed dHACAs heal diabetic foot wounds more reliably and statistically significantly faster than TESSs. Study limitations include the lack of blinding. Another limitation could be the withdrawal of participants at 6 weeks, rather than continuing through 12 weeks of treatment, if their wounds were not sufficiently responding to treatment to ensure individual safety and permit other treatment pathways. An additional limitation is the insufficient follow-up time needed to evaluate long-term outcomes or recurrence. Several of the study authors received research funds from MTF Biologics, which is the manufacturer of AmnioBand.

DiDomenico et al. (2018; reviewed in the Alvaro-Afonso et al. systematic review and ECRI report above) conducted a prospective, randomized, multicenter clinical trial and reported on the full trial results in 80 participants; AmnioBand Membrane dHACA was compared with SOC to evaluate achievement of wound closure in nonhealing DFUs. After a 2-week screening period, during which participants with DFUs were unsuccessfully treated with SOC, participants were randomized to either SOC alone or SOC with dHACA applied weekly for up to 12 weeks. At 12 weeks, 85% (34/40) of the dHACA-treated DFUs healed compared with 33% (13/40) of those treated with SOC alone. The mean time to heal in 12

weeks was significantly faster in the dHACA-treated group than the SOC group: 37 days vs. 67 days. The mean number of grafts used per healed wound during the same time period was 4.0. The authors concluded that aseptically processed dHACAs healed DFUs significantly faster than SOC at 12 weeks. Future studies should (1) consider a comparative arm that uses an advanced skin substitute and (2) allow wounds of greater severity or depth. The findings of the RCT need confirmation through an independently conducted RCT. MTF Biologics funded the study, and several of the study authors are consultants for MTF Biologics.

Paggiaro et al. (2018; reviewed in ECRI report above) performed a systematic review to analyze the scientific evidence found in the literature on the use of the amniotic membrane to stimulate DFU healing. Following the inclusion and exclusion criteria, RCTs were identified, and the risk of bias was analyzed according to the Cochrane Risk of Bias Tool. The authors conducted a meta-analysis of the two outcomes to evaluate the level of evidence. Six clinical trials were identified, with a total of 331 individuals. When examining the wound healing outcome, five studies (Zelen et al., 2016; Zelen et al., 2013b; Snyder et al., 2016; Lavery et al., 2014; DiDomenic et al., 2016) could be used for the meta-analysis. However, for wound healing time, only three studies (Zelen et al., 2016; Lavery et al., 2014; DiDomenic et al., 2016) could be used. The most common risks of bias in the studies were selection, attrition, and detection biases. From the meta-analysis, although the result difference of the intervention group (amnion) in relation to the control group was not statistically significant, it was found that wound healing in the group treated with amniotic membrane occurred 2.32 times more often and was 32 days faster than that in the group that used conventional dressings. The authors concluded that there is no statistical evidence to support the effectiveness of amniotic membrane compared with other conventional dressings. However, there is a clear tendency to use amniotic membrane treatment to result in a larger number of DFUs healing at a quicker rate. According to the authors, the main limitations of this study are the small number of RCTs found and the flaws found in the results that were published in these studies. The authors indicated that these two conditions impaired the statistical analysis and prevented the development of definitive evidence for the use of amniotic membrane for DFUs.

DiDomenico et al. (2017; reviewed in ECRI report above) conducted a retrospective crossover study to evaluate the effectiveness of dHACA in patients who did not respond to SOC treatments and who exited the original, recently published, prospective RCT after experiencing failure with up to 12 weeks of SOC treatment. The RCT, which is referenced above, compared aseptically processed dHACA with SOC; 85% wound closure rates were reported in the dHACA arm, while only 25% of participants in the SOC arm healed. Participants with nonhealing wounds in the SOC arm, after exiting from the original study, were offered weekly adjunctive applications of dHACA (AmnioBand) for up to 12 weeks. The primary end point was the proportion of wounds completely healed at 12 weeks. Secondary end points included the difference in wound area from baseline to the end of study and the PAR. Eleven participants were eligible to participate, and wounds in nine of the 11 participants (82%) healed. The mean wound area decreased from 1.7 to 0.2 $cm^2$, with a corresponding mean PAR of 92%. Of the two wounds that failed to heal, one DFU decreased in area by 91%, and the other decreased by 26%. The authors concluded that the results of this crossover study support the conclusions of the original RCT, which determined that aseptically processed dHACA is an effective means to treat recalcitrant DFUs. Further studies, including comparative clinical trials, may offer additional information on this unique, aseptically processed graft in the healing of chronic wounds.

DiDomenico et al. (2016; reviewed in the Alvaro-Afonso et al. and Paggiaro et al. systematic reviews above) compared aseptically processed dHACA vs. SOC in facilitating wound closure in nonhealing DFUs. Participants with DFUs treated with SOC (offloading, appropriate debridement, and moist wound care) after a 2-week screening period were randomized to either SOC or wound size-specific dHACA (AmnioBand; MTF Biologics) that was applied weekly for up to 12 weeks plus SOC. The primary end point was the percentage of wounds that were healed at 6 weeks between groups. At 6 weeks, 70% (14/20) of the dHACA-treated DFUs healed compared with 15% (3/20) treated with SOC alone. At 12 weeks, 85% (17/20) of the DFUs in the dHACA group healed compared with 25% (5/20) in the SOC group, with a corresponding mean time to heal of 36 and 70 days, respectively. At 12 weeks, the mean number of grafts used per healed wound in the dHACA group was 3.8. The mean wastage at 12 weeks was 40%. One adverse event and one serious adverse event occurred in the dHACA group; neither was graft related. Three adverse events and one serious adverse event occurred in the SOC group. The authors concluded that aseptically processed dHACA heals diabetic foot wounds significantly faster than SOC at 6 and 12 weeks, with minimal graft wastage. The authors indicated that the limitations of this trial include the lack of blinding (participant and investigator) and lack of a soft tissue matrices comparator. Future studies may consider comparing different amniotic tissue forms and allowing wounds of greater severity or depth.

### *AmnioBind or DermaBind TL*

There are few published studies that address the use of AmnioBind or DermaBind TL for wound treatment. Therefore, it is not possible to determine whether AmnioBind or DermaBind TL has a beneficial effect on health outcomes.

AmnioBind or DermaBind TL is a terminally sterilized, dehydrated, full-thickness placental membrane allograft consisting of amnion, chorion, and the associated intermediate (spongy) layer used to treat acute and chronic wounds.

### *AmnioCore*

There are few published studies that address the use of AmnioCore for wound treatment. Therefore, it is not possible to determine whether AmnioCore has a beneficial effect on health outcomes.

AmnioCore (Stability Biologics) is a dual-layer amniotic tissue allograft used to reduce scar tissue formation and modulate inflammation, with natural barrier properties to enhance healing.

### *Amniocyte Plus*

There are few published studies that address the use of Amniocyte Plus for wound treatment. Therefore, it is not possible to determine whether Amniocyte Plus has a beneficial effect on health outcomes.

Amniocyte Plus (Predictive Biotech) is a minimally manipulated amniotic fluid allograft. It is intended for use in repair, reconstruction, replacement, or supplementation of a recipient's cells or tissue.

### *AmnioDefend FT Matrix*

There are few published studies that address the use of AmnioDefend FT Matrix. Therefore, it is not possible to determine whether AmnioDefend FT Matrix has a beneficial effect on health outcomes.

AmnioDefend FT Matrix (Sequence™ LifeScience, Inc.) is a minimally manipulated human placental membrane product that is derived from donated tissue and contains all three layers: amnion, intermediate, and chorion. It preserves the tissue's natural structure and function and is intended to act as a barrier or barrier for acute and chronic wounds.

### *AmnioExcel, AmnioExcel Plus, or BioDExcel*

Evidence to support the use of AmnioExcel, AmnioExcel Plus, or BioDExcel is insufficient due to study limitations. Larger studies are needed to establish safety, efficacy, and long-term outcomes.

AmnioExcel, also marketed under the trade name BioDExcel (Integra LifeSciences Corporation), is a dehydrated human amnion-derived tissue allograft with intact extracellular matrix that is intended to advance soft tissue repair, replacement, and reconstruction. AmnioExcel Plus is an extension of the AmnioExcel and BioDExcel product line that incorporates additional layers of human-sourced amnion and chorion.

Refer to the above section titled Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes for additional articles/reports that evaluate AmnioExcel.

An ECRI report for AmnioExcel (Integra LifeSciences Corporation) for dressing wounds and repairing soft tissue defects indicates that the evidence for AmnioExcel is inconclusive. The studies reviewed have major limitations, which resulted in a high risk of bias. Therefore, the evidence is inconclusive. (ECRI, 2019.)

In an RCT, Lavery et al. (2025) examined the effectiveness of AmnioExcel human amniotic allograft, applied either weekly or biweekly, in the treatment of DFUs during a 12-week period. The study included 40 participants with Wagner grade 1A and 1D DFUs that lasted more than 30 days but less than 6 months. The results showed no statistically significant differences between weekly and biweekly applications in terms of healing incidence (30% vs. 50%; p = 0.20), time to heal (69.3 vs. 45.8 days; p = 0.15), infection rates, and wound area reduction. The findings revealed no statistically significant differences between the two treatment frequencies in terms of healing rates, time to closure, infection rates, and wound size reduction, suggesting that less frequent application may be equally effective. However, the study has several limitations, including a small sample size, which may have limited the statistical power to detect meaningful differences. Additionally, the trial was conducted at a single institution, which may affect the generalizability of the results. The use of a pilot design also indicates that findings are preliminary. Therefore, larger, multicenter trials, with more diverse populations and longer follow-up periods, are needed to confirm these results and better understand the optimal application frequency of AmnioExcel in DFU management.

Paggiaro et al. (2018; reviewed in the AHRQ Technical Report above) performed a systematic review to analyze the scientific evidence found in the literature on the use of the amniotic membrane to stimulate the healing of DFUs. Following the inclusion and exclusion criteria, RCTs were identified, and the risk of bias was analyzed according to the Cochrane Risk of Bias Tool. The authors conducted a meta-analysis of the two outcomes to evaluate the level of evidence. Six clinical trials were identified, with a total of 331 individuals. When examining the wound healing outcome, five studies

(Zelen et al., 2016; Zelen et al., 2013b; Snyder et al., 2016; Lavery et al., 2014; DiDomenic et al., 2016) could be used for the meta-analysis. However, for wound healing time, only three studies (Zelen et al., 2016; Lavery et al., 2014; DiDomenic et al., 2016) could be used. The most common risks of bias in the studies were selection, attrition, and detection biases. From the meta-analysis, although the result difference of the intervention group (amnion) in relation to the control group was not statistically significant, it was found that wound healing in the group treated with amniotic membrane occurred 2.32 times more often and was 32 days than that in the group that used conventional dressings. The authors concluded that there is no statistical evidence to support the effectiveness of amniotic membrane compared with other conventional dressings. However, there is a clear tendency to use amniotic membrane treatment to result in a larger number of DFUs healing at a quicker rate. According to the authors, the main limitations of this study are the small number of RCTs found and the flaws found in the results published in these studies. The authors indicated that these two conditions impaired the statistical analysis and prevented the development of definitive evidence for the use of amniotic membrane for DFUs.

Haugh et al. (2017; reviewed in the AHRQ Technical Report above) performed a meta-analysis that examined RCTs comparing amniotic tissue products with SOC for nonhealing DFUs. A search of three databases identified 596 potentially relevant articles. Application of selection criteria led to the selection of five RCTs. The five selected RCTs represented a total of 311 individuals. Three of the trials included compared EPIFIX, a dehydrated amniotic membrane product, with SOC (Zelen et al., 2013b; Zelen et al., 2015; Zelen et al., 2016). One trial compared the use of dehydrated amniotic membrane allograft (DAMA), which is also a dehydrated amniotic membrane product, and SOC with SOC alone (Snyder et al., 2016). One trial compared GRAFIX, a cryopreserved amniotic product, with SOC (Lavery et al., 2014). The pooled relative risk of healing with amniotic products compared with control was 2.7496. The authors concluded that the current meta-analysis indicates that the treatment of DFUs with amniotic membrane improves healing rates of DFUs. The authors stated that further studies are necessary to confirm the findings identified in these five trials and to determine whether amniotic products have the same impact in all individuals with diabetes seen in clinical practice. The authors also stated that although this analysis indicates that amniotic membrane has a great potential for use in DFUs in clinical practice, individuals in all five of the included trials had to have adequate tissue perfusion and a lack of any signs of infection to enroll. As many individuals who develop DFUs do not have adequate tissue perfusion and often have chronic infections, it is unclear how these products would translate into the everyday clinical care of individuals with diabetes. According to the authors, the lack of follow-up in individuals is a significant limitation of the identified studies and their review.

In a systematic review and meta-analysis, Laurent et al. (2018) assessed the efficacy and time sensitivity of human amnion/chorion membrane treatment in individuals with chronic DFUs. All RCTs that compared human amnion/chorion membrane plus standard therapy and standard therapy alone in individuals with DFUs were included in the analysis. Eligible studies were reviewed, and data were extracted into a standard form. The Cochrane Collaboration's tool for assessing the risk of bias was used. Review Manager version 5.3 software was used for statistical analysis. Data were analyzed using a random effect model. Overall, the initial search of the four databases identified 352 published studies; of these, seven RCTs were ultimately included in the meta-analysis (Zelen et al., 2013b; Zelen et al., 2015; Zelen et al., 2016; DiDomenico et al., 2016; Snyder et al., 2016; Lavery et al., 2014; Mohajeri-Tehrani et al., 2016). The analysis results showed that individuals receiving amniotic membrane plus standard therapy had far fewer incomplete healing wounds than those receiving SOC alone. Assessment of the wound healing state at 4 and 6 weeks revealed that the wound healing state was almost the same, but a net difference of wound healing state was observed at 12 weeks. The authors concluded that human amnion/chorion membrane plus SOC treatment heals DFUs significantly faster than SOC alone. When using the amnion in individuals with DFUs, the optimal times to assess progress in wound healing should be 4 and 12 weeks. According to the authors, the number of studies and sample sizes were not sufficiently large, which can increase biases. The authors stated that further large studies or RCTs are still needed to verify the findings and assess healing in infected DFUs.

Snyder et al. (2016; reviewed in the Paggiaro et al. 2018 systematic review, Haugh et al. 2017 meta-analysis, Laurent et al. 2017 systematic review and meta-analysis, and AHRQ Technology Report above) conducted a study to evaluate DAMA (AmnioExcel) plus SOC compared with SOC alone for the closure of chronic DFUs. This prospective, open-label, randomized, parallel group trial was implemented at eight clinical sites in the United States. Eligibility criteria included adults with type 1 or type 2 diabetes, who had (1) one or more ulcers; (2) a Wagner classification of grade 1 or superficial 2, measuring between 1 $cm^2$ and 25 $cm^2$ in area; (3) more than 1 month with no signs of infection/osteomyelitis; (4) Ankle-Brachial Index of > 0.7; (5) $HbA_{1c}$ of less than 12%; and (6) serum creatinine less than 3.0 mg/dL. Eligible participants were randomized (1:1) to receive either SOC alone (n = 14) or DAMA plus SOC (n = 15) until wound closure or 6 weeks, whichever occurred first. The end point was the proportion of participants with complete wound closure (defined as complete reepithelialization without drainage or need for dressings). Overall, 35% of participants in the DAMA plus SOC cohort achieved complete wound closure at or before week 6 compared with 0% in the SOC-alone cohort. A more robust response was noted in the per-protocol population, with 45.5% of participants in the DAMA plus SOC cohort achieving complete wound closure; 0% of SOC-alone participants achieved complete closure. No treatment-related adverse events

were reported. According to the authors, the results of this study suggest that DAMA is safe and effective in the management of DFUs, but additional research is needed.

## *AMNIOFIX*

There is insufficient evidence to support the use of AMNIOFIX due to study limitations. Larger studies are needed to establish safety, efficacy, and long-term outcomes.

AMNIOFIX (MIMEDX Group, Inc.) is a composite amniotic tissue membrane minimally manipulated to protect the collagen matrix and its natural properties. It is available in sheet/membrane, particulate, and wrap configurations for use in surgical (e.g., spinal fusion, discectomy), soft tissue, tendon, and nerve applications. Other AMNIOFIX products include AMNIOFIX Injectable that is intended for the treatment of tendon and soft tissue injuries.

An ECRI report for AmnioFill™ and AMNIOFIX Allografts (MIMEDX) for Use in Orthopedic Procedures indicates that the evidence is somewhat favorable for AMNIOFIX. Two RCTs and three cases series show that micronized AMNIOFIX injection is safe, relieves pain, and improved function up to 3 months in individuals with tendinopathies and arthritis. The RCTs were related to plantar fasciitis, with three case series related to arthritis and tendinosis. While the evidence is favorable for AMNIOFIX, larger RCTs are needed to validate results and assess long-term outcomes. No studies evaluated AmnioFill in orthopedic procedures (ECRI AmnioFill and AMNIOFIX Allografts (MIMEDX) for Use in Orthopedic Procedures, 2020).

An ECRI report for AMNIOFIX Amnion/Chorion Membrane Allograft (MIMEDX) for Treating Surgical Wounds indicates that the evidence for AMNIOFIX is inconclusive. RCTs comparing AMNIOFIX with other skin substitutes and reporting on individual outcomes (e.g., complete wound healing, quality of life) are warranted to determine the efficacy of AMNIOFIX [ECRI AMNIOFIX Amnion/Chorion Membrane Allograft (MIMEDX) for Treating Surgical Wounds, 2019].

A Hayes report for Human Amniotic Membrane Injections for Treatment of Chronic Plantar Fasciitis indicates that a low-quality body of evidence suggests that HAM injections may result in pain relief and improved function. None of the studies reviewed by Hayes evaluated the comparative effectiveness of amniotic tissue-derived treatments compared with that of other types of injections such as platelet-rich plasma or botulinum toxin; extracorporeal shockwave therapy; and surgery. Substantial uncertainty remains regarding the comparative effectiveness. The studies included for review had a limited follow-up of 12 weeks or less, making it difficult to assess the long-term effects of this treatment. Double-blinded RCTs, with active treatment comparators (injectables, surgery, and extracorporeal shockwave therapy), are needed to evaluate the effectiveness and safety of amniotic tissue–derived allograft treatments for plantar fasciitis. The products evaluated in this report included PalinGen SportFlow, CLARIX FLO, and AMNIOFIX (Hayes, 2019; updated 2022).

Cazzell et al. (2018) conducted a prospective, single-blinded RCT at 14 sites in the United States to evaluate the efficacy of micronized dHACM injection for plantar fasciitis. Participants were randomized to receive one injection, in the affected area, of micronized dHACM (AMNIOFIX Injectable; MIMEDX Group, Inc.) (n = 73) or 0.9% sodium chloride placebo (n = 72). Baseline visual analog scale (VAS) scores were similar between groups. At the 3-month follow-up, mean VAS scores in the treatment group were 76% lower; a 45% reduction occurred in the control group. Foot Function Index-Revised scores in treatment participants had reduced by 60% vs. baseline, whereas control participants had a mean reduction of 40% vs. baseline. Of four serious adverse events, none were related to study procedures. The authors concluded that pain reduction and functional improvement outcomes were statistically significant and clinically relevant, supporting the use of micronized dHACM injection as a safe and effective treatment for plantar fasciitis. The authors indicated that the study's results are limited, as the comparative group received placebo injection; thus, the effectiveness of micronized dHACM allograft vs. that of other advanced therapies cannot be determined. The study is also limited by a short follow-up time.

Ogaya-Pinies et al. (2018; reviewed in the ECRI report above) evaluated if the use of a dHACM allograft wrapped around the neurovascular bundles (NVBs) during a robotic-assisted radical prostatectomy (RARP) would accelerate the return to potency. A total of 940 individuals with a preoperative Sexual Health Inventory for Men of > 20 underwent RARP with some degree of bilateral nerve sparing. Of them, 235 underwent RARP with bilateral placement of a dHACM graft around the NVBs. They were matched in a 1:3 proportion with a similar group of individuals (n = 705) who did not receive the allograft (control group or group 2). The minimum follow-up was 12 months. Postoperative outcomes were analyzed between propensity-matched dHACM graft (group 1) and nongraft groups (group 2). No significant demographic differences were observed between the two groups. Potency was defined as the ability to achieve and maintain satisfactory erections that are firm enough for sexual intercourse, with or without the use of phosphodiesterase 5 inhibitors. The mean time to potency was significantly lower in group 1 (2.37 months) vs. group 2 (3.94 months). The potency recovery rates were superior for group 1 at all early time points measured, except at 12 months. Individuals who received the dHACM wrap around the NVBs after RARP had an accelerated return to potency compared with a similar

control group without the use of the allograft. The study also demonstrated that this faster return to potency occurred regardless of the degree of the nerve-sparing preservation. Younger individuals (< 55 years of age) had the highest overall advantage if they received the graft. The authors concluded that their results indicate that dHACM placement at the site of the prostatic NVB does not increase the risk of biochemical recurrence after RARP, neither in the presence of positive surgical margin, extraprostatic disease, nor high Gleason score. However, potency recovery rates did not differ between groups at 12 months post RARP.

In a systematic review and network meta-analysis, Tsikopoulos et al. (2016) compared the efficacy of different injection therapies for plantar fasciopathy (historically known as plantar fasciitis). Randomized trials comparing various injection therapies in adults with plantar fasciopathy were included. The primary outcome was pain relief. Secondary outcomes included functional disability and composite and health-related outcomes. All outcomes were assessed in the short term (up to 2 months), intermediate term (2-6 months), and medium term (more than 6 months to 2 years). Quality assessment was performed using the Cochrane Risk of Bias Tool. Overall, 22 trials, comprising 1,216 individuals, were included in the review. Dehydrated amniotic membrane injections were significantly superior to corticosteroids in the short term in achieving the primary and composite outcomes. The authors concluded that although dehydrated amniotic membrane provided significant clinical relief at 0 to 2 months, no data about this treatment were available at 2 months and beyond.

Zelen et al. (2013a) reported the results of a randomized clinical trial that examined the efficacy of micronized, dehydrated human amniotic/chorionic membrane (mDHACM) injection as a treatment for chronic refractory plantar fasciitis. Overall, 45 participants were randomized to receive an injection of 2 cc 0.5% Marcaine plain, then either 1.25 cc saline (controls), 0.5 cc mDHACM, or 1.25 cc mDHACM. Follow-up visits occurred over 8 weeks to measure function, pain, and functional health and well-being. Significant improvement in plantar fasciitis symptoms was observed in participants receiving 0.5 cc or 1.25 cc mDHACM vs. controls within 1 week of treatment and throughout the study period. The authors concluded that in individuals with refractory plantar fasciitis, mDHACM is a viable treatment option. According to the authors, larger studies are needed to confirm these findings.

### *AMNIOMATRIX or BioDMatrix*

There are few published studies that address the use of AMNIOMATRIX or BioDMatrix. Therefore, it is not possible to determine whether AMNIOMATRIX or BioDMatrix has a beneficial effect on health outcomes.

AMNIOMATRIX, also marketed under the trade name BioDMatrix (Integra LifeSciences Corporation), is a viable human placental allograft comprising morselized amniotic membrane and amniotic fluid components that are recovered from the same human donor. AMNIOMATRIX may be mixed with normal saline for application to surgical sites and open, complex, or chronic wounds or mixed with the recipient's blood to fill soft tissue defects.

### *Amnio-Maxx and Amnio-Maxx Lite*

There are few published studies that address the use of Amnio-Maxx or Amnio-Maxx Lite for wound treatment. Therefore, it is not possible to determine whether Amnio-Maxx or Amnio-Maxx Lite has a beneficial effect on health outcomes.

Amnio-Maxx (Royal Biologics) is a dehydrated amniotic tissue membrane graft. The dual-layer patch is used for chronic, nonhealing wounds such as DFUs and venous leg ulcers or soft tissue defects. The Amnio-Maxx Lite version is a single layer.

### *AmnioPlast 1 or AmnioPlast 2*

There are few published studies that address the use of AmnioPlast 1 or AmnioPlast 2 for wound treatment. Therefore, it is not possible to determine whether AmnioPlast 1 or AmnioPlast 2 have a beneficial effect on health outcomes.

AmnioPlast 1 (LifeCell) is a minimally manipulated, sterile, dehydrated, monolayered human amnion membrane allograft for homologous use. It is intended to be used as a protective barrier and cover that offers protection from the surrounding environment in repair or reconstruction procedures for ocular diseases and/or abnormalities.

AmnioPlast 2 (LifeCell) is a sterile, minimally manipulated, nonviable, cellular amnion-chorion membrane allograft for homologous use. It is intended to be used as a protective barrier and cover that offers protection from the surrounding environment in repair or reconstruction procedures for ocular diseases and/or abnormalities.

### *AmnioPlast Double*

Due to a lack of sufficient studies on AmnioPlast Double for wound treatment, it is currently not possible to determine whether AmnioPlast Double has a beneficial effect on health outcomes.

AmnioPlast Double (Cellution Biologics) is derived from human placental membrane and retains the tissue's natural structural and functional properties. It serves as a protective barrier for acute and chronic wounds, including partial- and full-thickness wounds, pressure ulcers, venous and diabetic ulcers, vascular ulcers, tunneled or undermined wounds, surgical wounds (e.g., donor sites, grafts, post laser or Mohs surgery, podiatric wounds, wound dehiscence), traumatic wounds (e.g., abrasions, lacerations, burns, skin tears), and draining wounds.

### *AmnioRepair or AltiPly*

There are few published studies that address the use of AmnioRepair or AltiPly for wound treatment. Therefore, it is not possible to determine if AmnioRepair or AltiPly has a beneficial effect on health outcomes.

AmnioRepair and AltiPly (Aziyo Biologics) are human cellular and tissue-based products. They are lyophilized placental membrane allografts that are indicated for use as a biological barrier or wound cover and form a protective cover for a variety of acute and chronic wounds.

### *AmnioText*

There are few published studies that address the use of AmnioText for wound treatment. Therefore, it is not possible to determine whether AmnioText has a beneficial effect on health outcomes.

AmnioText (Regenative Labs) is an amniotic membrane–derived human tissue allograft suspension product. It is intended to serve as a barrier to aid in the repair and healing of a defect.

### *AmnioText Patch*

There are few published studies that address the use of AmnioText Patch for wound treatment. Therefore, it is not possible to determine whether AmnioText Patch has a beneficial effect on health outcomes.

AmnioText Patch (Regenative Labs) is an amniotic membrane-derived human tissue allograft. The product serves as a wound covering and is intended for chronic, nonhealing wounds such as DFUs and venous leg ulcers.

### *Amnion Bio*

There are few published studies that address the use of Amnion Bio for wound treatment. Therefore, it is not possible to determine whether Amnion Bio has a beneficial effect on health outcomes.

The product information for Amnion Bio (Axolotl Biologix) is not currently available.

### *AMNIPLY*

There are few published studies that address the use of AMNIPLY. Therefore, it is not possible to determine whether AMNIPLY has a beneficial effect on health outcomes.

The product information on AMNIPLY is not currently available.

### *APIS*

There are few published studies that address the use of APIS. Therefore, it is not possible to determine whether APIS has a beneficial effect on health outcomes.

APIS (SweetBio® Inc.) is an absorbable, biodegradable skin substitute that comprises gelatin (porcine derived), Manuka honey, and hydroxyapatite that is bioengineered to protect wounds, manage exudate, and maintain a moist environment. Skin substitutes are used to protect large or nonhealing wounds and burns.

### *Apollo FT*

Due to a lack of sufficient studies on Apollo FT for wound treatment, it is currently not possible to determine whether Apollo FT has a beneficial effect on health outcomes.

Apollo FT (Dynamic Medical Services, LLC) is a full-thickness amnion/chorion membrane allograft that is intended for use as a sterile, single-use barrier that provides protective coverage for wounds.

## *Architect*

There are few published studies that address the use of Architect extracellular matrix for wound treatment. Therefore, it is not possible to determine whether Architect extracellular matrix has a beneficial effect on health outcomes.

Architect (Harbor MedTech, Inc.) is a sterile, extracellular, equine-derived collagen matrix that is intended to treat partial- or full-thickness skin wounds.

## *ArdeoGraft*

Studies are lacking regarding the use of ArdeoGraft for wound treatment. Therefore, it is not possible to determine whether ArdeoGraft has a beneficial effect on health outcomes.

ArdeoGraft (Surgenex) is a dehydrated, dual-layer human chorionic membrane allograft that is intended to act as a barrier and provides protective coverage for acute and chronic wounds.

## *Artacent AC, Artacent C, Artacent Trident, Artacent Velos, Artacent Vericlen, or Artacent Wound*

There are few published studies that address the use of Artacent C, Artacent AC, Artacent Trident, Artacent Velos, Artacent Vericlen, or Artacent Wound for wound treatment. Therefore, it is not possible to determine whether Artacent C, Artacent AC, Artacent Trident, Artacent Velos, Artacent Vericlen, or Artacent Wound has a beneficial effect on health outcomes.

Artacent Wound (Tides Medical®) is a wound-specific amniotic patch. It is derived from the submucosa of donated human placenta, and it consists of collagen layers, including basement membrane and stromal matrix. According to the manufacturer, it is indicated for diabetic ulcers, pressure ulcers, venous stasis ulcers, and burns.

Artacent AC (Tides Medical) is a dehydrated, micronized chorioamniotic membrane powder that is intended for acute and chronic wound applications, including diabetic ulcers, pressure ulcers, venous stasis ulcers, and burns that are refractory to more conservative treatment.

Artacent C (Tides Medical) is a dehydrated, sterilized human amniotic allograft (single-layer chorion membrane) that is intended for use as a protective wound covering for acute and chronic wounds.

Artacent Trident (Tides Medical) is a dehydrated, sterilized, triple-layer HAM allograft that is intended for use as a wound covering for acute and chronic wounds.

Artacent Vericlen (Tides Medical) is a single-use, dehydrated, sterilized human amnion-chorion membrane allograft that is intended for use as a wound covering for acute and chronic wounds.

Sledge et al. (2020) conducted an observational analysis of Artacent, a unique amniotic patch that contains two layers of amnion, and its ability to increase growth factor delivery for DFUs that failed to heal by 50% following SOC after 2 to 4 weeks. Overall, 26 individuals were previously randomized in a larger clinical trial (that was discontinued due to logistics) to either weekly or biweekly application of Artacent plus SOC and were included in per-protocol effectiveness analyses. The primary end point was complete closure at 12 weeks. The results showed that baseline ulcers were larger than in most DFU clinical trials (4.65 ±4.89 $cm^2$); for the primary end point, 17 of 26 (65%; 95% CI, 44%-83%) of the combined treatment arms achieved complete closure. The authors concluded that healing rates are similar to those in other placental-based tissue studies. In addition, the relatively larger size of the ulcers suggests that the dual-layer amniotic membrane may be effective in ulcers that are more resistant to SOC, and a clinical trial with a greater sample size is planned.

## *Artacent Cord*

There are few published studies that address the use of Artacent Cord. Therefore, it is not possible to determine whether Artacent Cord has a beneficial effect on health outcomes.

Artacent Cord (Tides Medical) is a wound-healing patch comprising the umbilical cord. It is intended for the treatment of acute and chronic wounds such as diabetic ulcers, venous stasis ulcers, and burns.

### *ArthroFLEX*

There is insufficient evidence to support the use of ArthroFLEX due to study limitations. Larger studies are needed to establish safety, efficacy, and long-term outcomes.

ArthroFLEX (Arthrex®, Inc.) is an acellular dermal matrix (ADM) that is intended for supplemental support and is a covering for soft tissue repair.

An ECRI report for ArthroFLEX indicated that evidence from three small studies is at too high of a risk of bias to determine how well ArthroFLEX repairs rotator cuff tears. Studies suggest that ArthroFLEX is safe, and one study suggests that ArthroFLEX may improve 2-year outcomes of arthroscopic repair. However, findings need validation in multicenter RCTs that report long-term outcomes [ECRI, ArthroFLEX Acellular Dermal Matrix (LifeNet Health and Arthrex, Inc.) for Repairing Large to Massive Rotator Cuff Tears 2017; updated 2022].

### *Ascendion*

Due to a lack of sufficient studies on Ascendion for wound treatment, it is currently not possible to determine whether Ascendion has a beneficial effect on health outcomes.

Ascendion (Ascension Biologics) is a minimally manipulated, dehydrated HAM allograft designed for homologous use as a wound covering. It provides a protective barrier for compromised integumentary tissue, including DFUs, venous leg ulcers, and pressure ulcers.

### *Ascent*

There are few published studies that address the use of Ascent. Therefore, it is not possible to determine whether Ascent has a beneficial effect on health outcomes.

Ascent (StimLabs® LLC) is a dehydrated cell and protein concentrate injectable derived from human amniotic fluid. It is intended for treating nonhealing wounds and burns.

### *AxoBioMembrane*

There are few published studies that address the use of AxoBioMembrane. Therefore, it is not possible to determine whether AxoBioMembrane has a beneficial effect on health outcomes.

AxoBioMembrane (Axolotl Biologix) is a dehydrated HAM allograft that is intended to accelerate and improve soft tissue repair.

### *Axolotl Ambient and Axolotl Cryo*

There are few published studies that address the use of Axolotl Ambient and Axolotl Cryo. Therefore, it is not possible to determine whether these products have a beneficial effect on health outcomes.

Axolotl Ambient and Axolotl Cryo (Axolotl Biologix) are human amniotic flowable allografts. These products are intended to support the repair of soft tissue injury.

### *Axolotl Graft, Axolotl DualGraft, and Axolotl DualGraft Ultra*

There are few published studies that address the use of Axolotl Graft, Axolotl DualGraft, and Axolotl DualGraft Ultra. Therefore, it is not possible to determine whether these products have a beneficial effect on health outcomes.

Axolotl Graft and Axolotl DualGraft (Axolotl Biologix) are human amniotic allograft, decellularized, dehydrated placental membrane that are intended to be used for the repair and regeneration of damaged or diseased tissues.

Axolotl DualGraft Ultra (Axolotl Biologix) is a resorbable, single-layer, cross-linked human amnion allograft that is chorion free and derived from donated human birth tissue. It is intended to serve as a structural barrier that protects the wound.

### *Barrera SL and Barrera DL*

There are few published studies that address the use of Barrera SL and Barrera DL. Therefore, it is not possible to determine whether Barrera SL and Barrera DL have a beneficial effect on health outcomes.

Barrera SL and Barrera DL (RegenTX Partners, LLC) are dehydrated amniotic allografts that are intended to serve as a protective wound cover to offer protection from the surrounding environment for wounds, including surgically created wounds.

### *BellaCell HD*

There are few published studies that address the use of BellaCell. Therefore, it is not possible to determine whether BellaCell has a beneficial effect on health outcomes.

BellaCell (HansBioMed) is a human acellular dehydrated dermis regenerative tissue matrix. It is intended for use in skin reconstruction to repair skin loss from injuries and wounds.

### *bio-ConneKt*

There are few published studies that address the use of bio-ConneKt for wound treatment. Therefore, it is not possible to determine whether bio-ConneKt has a beneficial effect on health outcomes.

The bio-ConneKt Wound Matrix (MLM Biologics Inc) is a wound dressing used for moderately to heavily exuding wounds and ulcers. It is made of reconstituted collagen derived from equine tendon.

### *BioDFence and BioDFence DryFlex*

There are few published studies that address the use of BioDFence or BioDFence DryFlex. Therefore, it is not possible to determine whether BioDFence or BioDFence DryFlex has a beneficial effect on health outcomes.

BioDFence and BioDFence DryFlex (BioD, LLC) are membrane allografts that are derived from human placental tissues for use as a tissue barrier that covers and protects the underlying tissues.

### *BioSkin*

There are few published studies that address the use of BioSkin for wound treatment. Therefore, it is not possible to determine whether BioSkin has a beneficial effect on health outcomes.

BioSkin (Wright Medical Group N.V.) is an amniotic wound matrix that is intended to support challenging wound care treatment and cover and protect acute and chronic wounds.

### *BioSkin Flow*

There are few published studies that address the use of BioSkin Flow for wound treatment. Therefore, it is not possible to determine whether BioSkin Flow has a beneficial effect on health outcomes.

The product information on BioSkin Flow is not currently available.

### *BIOVANCE, BIOVANCE Tri-Layer, and BIOVANCE 3L*

There are few published studies that address the use of BIOVANCE, BIOVANCE Tri-Layer, or BIOVANCE 3L. Therefore, it is not possible to determine whether BIOVANCE, BIOVANCE Tri-Layer, or BIOVANCE 3L has a beneficial effect on health outcomes.

BIOVANCE (Celularity Inc.) is an amniotic membrane allograft that is derived from the placenta of a healthy, full-term human pregnancy and is intended for the treatment of acute and chronic wounds, including burns, diabetic ulcers, pressure ulcers, and surgical wounds.

BIOVANCE 3L is a triple-layer, decellularized, dehydrated HAM that is sterilized using e-beam irradiation. BIOVANCE 3L is intended to be used as a cover or to provide protection from the surrounding environment in wound and surgical repair and reconstruction procedures.

In a 2020 ECRI Clinical Evidence Assessment, it was concluded that based on two very-low-quality, single-arm studies, the efficacy of BIOVANCE in treating chronic wounds compared with that of SOC and other skin grafts cannot be determined. Both studies had a high risk of bias due to four or more limitations, including a small study size; incomplete outcomes reporting; and lack of controls, randomization, and blinding. Studies did not report on some key individual-oriented outcomes (e.g., infection, quality of life, wound size reduction). The studies assessed individuals with different wound etiologies and different wound types; this means that the results are not generalizable across all individuals and

wound types. The pilot trial does not report outcomes for wound types separately (i.e., venous leg ulcers, DFUs, pressure ulcers, arterial ulcers, collagen vascular disease–associated ulcers).

Smiell et al. (2015) conducted a multicenter registry study to observe outcomes with decellularized, dehydrated human amniotic membrane (DDHAM; BIOVANCE) in uninfected, full-thickness, or partial-thickness wounds. Investigators were instructed to provide usual care regarding visit and application frequencies, concomitant therapies, and change in wound care regimens. The only exclusions were participants with actively infected wounds or known hypersensitivity to DDHAM. Fifteen sites, with practicing wound care clinicians of various specialties, participated in this review and enrolled participants with chronic wounds, including venous, diabetic, pressure, collagen vascular, and arterial ulcers; all wounds were of various severities, durations, and sizes, and previous treatments also varied. A total of 244 wounds were observed in this study; however, this review is limited to the 179 chronic wounds in 165 participants who were enrolled at 15 of the 19 participating centers. The four centers that enrolled acute wounds only were excluded. Results from the analysis of this very heterogeneous population demonstrated that during the usual course of an average of 8 weeks of wound management, participants experienced factors that significantly affected wound closure. These factors included wound infections, nonadherence to prescribed treatments (e.g., compression, offloading, wound care), reinjury of the wound, and systemic comorbidities. Nearly 50% of chronic wounds (including those that failed previous therapy with advanced biologics) with an average baseline area of 3.1 $cm^2$ achieved complete closure within a median of 6.3 weeks, without product-related adverse experiences. The authors concluded that this registry study demonstrated the safety and clinical benefit of DDHAM to support wound closure across a variety of chronic wound types and individual conditions in real-world environments. The authors recommended that these findings be validated in a prospective RCT for chronic wounds that has stricter enrollment criteria and monitoring of a standard of good wound care.

### *BioWound, BioWound Plus, and BioWound Xplus*

There are few published studies that address the use of BioWound, BioWound Plus, and BioWound Xplus. Therefore, it is not possible to determine whether these products have a beneficial effect on health outcomes.

BioWound, BioWound Plus, and BioWound Xplus (Human Regenerative Technologies, LLC) are single-layer wound coverings. These products are intended for use as a wound covering, surgical covering, or wrap or barrier for acute and chronic wounds.

### *CaregraFT*

Studies are lacking regarding the use of CaregraFT for wound treatment. Therefore, it is not possible to determine whether CaregraFT has a beneficial effect on health outcomes.

CaregraFT (RegenTX Partners, LLC) is a dehydrated amnion and chorion membrane allograft that is intended to act as a barrier and provides protective coverage from the surrounding environment for acute and chronic wounds.

### *CarePATCH*

There are few published studies that address the use of CarePATCH. Therefore, it is not possible to determine whether CarePATCH has a beneficial effect on health outcomes.

CarePATCH (ExtremityCare®) is a dehydrated HAM allograft that is intended to be used as a wound cover or protective wound barrier. It is processed following aseptic techniques to preserve the native physical integrity, tensile strength, and elasticity characteristics of the amnion.

### *Celera Dual Layer or Celera Dual Membrane*

There are few published studies that address the use of Celera Dual Layer or Celera Dual Membrane for wound treatment. Therefore, it is not possible to determine whether Celera Dual Layer or Celera Dual Membrane has a beneficial effect on health outcomes.

Celera Dual Membrane and Celera Dual Layer (Nvision Biomed) are products that are minimally manipulated human amniotic and/or chorionic membrane products derived from placental tissues that retain the structural and functional characteristics of the tissues. These products are intended to serve as a wound cover or skin substitute for cutaneous wounds.

### *Cellesta and Cellesta Flowable Amnion*

There are few published studies that address the use of Cellesta or Cellesta Flowable Amnion. Therefore, it is not possible to determine whether Cellesta or Cellesta Flowable Amnion has a beneficial effect on health outcomes.

Cellesta (Ventris Medical, LLC.) is a minimally manipulated amniotic membrane allograft that is intended as a covering or barrier to offer protection from the surrounding environment in reparative and reconstructive procedures. These procedures include but are not limited to chronic wound repair, urological and gynecologic surgeries, and burn wound reconstruction.

Cellesta Flowable Amnion (Ventris Medical, LLC.) is a chorion-free HAM that is intended for use as a regenerative wound filler for the treatment of acute, chronic, or surgically created wounds.

### *Cellesta Duo*

There are few published studies that address the use of Cellesta Duo. Therefore, it is not possible to determine whether Cellesta Duo has a beneficial effect on health outcomes.

Cellesta Duo (Ventris Medical, LLC.) is a dual-layer HAM allograft. It is intended for use as a regenerative wound covering for the treatment of acute, chronic, or surgically created wounds.

### *Cellesta Cord*

There are few published studies that address the use of Cellesta Cord. Therefore, it is not possible to determine whether Cellesta Cord has a beneficial effect on health outcomes.

Cellesta Cord (Ventris Medical, LLC.) is an umbilical cord allograft product. Cellesta Cord is intended for use as a regenerative wound covering for the treatment of acute, chronic, or surgically created wounds.

### *Choriply*

Studies are lacking regarding the use of Choriply for wound treatment. Therefore, it is not possible to determine whether Choriply has a beneficial effect on health outcomes.

Choriply (International Tissue Inc.) is a single-layer amniotic membrane graft that is derived from placental submucosa. Rich in collagen, it supports tissue regeneration and is used in surgical procedures, such as tendon repairs and spinal fusions, and as a wound covering for chronic, nonhealing wounds like DFUs, venous leg ulcers, and pressure ulcers. It is applied directly to the wound bed or affected area.

### *CLARIX Regenerative Cord 1K Matrix/CLARIX 100 Quick-Peel Regenerative Matrix*

There are few published studies that address the use of CLARIX. Therefore, it is not possible to determine whether CLARIX has a beneficial effect on health outcomes.

CLARIX Regenerative Matrix (Amniox Medical, Inc.) comprises cryopreserved HAM and umbilical cord. It is intended for wound healing and surgical coverings. The CLARIX Quick-Peel Regenerative Matrix is indicated for situations in which excess bulk may not be tolerated.

### *CLARIX FLO*

There are few published studies that address the use of CLARIX FLO. Therefore, it is not possible to determine whether CLARIX FLO has a beneficial effect on health outcomes.

CLARIX FLO (Amniox Medical, Inc.) is a particulate form of CLARIX and comprises amniotic membrane and umbilical cord products that are derived from human placental tissue. It is intended to facilitate replacement and supplement damaged or inadequate skin.

A Hayes report for Human Amniotic Membrane Injections for Treatment of Chronic Plantar Fasciitis indicates that a low-quality body of evidence suggests that HAM injections may result in pain relief and improved function. None of the studies reviewed by Hayes evaluated the comparative effectiveness of amniotic tissue-derived treatments compared with other types of injections such as platelet-rich plasma or botulinum toxin, extracorporeal shockwave therapy, or surgery. Substantial uncertainty remains regarding the comparative effectiveness. The studies included for review had a limited follow-up of 12 weeks or less, making it difficult to assess the long-term effects of this treatment. Double-blinded RCTs, with active treatment comparators (injectables, surgery, or extracorporeal shockwave therapy) are needed to evaluate the effectiveness and safety of amniotic tissue–derived allograft treatments for plantar fasciitis. The products evaluated in this report included PalinGen SportFlow, CLARIX FLO, and AMNIOFIX (Hayes, Human Amniotic Membrane Injections for Treatment of Chronic Plantar Fasciitis, 2021).

## *Cocoon Membrane*

There are few published studies that address the use of Cocoon Membrane. Therefore, it is not possible to determine whether Cocoon Membrane has a beneficial effect on health outcomes.

Cocoon Membranes (Pinnacle Transplant Technologies) are human-derived amnion allografts that are a minimally manipulated placental membrane and are used as a wound covering and barrier. Cocoon Membranes are intended to serve as a covering and barrier for full- and partial-thickness, chronic, or acute wounds.

## *Cogenex*

There are few published studies that address the use of Cogenex amniotic membrane or Cogenex flowable amnion for wound treatment. Therefore, it is not possible to determine whether Cogenex amniotic membrane or Cogenex flowable amnion have a beneficial effect on health outcomes.

Cogenex amniotic membrane (Ventris Medical, LLC.) is a minimally manipulated amniotic membrane allograft that is intended for use as a covering or barrier in wound repair or complex burn reconstruction.

Cogenex flowable amnion (Ventris Medical, LLC.) is an amniotic membrane that is suspended in a saline solution and intended for the treatment of deep or complex wound repair.

## *Cohealyx Collagen Dermal Matrix*

Due to a lack of sufficient studies on Cohealyx for wound treatment, it is not currently possible to determine whether Cohealyx has a beneficial effect on health outcomes.

Cohealyx (AVITA Medical, Inc.) is a purified collagen matrix that is derived from young bovine dermis and contains both type I and type III collagen. It is intended for use in the treatment of full-thickness wounds and burns.

## *Coll-e-Derm*

There are few published studies that address the use of Coll-e-Derm. Therefore, it is not possible to determine whether Coll-e-Derm has a beneficial effect on health outcomes.

Coll-e-Derm (Parametrics Medical) is a dermal allograft that is derived from human dermal tissue. It is intended to support healing of wounds and burns that have not healed with conventional care.

## *Complete AA, Complete ACA, Complete SL, and Complete FT*

There are few published studies that address the use of Complete AA, Complete ACA, Complete SL, and/or Complete FT. Therefore, it is not possible to determine if Complete AA, Complete ACA, Complete SL, and/or Complete FT have a beneficial effect on health outcomes.

Samaritan Biologics, LLC is the manufacturer of Complete SL and Complete FT. Complete SL is a single-layer, amnion-derived allograft, and Complete FT is a full-thickness, amnion-chorion–derived allograft. They both provide a barrier for acute and chronic wounds.

Complete AA from Samaritan Biologics, LLC is a dual-layer, amnion-derived allograft that serves as a barrier and provides protective coverage from the surrounding environment for acute and chronic wounds. Complete AA is a sterile, single-use, dehydrated allograft that is derived from donated human amnion membrane.

Complete ACA from Samaritan Biologics, LLC is a three-layer, amnion-chorion-amnion–derived allograft that serves as a barrier and provides protective coverage from the surrounding environment for acute and chronic wounds. Complete ACA is a sterile, single-use, dehydrated allograft that is derived from donated human amnion-chorion membrane.

## *Conexa*

There are few published studies that address the use of Conexa. Therefore, it is not possible to determine if Conexa has a beneficial effect on health outcomes.

Conexa (Tornier, Inc.) is a porcine dermis tissue substitute that is intended for the reinforcement of soft tissue that has been repaired with sutures or suture anchors during tendon repair surgery and reinforcement of rotator cuff, patellar, Achilles, biceps, quadriceps, and other tendons. Other indications include the repair of body wall defects, which require the use of reinforcing or bridging material to obtain the desired surgical outcome.

## *Corecyte*

There are few published studies that address the use of Corecyte for any other indications. Therefore, it is not possible to determine whether Corecyte has a beneficial effect on health outcomes.

Corecyte (Predictive Biotech) is a minimally manipulated human tissue allograft that is derived from the Wharton jelly of the umbilical cord. It is intended for use as an effective and pain-free alternative to lipoaspirate and bone marrow aspirate procedures for cartilage repair.

## *Coretext or Protext*

There are few published studies that address the use of Coretext or Protext for wound treatment. Therefore, it is not possible to determine whether Coretext or Protext has a beneficial effect on health outcomes.

Coretext is an amniotic membrane–derived human tissue allograft suspension product. It acts as an anti-inflammatory and is intended to provide a barrier to aid in the healing of a defect. Protext is used as replacement tissue that is inserted or injected into the joint and other injured areas.

## *CorMatrix*

Evidence to support the use of CorMatrix is insufficient due to study limitations. Larger studies are needed to establish safety, efficacy, and long-term outcomes.

CorMatrix porcine small intestinal submucosa extracellular matrix (CorMatrix Cardiovascular, Inc.) is a non–cross-linked extracellular matrix that is made from porcine small intestinal submucosa, which supposedly contains structural proteins (such as collagens) and adhesion molecules to promote tissue ingrowth and regeneration. CorMatrix is also available in envelope form (CorMatrix Cangaroo®) to hold and restrict migration of implantable electronic devices and impede infection. CorMatrix has been used in a wide variety of cardiac applications, including congenital cardiac and vascular surgery, pericardial reconstruction, valve reconstruction, and acquired vascular defects at different sites.

Bruun et al. (2025) conducted a systematic review examining tissue response and clinical outcomes following cardiovascular applications of porcine small intestinal submucosal extracellular matrix. The review included 66 studies published between 2013 and 2023, which covered both preclinical and clinical data. Preclinical findings were largely positive, with eight of nine studies reporting no signs of inflammation, and six demonstrating tissue remodeling. However, clinical cohort studies presented mixed results: while histological assessments were performed in 13 studies, they showed varying degrees of inflammation and minimal evidence of regeneration or remodeling. The reintervention rates among clinical cohort studies ranged from 4.5% to 87.5%. Eleven studies reported a reintervention rate exceeding 15%, while six reported a reintervention rate below 15%. Limitations of the review include the heterogeneity of the study designs, variability in reporting standards, and lack of long-term outcome data. Additionally, the clinical evidence was less consistent than the preclinical findings, which raised concerns about the generalizability and reliability of porcine small intestinal submucosal extracellular matrix in cardiovascular applications. These discrepancies highlight the need for further high-quality, standardized clinical trials to better understand the material's long-term safety, efficacy, and regenerative potential in cardiovascular surgery.

Al Haddad et al. (2018) conducted a retrospective review of clinical outcomes following complete atrioventricular canal (CAVC) repair. A total of 73 patients were analyzed, with an average operative age of 22 weeks. The majority (71%) of the patients underwent a two-patch repair. A CorMatrix patch was used for ventricular septal defect closure in 77% of the patients and/or in 75% of atrial septal defect closures. One in-hospital mortality (1.4%) occurred due to respiratory failure. One patient required a pacemaker. At the mid-term follow-up (1.6 years), a total of seven patients required eight reoperations due to cardiac-related indications, including five for left atrioventricular valve repair, one for left atrioventricular valve replacement, and two for isolated residual ventricular septal defects. The authors concluded that a standardized repair for CAVC resulted in excellent outcomes, with low rates of reoperations. According to the authors, CorMatrix for the closure of CAVC produced good results, with equivalent outcomes to other patch materials. This study is limited by the retrospective nature of the data collection.

Kelley et al. (2017) reported on the treatment of Carpentier type IIIa and type IIIb mitral regurgitation (MR) with a large patch anterior mitral valve leaflet augmentation technique using CorMatrix extracellular matrix. A single-site chart review was conducted in patients who underwent anterior leaflet augmentation performed with the da Vinci surgical robot or through a median sternotomy. Only patients who had anterior leaflet augmentation with porcine intestine extracellular matrix or autologous pericardium were included. Follow-up echocardiography was performed in all patients. Histological specimens were available on extracellular matrix patches from a subset of patients who required reoperation. A total of 44 patients (mean age, 62.6 ±12.2 years) underwent anterior leaflet augmentation with either porcine intestinal extracellular

matrix or autologous pericardium. Eight (32%) of the patients with extracellular matrix had recurrence of severe MR on echocardiography, with an average time of 201 ±98 days. Seven patients (28%) required reoperation because of failure of the extracellular matrix patch, including perforation (4%), excessive patch dilation (20%), and suture line dehiscence (4%). In contrast, none of the patients with pericardial augmentation developed severe MR or required operation. The authors concluded that for type III MR, a large anterior leaflet patch technique with porcine extracellular matrix was associated with a 32% recurrence rate of severe MR related directly to patch failure. According to the authors, further research and development should be performed for the use of extracellular matrix materials, with a goal to decrease the failure rate experienced in this study.

Mosala Nezhad et al. (2016) attempted to systematically review preclinical and clinical literature on the use of CorMatrix in cardiovascular surgery. The authors found that the published clinical and preclinical studies lacked systematic reporting of functional and pathological findings in sufficient numbers of individuals. The authors identified only one level II study and only four studies that could reasonably be classified as level III studies; the remainder represented level IV studies, which were case reports or small case series. The majority of published studies only reported immediate or very early postoperative findings, although a handful of case reports examined outcomes past 1 year or more. According to the authors, there are emerging reports to suggest that, contrary to expectations, an undesirable inflammatory response may occur in CorMatrix implants in humans, and longer-term outcomes at particular sites, such as the heart valves, may be suboptimal. According to the authors, large-scale clinical studies are needed and should be driven by robust protocols that aim to quantify the pathological process of tissue repair.

### *Corplex*

There are few published studies that address the use of Corplex for wound treatment. Therefore, it is not possible to determine whether Corplex has a beneficial effect on health outcomes.

Corplex (StimLabs LLC) is a sheet of dehydrated human umbilical cord tissue that is used as a wound covering or barrier membrane for acute and chronic wounds.

### *Corplex P/Theracor P/Allacor P*

There are few published studies that address the use of Corplex P/Theracor P/Allacor P for wound treatment. Therefore, it is not possible to determine whether Corplex P/Theracor P/Allacor P has a beneficial effect on health outcomes.

Corplex P/Theracor P/Allacor P (StimLabs LLC) is a sterile, jelly allograft that is dehydrated into small pieces and packaged in sterile glass vials to supplement connective tissue voids in open-wound environments. Corplex P/Theracor P/Allacor P is to be packed into the wound environment and is not intended to be used as a wound covering or barrier membrane.

### *Cryo-Cord*

There are few published studies that address the use of Cryo-Cord for wound treatment. Therefore, it is not possible to determine whether Cryo-Cord has a beneficial effect on health outcomes.

Cryo-Cord (Royal Biologics) is a cryopreserved, semitransparent, collagenous membrane allograft. It is intended for use as a soft tissue barrier or wound covering for chronic nonhealing wounds.

### *CYGNUS, CYGNUS Dual, and CYGNUS Matrix*

There are few published studies that address the use of CYGNUS, CYGNUS Dual, and CYGNUS Matrix. Therefore, it is not possible to determine whether CYGNUS, CYGNUS Dual, and CYGNUS Matrix have a beneficial effect on health outcomes.

CYGNUS products (VIVEX Biologics, Inc.) are available in multiple thicknesses and are dried human amnion membrane allografts that are composed of a single layer of epithelial cells, basement membrane, and avascular connective tissue matrix. It is intended to treat acute and chronic wounds and burns and has indications for foot and ankle, ophthalmology, and oral surgery use. CYGNUS Dual is a semitransparent, collagenous membrane allograft obtained with consent from healthy mothers during cesarean section delivery.

### *CYGNUS Disk*

Studies are lacking regarding the use of CYGNUS Disk for wound treatment. Therefore, it is not possible to determine whether CYGNUS Disk has a beneficial effect on health outcomes.

CYGNUS Disk (VIVEX Biologics, Inc.) is a multilayer allograft that is derived from the amnion and chorion layers of the placental membrane and is manufactured using Integrity Processing Methodology, which helps to maintain the inherent levels of key extracellular matrices, including proteins, carbohydrates, growth factors, and cytokines. CYGNUS Disk is most often used for acute or chronic complex wounds and burns.

## *Cymetra*

There are few published studies that address the use of Cymetra. Therefore, it is not possible to determine whether Cymetra has a beneficial effect on health outcomes.

Cymetra (LifeCell) is a micronized, particulate form of AlloDerm™, which is an ADM. It is intended for soft tissue grafting and injection laryngoplasty.

Tan and Woo (2010) conducted a retrospective review, from a single surgeon, of 381 injections of micronized dermis in 344 patients from 2000 to 2010 to determine whether the material is temporary or permanent. The indications for micronized dermis were for both temporary and permanent correction of glottic insufficiency. Overall, 29% of all injections resulted in unwanted absorption. Over-injection was needed, and a transcervical approach was preferred to prevent implant extrusion with over-injection (the median volume of injected material increased from 0.8 cc to 1.0 cc during the decade). In 159 patients with long-term follow-up (> 1 year), a 14% incidence of reinjection was observed. The operative and postoperative complication rate was 1.05%. Despite this, the overall need for open procedures in patients with long-term follow-up was 20%. The authors concluded that despite the problems of inconsistency in preparation, slow absorption, and the need for over-injection, micronized dermis is a safe allograft material that has long-term (> 1 year) stability. The material may reduce the need for open surgery and can be used for both temporary and permanent vocal fold augmentation. Further investigation is needed before the clinical usefulness of this procedure is proven, and research that includes RCTs is needed to validate these findings.

## *Cytal*

There are few published studies that address the use of Cytal. Therefore, it is not possible to determine whether Cytal has a beneficial effect on health outcomes.

Cytal Wound Matrix products (ACell, Inc.) are composed of a porcine-derived extracellular matrix, also known as urinary bladder matrix. Cytal is intended for the management of acute or chronic wounds and second-degree burns and injuries.

An ECRI report for Cytal Wound Matrix stated that the evidence is mixed as to whether Cytal Wound Matrix is more effective or better tolerated than other skin substitutes for treating wounds. Evidence gaps remain on how well Cytal performs compared with other skin substitutes (ECRI, 2019).

An ECRI report for Cytal Burn Matrix stated that evidence regarding the effectiveness of Cytal for treating burns is limited (ECRI, 2018).

## *DermaBind CH, DermaBind DL, DermaBind FM, and DermaBind SL*

There are few published studies that address the use of DermaBind CH, DermaBind DL, DermaBind FM, and/or DermaBind SL for wound treatment. Therefore, it is not possible to determine whether DermaBind CH, DermaBind DL, DermaBind FM, or DermaBind SL has a beneficial effect on health outcomes.

DermaBind CH (HealthTech Wound Care) is a dehydrated, human chorion-derived membrane allograft that comprises an extracellular matrix that is rich in collagen, fibrin, and elastin fibers native to the tissue. It is designed for direct application to acute or chronic wounds, is flexible, and is a conforming cover that adheres to complex anatomies.

DermaBind DL (HealthTech Wound Care) is designed for direct application to acute or chronic wounds, is flexible, and is a conforming cover that adheres to complex anatomies. DermaBind DL membrane is intended for use as a wound covering; it provides protection for the wound from the external environment and maintains a moist environment.

DermaBind FM (HealthTech Wound Care) is a dehydrated human placental membrane allograft that comprises an extracellular matrix that is rich in collagen, fibrin, and elastin fibers native to the tissue; it is intended for use as a wound covering.

DermaBind SL (HealthTech Wound Care) is an amnion-derived allograft for the management of wounds and burn injuries.

## *DermACELL, DermACELL AWM, and DermACELL AWM Porous*

Evidence to support the use of DermACELL, DermACELL AWM, and DermACELL AWM Porous is insufficient due to study limitations. Larger studies are needed to establish safety, efficacy, and long-term outcomes.

DermACELL, DermACELL AWM, and DermACELL AWM Porous (LifeNet Health) are decellularized human dermal allografts that are intended for the management of chronic nonhealing wounds such as diabetic and venous stasis ulcers, acute burns, and other associated soft tissue injuries.

Refer to the above section titled Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes for additional articles/reports that evaluate DermACELL.

In a 2020 ECRI Clinical Evidence Assessment regarding DermACELL AWM for the treatment of chronic wounds, it was concluded that based on the evidence from one RCT, DermACELL AWM appears to be safe and effective and achieves complete healing in more DFUs than SOC. One small RCT provides insufficient evidence to determine how well DermACELL works to treat chronic venous leg ulcers compared with standard care. RCTs that compare DermACELL AWM with SOC and other ADMs used for treating chronic wounds are needed; three ongoing RCTs may partially address evidence gaps.

Luthringer et al. (2020) conducted a meta-analysis to compare human-derived acellular dermal matrices (H-ADMs) with SOC to evaluate the number of healed ulcers at 12 and 16 weeks and number of days to complete healing. As a secondary outcome, the efficacy of three H-ADM subtypes were studied. The six studies included in this meta-analysis investigated three subtypes of H-ADMs: AlloPatch® Pliable, DermACELL, and GraftJacket. These three H-ADM subtypes were chosen for analysis, among other commercially available H-ADMs, solely based on their mention in published studies that met inclusion criteria. The inclusion criteria included articles on RCTs that investigated the effects on neuropathic, nonischemic DFUs. Data from 312 DFUs in total were included in the meta-analysis. The results show that H-ADMs are more effective at healing individuals in 12-week (3.14; range, 2.04-4.83) and 16-week periods (2.35; range, 1.25-4.43) compared with SOC. Further, the mean time to complete healing was shorter in the H-ADM group (-2.31 days; range, -2.67 to -1.95 days) compared with the SOC group. In the subgroups, two H-ADMs were associated with a higher likelihood of complete healing in 12 weeks compared with SOC. The third H-ADM had a point estimate, which suggested superiority over SOC. According to the investigators, this study shows that H-ADMs are associated with a higher likelihood of complete healing and fewer days to complete healing in 12-week and 16-week periods compared with SOC. The investigators noted that the commercial products performed similarly. The investigators indicated that the meta-analysis had several limitations. First, the studies were significantly heterogeneous. Of note, the SOC used and frequency of H-ADM application were not consistent in the included studies. The overall heterogeneity between studies was addressed by using a random-effects model for analysis. Still, this brings the external validity of the data into question. The available studies are few, and the total number of DFUs in the studies covered is relatively low and often industry associated; therefore, the results are likely somewhat confounded by publication bias. According to the investigators, further research is needed to better characterize the effects of H-ADM on DFUs at increased follow-up. More studies, with larger sample sizes that are non-industry related, are needed to investigate the efficacy of H-ADM.

In a multicenter, randomized controlled, open-label trial, Cazzell (2019a; reviewed in the ECRI report above) evaluated the safety and efficacy of decellularized human acellular dermal matrices (D-ADMs; DermACELL AWM) compared with those of conventional wound care management in participants with chronic venous leg ulcers of the lower extremity. Participants were randomly assigned to receive either D-ADM or SOC (control) in a 2:1 ratio. Treatment began at week 0, and wounds were evaluated on a weekly basis until wound closure was observed or the participant completed 24 weekly follow-up visits. Overall, 18 participants were included in the D-ADM arm, and 10 were included in the control arm. A strong trend of reduction in percent wound area was observed in D-ADM participants, with an average reduction of 59.6% at 24 weeks vs. 8.1% at 24 weeks in control participants. In addition, healed ulcers in the D-ADM arm remained closed at a substantially higher rate after termination than healed ulcers in the control arm. The authors concluded that D-ADMs demonstrated increased healing rates and reduction in wound size compared with conventional care. The small participant population and unbalanced proportion between the two groups (2:1) were limitations of this study. According to the authors, larger, prospective, randomized controlled studies are needed to better assess the use of DermACELL AWM in clinical practice.

Cazzell et al. (2019b; reviewed in the ECRI report above) conducted a prospective, multicenter study to evaluate the efficacy and safety of an ADM allograft, DermACELL (D-ADM; LifeNet Health), in the treatment of large, complex DFUs that are probed to tendon or bone. The inclusion criterion was Wagner grade 3 or 4 DFUs between 4 weeks and 1 year in duration. All participants received one application of D-ADM at baseline and could receive one additional application if wound healing arrested. Ulcers were assessed weekly for 16 weeks using a laser measuring device. Overall, 61 participants were included in the study, with an average wound area of 29.0 cm; 59 of these ulcers showed exposed

bone. The entire per-protocol population (n = 47) achieved 100% granulation. The mean time to 100% granulation was 4.0 weeks, with an average of 1.2 applications of D-ADM. The mean percent wound area reduction was 80.3% at 16 weeks. Those DFUs that were 15 cm or smaller were substantially more likely to close than DFUs larger than 29 cm during a 16-week duration. The authors concluded that D-ADM demonstrated the ability to rapidly reduce the size of large, complex DFUs with exposed bone. Some wounds did not completely heal by 16 weeks; however, the significant reduction in size suggests that these large, complex wounds may heal if given more time. A major limitation of this study is that it was uncontrolled, and it was not possible to make direct comparisons to results with SOC. Another study limitation was that the study follow-up ended after 16 weeks, which was an insufficient length of time to evaluate large ulcer healing.

Cazzell et al. (2017; reviewed in the Luthringer et al., 2020, meta-analysis and ECRI report above) compared the efficacy and safety of a human ADM, D-ADM (DermACELL AWM; LifeNet Health), with a conventional care arm and an active comparator arm comprising a human ADM, GJ-ADM, for the treatment of chronic DFUs. The study was a prospective RCT that enrolled 168 participants with DFUs in 13 centers across nine states. Participants in the ADM arms received one application but could receive one additional application of ADM if deemed necessary. Screen failures and early withdrawals left 53 participants in the D-ADM arm, 56 in the conventional care arm, and 23 in the GJ-ADM arm. Participants were followed up through 24 weeks, with major end points at weeks 12, 16, and 24. Single-application D-ADM participants had significantly greater wound closure rates than those receiving conventional care at all three end points, while all D-ADM applications had a significantly higher healing rate than conventional care at week 16 and week 24. GJ-ADM did not show a significantly greater healing rate over conventional care at any of these time points. A blinded, third-party adjudicator analyzed healing at week 12 and expressed strong agreement. Closed ulcers in the single-application D-ADM arm remained healed at a significantly greater rate than in the conventional care arm at 4 weeks post termination (100% vs. 86.7%). No significant difference between GJ-ADM and conventional care for healed wounds remaining closed was observed. Single-application D-ADM demonstrated significantly greater average percent wound area reduction than conventional care at weeks 2 to 24, while single-application GJ-ADM showed significantly greater wound area reduction over conventional care at weeks 4 to 6, 9, and 11 to 12. According to the authors, D-ADM demonstrated significantly greater wound healing, larger wound area reduction, and a better capability of keeping healed wounds closed than conventional care in the treatment of chronic DFUs. This study was funded by LifeNet Health, which is the organization that manufactures DermACELL. The authors indicated that a potential weakness of this study is that the investigators were not blinded to the treatment type when assessing wound closure.

Walters et al. (2016; reviewed in the Luthringer et al., 2020, meta-analysis above) conducted a 16-week, multicenter RCT to assess the healed ulcer rate with a human ADM, DermACELL, compared with that with conventional care and a second ADM, GraftJacket, in the treatment of full-thickness DFUs. Overall, 168 participants were randomized into DermACELL, conventional care, and Graftjacket treatment arms in a 2:2:1 ratio. Participants in the ADM groups received either one or two applications of the graft at the discretion of the investigator. Weekly follow-up visits were conducted until the ulcer healed or the end point was reached. The results showed that at 16 weeks, the DermACELL arm had a significantly higher proportion of completely healed ulcers than the conventional care arm and a higher proportion (nonsignificant) than the GraftJacket arm (67.9% vs. 47.8%). The DermACELL arm also had a greater average percent reduction in wound area than the conventional care arm (91.4% vs .80.3%) and the GraftJacket arm (91.4% vs. 73.5%). The proportion of severe adverse events and the proportion of overall early withdrawals were similar among the three groups, based on relative population size. The authors concluded that DermACELL is an appropriate clinical option in the treatment of DFUs compared with conventional care options, with significant increases in healing rates and the rate of percentage wound closure. This study was sponsored by LifeNet Health, which is the manufacturer of DermACELL.

## *Dermacyte or Dermacyte AC Matrix Amniotic Membrane Allograft*

There are few published studies that address the use of Dermacyte AC Matrix Amniotic Membrane Allograft or Dermacyte Amniotic Wound Care Matrix for wound treatment. Therefore, it is not possible to determine whether Dermacyte AC Matrix Amniotic Membrane Allograft or Dermacyte Amniotic Wound Care Matrix has a beneficial effect on health outcomes.

Dermacyte AC Matrix Amniotic Membrane Allograft Matrix (Merakris Therapeutics, Inc.) is a sterile, lyophilized, gamma irradiated, full-thickness allograft that includes amnion and chorion and is intended for use as a protective covering and barrier.

Dermacyte Amniotic Wound Care Matrix (Merakris Therapeutics, Inc.) is a cross-linked HAM allograft. It is intended to provide a protective covering and support for cell growth during the healing process of diabetic ulcers, venous ulcers, pressure ulcers, and burn wounds with exposed vital structures.

## *Derma-Gide*

There are few published studies that address the use of Derma-Gide. Therefore, it is not possible to determine whether Derma-Gide has a beneficial effect on health outcomes.

Derma-Gide is a collagen wound dressing for covering and regenerating soft tissue defects or soft tissue wounds.

In an observational pilot study, Armstrong et al. (2020) evaluated the safety and preliminary efficacy of Derma-Gide, a novel, decellularized purified reconstituted bilayer matrix (PRBM) in treating DFUs. Ten consecutive diabetic wounds that failed 4 weeks of SWC were treated weekly with PRBM for up to 12 weeks. At each weekly visit, the wound was evaluated, photographed, and cleaned; a new graft was applied if the wound was not completely epithelialized. The assessment included measurement of the wound area and inspection of the wound site for signs of complications. The primary outcome measure was wound closure, as adjudicated by independent reviewers. Secondary outcomes included assessment of overall adverse events, time to closure, PAR, and the cost of product(s) used. Nine of 10 individuals achieved complete wound closure within 4 weeks, and one did not heal completely within 12 weeks. The mean time to heal was 2.7 weeks. The mean wound area reduction at 12 weeks was 99%. No adverse events or wound complications were observed. The authors noted that these are the first published data using PBRM to treat a nonhealing DFU. These early clinical findings suggest that PRBM may be an effective tool in the treatment of DFUs. Large, randomized studies are needed to validate the finding in this small observational study.

## *DermaPure*

There are few published studies that address the use of DermaPure. Therefore, it is not possible to determine whether DermaPure has a beneficial effect on health outcomes.

DermaPure (Tissue Regenix Group plc) is a decellularized human dermis product for the treatment of acute or chronic wounds and provides an environment that supports cell migration to facilitate the body's repair or replacement of damaged or inadequate skin tissue.

The 2024 ECRI report on DermaPure Decellularized Dermal Allograft (ARMS Medical) concludes that existing studies are limited in size and quality and offer insufficient evidence to determine the product's effectiveness for acute or chronic wound treatment. Preliminary data from two small, retrospective case series suggest that DermaPure is safe and may promote healing in select wound types. However, the absence of comparative studies with other skin substitutes and therapies highlights the need for rigorous, prospective research to guide clinical decision-making.

In a 2017 analysis, Kimmel and Gittleman evaluated the use of DermaPure, a decellularized human skin allograft, in the treatment of a variety of challenging wounds. This retrospective, observational analysis reviewed a total of 37 patients from 29 different wound clinics. Each patient received one application of DermaPure, and the wound was followed up until complete closure. A statistical analysis was performed, with the end point being complete healing. All wounds had, on average, a duration of 56 weeks and healed in an average time of 10 weeks. Individual wound categories included DFUs, which healed in 8 weeks; venous leg ulcers, which healed in 11 weeks; and surgical/traumatic wounds, which healed in 11 weeks. This study was limited by a small sample size and lack of a control group.

## *DermaSpan*

There are few published studies that address the use of DermaSpan. Therefore, it is not possible to determine whether this product has a beneficial effect on health outcomes.

DermaSpan (Zimmer Biomet Sports Medicine) is an ADM that is derived from human allograft tissue. It is intended for use in various practices, including orthopedics, plastic surgery, and general surgery, and for repair and replacement of damaged or inadequate skin tissue (wound coverage).

## *Dermavest and Plurivest*

There are few published studies that address the use of Dermavest or Plurivest. Therefore, it is not possible to determine whether Dermavest or Plurivest has a beneficial effect on health outcomes.

Dermavest and Plurivest (Aedicell, Inc.) are human amnion/chorion umbilical cord and placental disk tissue matrices that are intended to replace or supplement damaged or inadequate skin tissue and restabilize a debrided wound.

### *Derm-Maxx*

There are few published studies that address the use of Derm-Maxx for wound treatment. Therefore, it is not possible to determine whether Derm-Maxx has a beneficial effect on health outcomes.

Derm-Maxx (Royal Biologics) is a freeze-dried, decellularized dermal matrix allograft. It is intended for integumentary augmentation and serves as a covering for wounds and skin defects.

### *Dual Layer Amnio Burgeon X-Membrane*

Studies are lacking regarding the use of Dual Layer Amnio Burgeon X-Membrane for wound treatment. Therefore, it is not possible to determine whether Dual Layer Amnio Burgeon X-Membrane has a beneficial effect on health outcomes.

Dual Layer Amnio Burgeon X-Membrane is an amniotic membrane product that is used as a wound covering and acts as a barrier for full- or partial-thickness, chronic, and acute wounds.

### *Dual Layer Impax Membrane*

There are few published studies that address the use of Dual Layer Impax Membrane. Therefore, it is not possible to determine whether Dual Layer Impax Membrane has a beneficial effect on health outcomes.

Dual Layer Impax Membrane (Legacy Medical Consultants) is a sterile, dehydrated, dual-layered HAM allograft that is intended to serve as a barrier or cover for acute or chronic wounds and is used as a barrier to protect wounds from the surrounding environment.

### *DuoAmnion*

Studies are lacking regarding the use of DuoAmnion for wound treatment. Therefore, it is not possible to determine whether DuoAmnion has a beneficial effect on health outcomes.

DuoAmnion (Samaritan Biologics, LLC) is a dehydrated allograft that is derived from donated HAM that serves as a barrier and provides protective coverage from the surrounding environment for acute and chronic wounds.

### *Duograft AA, duoGRAFT AC, and triGRAFT FT*

Studies are lacking regarding the use of Duograft AA, duoGRAFT AC, and triGRAFT FT for wound treatment. Therefore, it is not possible to determine whether Duograft AA, duoGRAFT AC, or triGRAFT FT has a beneficial effect on health outcomes.

Duograft AA is a dehydrated, dual-layer amniotic membrane allograft that is designed to serve as a protective barrier at injury and surgical sites.

duoGRAFT AC (RegenTX Partners, LLC) is a dehydrated, dual-layer amniotic membrane that is intended to act as a barrier and protective cover at the site of injury or surgical site.

triGRAFT FT (RegenTX Partners, LLC) is a dehydrated, triple-layer placental membrane; its three layers consist of amnion, a spongy layer, and chorion, and it is intended to act as a barrier and protective cover at the local site of injury or surgical site.

### *E-Graft*

Studies are lacking regarding the use of E-Graft for wound treatment. Therefore, it is not possible to determine whether E-Graft has a beneficial effect on health outcomes.

E-Graft (Skye Biologics Holdings, LLC) is a thick-layer, amnion-only, rolled membrane allograft that is intended for use as a barrier, wrap, and cover for acute or chronic wounds.

### *Emerge Matrix*

Studies are lacking regarding the use of Emerge Matrix for wound treatment. Therefore, it is not possible to determine whether Emerge Matrix has a beneficial effect on health outcomes.

Emerge Matrix (Sequence LifeScience, Inc.) is a dual-membrane, minimally manipulated human amniotic and chorionic membrane product that is derived from placental tissue that retains the structural and functional characteristics of the tissue. Emerge Matrix consists primarily of extracellular matrix proteins and serves as a natural, biological barrier and

wound cover. The typical population includes those with full-thickness acute or chronic wounds for which a biological barrier or wound cover is required.

### *Enclose TL Matrix*

Studies are lacking regarding the use of Enclose TL Matrix for wound treatment. Therefore, it is not possible to determine whether Enclose TL Matrix has a beneficial effect on health outcomes.

Enclose TL Matrix (Sequence LifeScience, Inc.) is a tri-layered, minimally manipulated human placental membrane product that is derived from donated placental tissues that retain the structural and functional characteristics of the tissues. The product is typically used for individuals with chronic, full-thickness ulcers and other skin defects for which a biological barrier or cover is required.

### *Enverse*

There are few published studies that address the use of Enverse for wound treatment. Therefore, it is not possible to determine whether Enverse has a beneficial effect on health outcomes.

Enverse (StimLabs LLC) comprises dehydrated HAM that is obtained from donated placental tissue. Enverse contains nonviable cells and is to be used as a wound covering and barrier membrane over chronic and acute wounds, including dermal ulcers and defects.

### *EPICORD*

There are several published studies that address the use of EPICORD, and all the studies have limitations. Therefore, it is not possible to determine whether EPICORD has a beneficial effect on health outcomes.

EPICORD (MIMEDX Group, Inc.) is a minimally manipulated, dehydrated, nonviable cellular umbilical cord allograft. EPICORD is intended to be used in the treatment and management of chronic or acute wounds and burns to replace or supplement damaged and inadequate skin tissue.

Refer to the above section titled Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes for additional articles/reports that evaluate EPICORD.

An ECRI report for EPICORD Umbilical Cord Allograft (MIMEDX) for Treating DFUs reviewed one small RCT (Tettelbach et al., 2019b), which was of moderate quality. The results from this study need confirmation from further controlled trials; therefore, the evidence is inconclusive (ECRI, 2020).

Tettelbach et al. (2019b; reviewed in the ECRI report above) evaluated the safety and effectiveness of dehydrated human umbilical cord allograft (EPICORD) compared with those of alginate wound dressings for the treatment of chronic, nonhealing DFUs. A multicenter RCT was conducted at 11 centers in the United States. Participants with a confirmed diagnosis of type 1 or type 2 diabetes who presented with a 1- to 15-$cm^2$ ulcer that was located below the ankle and had persisted for at least 30 days were eligible for the 14-day study run-in phase. After 14 days of weekly debridement, moist wound therapy, and offloading, those with ≤ 30% wound area reduction post debridement (n = 155) were randomized in a 2:1 ratio to receive a weekly application of EPICORD (n = 101) or standardized therapy with an alginate wound dressing, nonadherent silicone dressing, absorbent nonadhesive hydropolymer secondary dressing, and gauze bandage roll (n = 54). Study visits were conducted for 12 weeks. At each weekly visit, the DFU was cleaned and debrided as necessary; the wound was photographed prior to and post debridement and measured before the application of treatment group–specific dressings. A follow-up visit was performed at week 16. The primary study end point was the percentage of complete closure of the study ulcer within 12 weeks, as assessed by the Silhouette camera. Data for randomized participants who met study inclusion criteria were included in an intent-to-treat (ITT) analysis. An additional analysis was conducted in a group of participants (n = 134) who completed the study per protocol (EPICORD, n = 86; alginate, n = 48) and in those participants who received adequate debridement (EPICORD, n = 67; alginate, n = 40). The ITT analysis showed that DFUs treated with EPICORD were more likely to heal within 12 weeks than those receiving alginate dressings: 71 of 101 (70%) vs. 26 of 54 (48%) with EPICORD and alginate dressings, respectively. The healing rates at 12 weeks in participants treated per protocol were 70 of 86 (81%) for EPICORD-treated and 26 of 48 (54%) for alginate-treated DFUs. Among DFUs that received adequate debridement (n = 107, ITT population), 64 of 67 (96%) of the EPICORD-treated ulcers healed completely within 12 weeks compared with 26 of 40 (65%) of adequately debrided, alginate-treated ulcers. No adverse events related to either EPICORD or alginate dressings were observed. According to the authors, these results demonstrate the safety and efficacy of EPICORD as a treatment for nonhealing DFUs. MIMEDX Group, Inc. sponsored the study and provided study oversight and data compilation.

### *EPIEFFECT*

There are few published studies that address the use of EPIEFFECT. Therefore, it is not possible to determine whether EPIEFFECT has a beneficial effect on health outcomes.

EPIEFFECT (MIMEDX Group, Inc.) is a lyophilized, human placental-based allograft membrane that includes the amnion layer, intermediate layer, and chorion layer. EPIEFFECT is intended for use as a barrier to provide a protective environment for acute and chronic wounds.

### *EPIFIX Injectable*

There are few published studies that address the use of EPIFIX Injectable. Therefore, it is not possible to determine whether EPIFIX Injectable has a beneficial effect on health outcomes.

EPIFIX Injectable (MIMEDX Group, Inc.) is a micronized powder form of EPIFIX amniotic membrane that can be injected where direct sheet application would not be feasible.

### *EPIFIX Amnion/Chorion Membrane (Noninjectable)*

EPIFIX (MIMEDX Group, Inc.) is a dehydrated amnion/chorion membrane extracellular collagen allograft that comprises an epithelial layer and two fibrous connective tissue layers and is proposed for acute or chronic wound care.

Refer to the above section titled Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes for additional articles/reports that evaluate EPIFIX.

The National Institute for Health and Care Excellence (NICE) MedTech innovation briefing on EPIFIX indicates that five reviewed studies suggest that EPIFIX may be an effective addition to standard care and compression therapy in people with chronic wounds. According to NICE, the key uncertainties are that there are no comparisons of EPIFIX with standard National Health Service care for any indication. Two of the five studies that were included in the report were written by the same group of authors, and four studies were funded by the manufacturer of EPIFIX (National Institute for Health and Care Excellence, 2018).

## Diabetic Foot Ulcers

Mohammed et al. (2022) conducted a systematic review and meta-analysis that compared the use of dHACA plus SOC vs. SOC alone in the treatment of DFUs. The results included 10 published RCTs and one unpublished RCT. The pooled effect estimate from 11 RCTs showed that dHACA was superior to SOC regarding complete wound healing in both the sixth and twelfth weeks (RR, 3.78; 95% CI, 2.51-5.70; $p < 0.00001$ and RR, 2.00; 95% CI, 1.67-2.39; $p < 0.00001$, respectively). Additionally, the analysis favored dHACA regarding the mean time to heal in the twelfth week (MD, -12.07; 95% CI, -19.23 to -4.91; $p = 0.001$). The wound size reduction was better with dHACA (MD = 1.18; 95% CI, -0,10 to 2.26; $p = 0.03$). The authors noted that some limitations exist, yet the strength of the RCTs indicated that dHACA with SOC had better efficacy than SOC alone in enhancing wound healing, reducing the mean time to wound healing, and diminishing the risk of adverse events. (Tettelbach et al., 2019, Zelen et al., 2016, and Zelen et al., 2015, included below.)

Lakmal et al. (2021) conduced a systematic review to assess the impact of amniotic membrane in DFUs. The potential of HAM to act as an allograft has been studied in diabetic foot wounds; the intent of this study was to evaluate the current scientific evidence on its effectiveness in healing DFUs. Research included studies from January 2000 to March 30, 2020. When searched with MeSH terms, 12 citations in PubMed, 22 citations in the Cochrane Library, and 30 citations in other databases were found. After screening the studies and their reference lists, 12 studies met the inclusion criteria, and the others were excluded. There were eight RCTs, two prospective studies, and two retrospective studies that used different preparation methods for the amniotic membranes. A wide variation in study end points was noted. The majority of the RCTs (n = 7) were concluded with a significantly higher wound closure rate than that in the conventional treatment groups. In prospective and retrospective studies, it was shown that large, chronic ulcers, which were resistant to closure with standard therapy, achieved wound closure with amniotic membrane allografts. A meta-analysis could not be performed due to study heterogeneity, and publication bias was not assessed due to the small number of available studies, which was not sufficient for accurate comparison. According to this systematic review, the current studies that use amniotic membrane allografts provide reliable evidence of reduction in healing time over conventional methods. Further prospective RCTs, with larger populations and long-term follow-up, are needed to strengthen the evidence.

Su et al. (2020) conducted a systematic review and meta-analysis to evaluate the efficacy and safety of HAM allograft in treating chronic DFUs. Nine studies were included in the qualitative systematic review, and seven studies were included in the final meta-analysis. The primary outcome was the proportion of complete healing at 6 and 12 weeks. The secondary outcomes were the mean time to complete healing and adverse events. The proportion of complete wound healing in the

HAM plus SOC group was 3.88 times as high as that with SOC alone (RR, 3.88; 95% CI, 2.34-6.44) at 6 weeks and 2.01 times at 12 weeks (RR, 2.01; 95% CI, 1.45-2.77). The intervention group had a significantly shorter time to complete healing (MD, -30.33 days; 95% CI, -37.95 to -22.72 days). The number needed to treat within 6 weeks was 2.3 (95% CI, 1.8-3.1). No significant difference was shown in adverse events. Results were consistent in a sensitivity analysis. According to the investigators, HAM plus SOC is effective and safe in treating chronic DFUs at 6 weeks and 12 weeks. According to the investigators, this review had several limitations. First, there were some potential biases, especially from the implementation of masking individuals due to the special feature of surgical trials [eight studies (88.9%) were unable to mask individuals]. Second, change in quality of life is important for individuals with DFUs, but the meta-analysis failed to pool them together because no original study investigated it.

An ECRI report for EPIFIX for treating chronic wounds, including DFUs, indicated that evidence from four small RCTs on DFUs indicates that EPIFIX promotes healing better than SOC. Weekly EPIFIX healed 70% of wounds in 12 weeks, and biweekly EPIFIX healed 92% of wounds in 6 weeks; one RCT showed that 97% were healed at 12 weeks with biweekly EPIFIX. One RCT reported that weekly EPIFIX treatment healed more wounds in 4 weeks than biweekly EPIFIX (90% vs. 50%; p = 0.014). Weekly treatment also lowered the mean time to complete healing (2.4 vs. 4.1 weeks; p = 0.039). All studies were funded by the manufacturer. Although the evidence is somewhat favorable, further studies are needed to address the evidence limitations. [ECRI Institute. EPIFIX Amnion/Chorion Membrane Allograft (MIMEDX) for Treating Chronic Wounds. December 2019.]

In another systematic review evaluation of the literature, Luck et al. (2019) evaluated the efficacy and safety of allogeneic skin substitutes and human placental membrane allografts in the management of DFUs. Any RCT with an allogeneic skin substitute or placental membrane allograft intervention group was included. The primary outcome measure was the proportion of completely healed ulcers. Secondary outcome measures included time to complete wound healing and local adverse event rates. Each study was assessed for risk of bias, and the quality of evidence was appraised using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. Moderate-quality evidence from the 11 included RCTs demonstrated that both allogeneic cellular approaches improve the proportion of completely healed ulcers at 6 and 12 weeks. Evidence (Zelen et al., 2015; Zelen et al., 2016) showed that a placental membrane allograft (EPIFIX) was superior to an allogeneic skin substitute (Apligraf), although this has yet to be repeated in other studies. The authors concluded that the addition of allogeneic cellular wound products to SWC improves DFU outcomes. According to the authors, further studies are required to establish if placental membrane allografts are superior to allogeneic skin substitutes. A limitation of this review is that outcome measures reporting heterogeneity precluded meta-analysis, and extracted data are synthesized in narrative form only.

Tettelbach et al. (2019a; reviewed in the systematic review and ECRI report above) conducted a manufacturer-sponsored, randomized controlled, multicenter clinical trial (NCT01693133) at 14 wound care centers in the United States to confirm the efficacy of dHACM allograft (EPIFIX) for the treatment of chronic lower extremity ulcers in persons with diabetes. Inclusion criteria for the study included the following: an ulcer size of ≥ 1 $cm^2$ and < 25 $cm^2$; type 1 or 2 diabetes; an ulcer duration of ≥ 4 weeks; no response to SWC; no clinical signs of infection; a serum creatinine of < 3.0 mg/dL (in the last 6 months); an $HbA_{1c}$ of < 12% (in the last 60 days); and adequate circulation to the affected extremity, as demonstrated by a dorsum transcutaneous oxygen test of ≥ 30 mmHg, Ankle-Brachial Index between 0.7 and 1.2, or triphasic or biphasic Doppler arterial waveforms at the ankle of the affected leg. The exclusion criteria included current participation in another trial; Charcot foot; an index wound duration of > 52 weeks, without intermittent healing index; ulcer probing to the tendon, muscle, capsule, or bone; current receipt of radiation or chemotherapy; known or suspected malignancy of the current ulcer; a diagnosis of autoimmune connective tissue disease; use of biomedical/topical growth factor in the previous 30 days; current pregnancy or currently breastfeeding; use of medications that are considered to be immune system modulators; an allergy or known sensitivity to gentamicin or streptomycin; wounds that are improving greater than 25% in the 2-week run-in period of the trial using an SOC dressing and Camboot offloading; use of cyclooxygenase-2 inhibitors; and planned use of Dakin solution, mafenide acetate, scarlet red dressing, Tincoben, zinc sulfate, povidone-iodine solution, polymyxin/nystatin, or chlorhexidine during the trial. Participants with a lower extremity ulcer of at least 4 weeks' duration were entered into a 2-week study run-in phase and treated with alginate wound dressings and appropriate offloading. Those with ≤ 25% wound closure after the run-in were randomly assigned to receive weekly EPIFIX application in addition to offloading or SOC with alginate wound dressings for 12 weeks. A total of 110 participants were included in the ITT analysis, with 54 in the dHACM group and 56 in the no-dHACM group. Of the participants, 98 completed the study per protocol, with 47 receiving dHACM and 51 not receiving dHACM. The primary study outcome was the percentage of study ulcers that were completely healed in 12 weeks, with both ITT and per-protocol participants who were receiving weekly dHACM significantly more likely to completely heal than those who were not receiving dHACM. A Kaplan-Meier analysis was performed to compare the time-to-healing performance with/without dHACM and showed a significantly improved time to healing with the use of the allograft. A Cox regression analysis showed that dHACM-treated participants were more than twice as likely to heal completely in 12 weeks than participants who were not treated with dHACM. At the final follow-up at 16 weeks, 95% of dHACM-healed ulcers and 86% of healed ulcers in the no-dHACM group remained

closed. According to the authors, these results confirm that dHACM is an efficacious treatment for lower extremity ulcers in a heterogeneous population of individuals.

Zelen et al. (2016; reviewed in the Su et al., 2020, Alvaro-Alfonso et al., 2020, Luck et al., 2019, and ECRI systematic reviews above) continued the below study (Zelen et al., 2015) to enroll at least 100 participants and assess the rates and time to closure. With the larger cohort, clinical outcomes were compared at 12 weeks in 100 participants with chronic lower extremity diabetic ulcers that were treated with weekly applications of Apligraf (n = 33), EPIFIX (n = 32), or SWC (n = 35), with collagen alginate dressing as controls. A Cox regression was performed to analyze the time to heal in 12 weeks, adjusting for all significant covariates. A Kaplan-Meier analysis was conducted to compare time to heal in 12 weeks for the three treatment groups. Clinical characteristics were well matched across the study groups. The proportions of wounds that achieved complete closure in the 12-week study period were 73% (24/33), 97% (31/32), and 51% (18/35) with Apligraf, EPIFIX, and SWC, respectively. Participants treated with EPIFIX had a significantly higher probability of their wounds healing compared with those receiving SWC alone. No difference in probability of healing was observed in the Apligraf and SWC groups. Participants treated with Apligraf were less likely to heal than those treated with EPIFIX. Increased wound size and presence of hypertension were significant factors that influenced healing. The mean time to heal in 12 weeks was 47.9 days with Apligraf, 23.6 days with EPIFIX, and 57.4 days with SWC. The median number of grafts used per healed wound was six (range, 1-13) and 2.5 (range, 1-12) in the Apligraf and EPIFIX groups, respectively. The investigators concluded that these results provide further evidence of the clinical and resource utilization superiority of EPIFIX compared with Apligraf for the treatment of lower extremity diabetic wounds. The authors indicated the following limitation for this study: participants were followed up for only 1 week after complete healing, and wound recidivism was not recorded. According to the authors, additional studies will evaluate the recurrence rate over time. This study did not report a funding source.

Zelen et al. (2015) conducted a prospective, randomized controlled, parallel-group, multicenter clinical trial at three sites to compare the healing effectiveness of the treatment of chronic lower extremity diabetic ulcers with either weekly applications of Apligraf (Organogenesis Inc.), EPIFIX (MIMEDX Group, Inc.), or SWC with collagen alginate dressing. The primary study outcome was the percent change in complete wound healing after 4 and 6 weeks of treatment. Secondary outcomes included the percent change in wound area per week and velocity of wound closure. A total of 65 participants entered the 2-week run-in period, and 60 were randomized (20 per group). The proportion of participants in the EPIFIX group who achieved complete wound closure within 4 and 6 weeks was 85% and 95%, which is significantly higher than that of participants receiving Apligraf (35% and 45%) or standard care (30% and 35%). After 1 week, wounds treated with EPIFIX had reduced in area by 83.5% compared with 53.1% for wounds treated with Apligraf. The median time to healing was significantly faster with EPIFIX (13 days) than Apligraf (49 days) or standard care (49 days). According to the authors, the results of this study demonstrate the clinical and resource utilization superiority of EPIFIX compared with Apligraf or SOC for the treatment of diabetic ulcers of the lower extremities.

Kirsner et al. (2015) evaluated the comparative effectiveness of a bioengineered living cellular construct (BLCC; Apligraf) and a dHACM (EPIFIX) for the treatment of DFUs. Using a wound care-specific electronic medical record (EMR) database, the authors assessed real-world outcomes in 218 individuals with 226 DFUs who received treatment in 2014 at 99 wound care centers. The analysis included DFUs of ≥ 1 and < 25 $cm^2$, with a duration of ≤ 1 year and an area reduction of ≤ 20% in the 14 days prior to treatment (n = 163, BLCC; n = 63, dHACM). The average baseline areas and durations were 6.0 $cm^2$ and 4.4 months with BLCC, respectively, and 5.2 $cm^2$ and 4.6 months with dHACM. Individuals treated with dHACM had more applications than those treated with BLCC (median, 3.0 vs. 2.0). A Cox model that was adjusted for key covariates, including area and duration, found that the median time to closure with BLCC was 13.3 weeks compared with 26 weeks with dHACM, and the proportion of wounds healed were significantly higher with BLCC by 12 weeks (48% vs. 28%) and 24 weeks (72% vs. 47%). Treatment with a bioengineered living cellular technology increased the probability of healing by 97% compared with a dehydrated amniotic membrane. This study is limited by its retrospective design, and according to the authors, the database used for the study was not designed specifically for research purposes; as such, there may be missing data or data entry errors.

In 2014, Zelen et al. (2014a) published follow-up data from the Zelen et al. (2013) trial that is described above. Eighteen of 22 eligible participants returned for a follow-up examination. At the 9- to 12-month follow-up visit, 17 of 18 wounds (94.4%) treated with dHACM remained fully healed. According to the authors, the limitations of this study include the retrospective study design and small sample size. The authors stated that larger studies are needed to confirm their findings.

Zelen et al. (2014b) assessed if weekly application of dHACM allograft reduces time to heal more effectively than biweekly application for treatment of DFUs. The study was an institutional review board-approved, registered, prospective, randomized, comparative, nonblinded, single-center clinical trial. Participants with noninfected ulcers of ≥ 4 weeks' duration were included and randomized to receive weekly or biweekly application of an allograft in addition to a

nonadherent, moist dressing with compressive wrapping. The primary study outcome was the mean time to healing. Overall, during the 12-week study period, 92.5% of ulcers (37/40) completely healed. The mean time to complete healing was 4.1 ±2.9 vs. 2.4 ±1.8 weeks in the biweekly vs. weekly groups, respectively. According to the authors, these results validate previous studies that showed that the allograft is an effective treatment for diabetic ulcers and show that wounds that are treated with weekly application heal more rapidly than those with biweekly application. Limitations of this study include a small sample size. The lack of a standard care group that did not receive dHACM can be perceived as a study weakness, although according to the authors, the intent of the study was solely to examine rates of healing according to the frequency of application and not to compare them with rates seen with other treatment modalities. The authors stated that their findings should be confirmed and expanded with subsequent multicenter clinical trials and long-term follow-up data to validate the durability of healed wounds.

In a prospective, randomized, single-center clinical trial, Zelen et al. (2013b; reviewed in the Su et al., 2020, Alvaro-Alfonso et al., 2020, Luck et al., 2019, and ECRI systematic reviews above) compared the healing characteristics of DFUs that were treated with dehydrated HAM allografts (EPIFIX; MIMEDX Group, Inc.) vs. SOC. The study criteria included the following: an ulcer size of ≥ 1 $cm^2$ and < 25 $cm^2$; type 1 or 2 diabetes; an ulcer duration of ≥ 4 weeks; no response to SWC; no clinical signs of infection; a serum creatinine of < 3.0 mg/dL (in the last 6 months); an $HbA_{1c}$ of < 12% (within the last 60 days); and adequate circulation to the affected extremity, as demonstrated by a dorsum transcutaneous oxygen test of ≥ 30 mmHg, Ankle-Brachial Index between 0.7 and 1.2, or triphasic or biphasic Doppler arterial waveforms at the ankle of the affected leg. The exclusion criteria included current participation in another trial; Charcot foot; an index wound duration of > 52 weeks, without intermittent healing index; ulcer probing to the bone; current receipt of radiation or chemotherapy; known or suspected malignancy of the current ulcer; a diagnosis of autoimmune connective tissue disorder; use of biomedical/topical growth factor in the previous 30 days; current pregnancy or currently breastfeeding; use of medications that are considered to be immune system modulators; and an allergy or known sensitivity to gentamicin or streptomycin. Participants were randomized to receive standard care alone or standard care with the addition of EPIFIX. EPIFIX was applied at 2, 4, 6, 8, and 10 weeks if the ulcer was unhealed. Wound size reduction and rates of complete healing after 4 and 6 weeks were evaluated. In the standard care group (n = 12) and the EPIFIX group (n = 13), wounds reduced in size by a mean of 32.0% ±47.3% vs. 97.1% ±7.0% after 4 weeks, whereas at 6 weeks, wounds were reduced by -1.8% ±70.3% vs. 98.4% ±5.8% with standard care vs. EPIFIX, respectively. After 4 and 6 weeks of treatment, the overall healing rate with application of EPIFIX was shown to be 77% and 92%, respectively, whereas standard care healed 0% and 8% of the wounds. The authors concluded that participants treated with EPIFIX achieved superior healing rates vs. those receiving standard treatment alone and that these results show that using EPIFIX in addition to standard care is efficacious for wound healing. Limitations of this study include a small sample size. An additional limitation is that the comparative group in the study did not receive other advanced therapies to assess if the EPIFIX allograft is as good as or is better than other available advanced wound care products. According to the authors, additional comparative effectiveness studies are required to address this issue. The study is further limited by a possible conflict of interest and lack of masking to the intervention.

## Venous Leg Ulcers

Evidence related to the safety of and long-term outcomes with EPIFIX for treating venous leg ulcers is limited.

An ECRI report for EPIFIX for treating chronic wounds, including venous leg ulcers, reported evidence from two small RCTs regarding venous leg ulcers. One RCT reported that weekly EPIFIX plus compression treatment healed more wounds than a moist wound dressing plus compression in 12 weeks (60% vs. 35%; p = 0.0128). The other RCT reported that 62% of wounds that were treated with EPIFIX plus compression therapy achieved > 40% closure at 4 weeks compared with 32% of wounds treated with compression therapy alone (p = 0.005). All studies were funded by the manufacturer. Although evidence is somewhat favorable, further studies are needed to address the evidence limitations [ECRI Institute. EPIFIX Amnion/Chorion Membrane Allograft (MIMEDX) for Treating Chronic Wounds. December 2019].

The earlier study reported by Bianchi et al. (2018; refer below) only reported per-protocol study results (n = 109; 52 EPIFIX and 57 standard care participants), although 128 participants were randomized: 64 to the EPIFIX group and 64 to the standard care group. The purpose of the present study (Bianchi et al., 2019; reviewed in the ECRI report above) is to report ITT results for all 128 randomized participants and assess if both ITT and per-protocol data analyses arrive at the same conclusion for the efficacy of EPIFIX as a treatment for venous leg ulcers. Rates of healing in the ITT and per-protocol populations were 50% and 60%, respectively, in those receiving EPIFIX and 31% and 35% in those in the standard care cohort. In both the ITT and per-protocol analyses, these differences were statistically significant. The authors concluded that the results of this study show that, in both the ITT and per-protocol analyses, venous leg ulcers treated with EPIFIX as an adjunct to debridement, moist wound dressings, and compression had significantly higher rates of healing than those treated with comprehensive wound care alone. This study was funded by the manufacturer, MIMEDX Group, Inc.

Bianchi et al. (2018; reviewed in the ECRI report above) conducted a randomized controlled, multicenter clinical trial to evaluate the efficacy of EPIFIX, a dHACM allograft as an adjunct to multilayer compression therapy for the treatment of nonhealing, full-thickness venous leg ulcers. A total of 109 participants were randomly assigned to receive EPIFIX and multilayer compression (n = 52) or dressings and multilayer compression therapy alone (n = 57). Participants were recruited from 15 centers around the United States and were followed up for 16 weeks. The primary end point of the study was defined as the time to complete ulcer healing. Participants receiving weekly application of EPIFIX and compression were significantly more likely to experience complete wound healing than those receiving SWC and compression (60% vs. 35% at 12 weeks and 71% vs. 44% at 16 weeks). A Kaplan-Meier analysis was performed to compare the time-to-healing performance with or without EPIFIX, showing a significantly improved time to healing with the allograft. A Cox regression analysis showed that participants treated with EPIFIX had a significantly higher probability of complete healing within 12 weeks vs. those without EPIFIX. According to the authors, these results confirm the advantage of the EPIFIX allograft as an adjunct to multilayer compression therapy for the treatment of nonhealing, full-thickness venous leg ulcers. These findings require confirmation in larger RCTs. This study was sponsored and funded by the manufacturer of EPIFIX, MIMEDX Group, Inc.

Miranda et al. (2016) conducted a retrospective analysis of prospectively acquired data for eight lower extremity free flaps with ulcerations in the context of venous insufficiency and/or lymphedema. The first four were flaps that had been treated with conservative wound care to healing. The second group was treated conservatively initially but then converted to treatment with dHACM (EPIFIX) grafts. The primary end point was time to healing. A comparison of Kaplan-Meier survival curves revealed a significant difference between the conservatively and dHACM-treated flap ulcers, favoring graft treatment. In those ulcers that healed, the average time to healing was 87 days in the conservative treatment group and 33 days in the dHACM treatment group (with an average of 1.7 grafts per ulcer). The authors concluded that dHACM may accelerate the healing of ulcers on lower extremity free flaps in individuals with lymphedema and/or venous disease in the treated leg. The authors stated that is study was limited by a small sample size, which limits sweeping conclusions. No true randomized control or comparison group was available, so it cannot be firmly concluded that dHACM accelerates the healing of ulcers on free flaps with lymphedematous or venous-insufficient limbs.

Serena et al. (2015) evaluated the correct correlation between an intermediate rate of wound reduction (40% wound area reduction after 4 weeks of treatment) and complete healing at 24 weeks in patients with a venous leg ulcer in a retrospective follow-up of the study by Serena et al. (2014) described above. The outcomes that were assessed were rates of complete healing within 24 weeks of enrollment and days to healing. Data were divided into two groups based on status at RCT completion (healed at least 40% yes or no). The correct correlation with status at 4 weeks and complete healing within 24 weeks was determined. Clinical characteristics were also compared for patients with and without correct correlation between the 4-week and 24-week status. Overall, 55 patients at five study sites were included. In total, 47 patients without complete healing during the initial study were eligible. Three patients were lost to follow-up; therefore, a total of 44 records were evaluated. Of them, 20 (45.4%) had a reduced wound size of ≥ 40%, and 24 (55%) had a < 40% reduction during the initial study. Complete healing occurred in 16 of 20 (80%) in the ≥ 40% group, at a mean of 46 days, and 8 of 24 (33.3%) in the < 40% group, at a mean of 103.6 days. Overall, the correct correlation of status at 4 weeks and ultimate healing status of venous legs ulcers occurred in 32 of 44 patients (73%). The authors indicated that these results confirm that the intermediate outcome used in our initial study is a viable predictor of ultimate venous leg ulcer healing. According to the authors, there are limitations to the present study. During the follow-up period, after completion of the initial 4-week RCT, patients received various treatments that may or may not have included initiation of or additional application of dHACM, or other advanced treatments. Also, in the initial RCT, dHACM was only applied once or twice during the study period, which may not be reflective of how the treatment is used in a real-world setting.

Serena et al. (2014; reviewed in the ECRI report above) conducted a multicenter RCT to evaluate the safety and efficacy of one or two applications of dHACM allograft and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. Individual inclusion criteria included the presence of a venous leg ulcer that extended through the full thickness of the skin but not down to muscle, tendon, or bone; a venous leg ulcer present for at least 1 month; and a venous leg ulcer that has been treated with compression therapy for at least 14 days. The primary study outcome was the proportion of participants achieving 40% wound closure at 4 weeks. Of the 84 participants who were enrolled, 53 were randomized to receive the allograft, and 31 were randomized to the control group of multilayer compression therapy alone. At 4 weeks, 62% in the allograft group and 32% in the control group had a greater than 40% wound closure, thus highlighting a significant difference between the allograft-treated groups and the multilayer compression therapy alone group at the 4-week surrogate end point. After 4 weeks, wounds treated with the allograft had reduced in size by a mean of 48.1% compared with 19.0% for controls. The authors concluded that venous leg ulcers treated with the allograft had a significant improvement in healing at 4 weeks compared with multilayer compression therapy alone. According to the authors, the lack of long-term follow-up data did not allow for the validation of duration of healed wounds.

### *EPIXPRESS*

Studies are lacking regarding the use of EPIXPRESS for wound treatment. Therefore, it is not possible to determine whether EPIXPRESS has a beneficial effect on health outcomes.

EPIXPRESS (MIMEDX Group, Inc.) is a minimally manipulated, lyophilized, nonviable cellular allograft that is derived from HAM. EPIXPRESS preserves multiple extracellular matrix components and other proteins that are present in amniotic tissue. EPIXPRESS includes the amnion layer, intermediate layer, and chorion layers that are obtained from donated human placental tissue.

### *Esano A, Esano AAA, Esano AC, or Esano ACA*

There are few published studies that address the use of Esano A, Esano AAA, Esano AC, or Esano ACA for wound treatment. Therefore, it is not possible to determine whether Esano A, Esano AAA, Esano AC, or Esano ACA has a beneficial effect on health outcomes.

Esano A (Evolution Biologyx™) is a dehydrated amniotic membrane sheet protective covering to aid in wound management.

Esano AAA (Evolution Biologyx) is a tri-layered DDHAM with a preserved natural epithelial basement membrane and intact extracellular matrix structure, with biochemical components; it provides a protective cover and aids in wound care and surgical sites.

Esano AC (Evolution Biologyx) is a dual-layer DDHAM allograft that is intended for use as a cover and barrier for acute or chronic wounds and provides protective coverage from the surrounding environment for acute or chronic wounds.

Esano ACA (Evolution Biologyx) is a dehydrated allograft that consists of a dehydrated, triple-layer amnion/chorion/amnion allograft tissue matrix that accommodates a variety of handling characteristics.

### *Excellagen*

There are few published studies that address the use of Excellagen for wound treatment. Therefore, it is not possible to determine whether Excellagen has a beneficial effect on health outcomes.

Excellagen (Generex Biotechnology Corporation) is a pharmaceutically formulated fibrillar type I bovine collagen gel for wound care management.

### *E-Z Derm*

There are limited studies that are related to E-Z Derm for use on partial-thickness skin loss, donor sites, and skin ulcerations and abrasions. Therefore, it is not possible to determine whether E-Z Derm has a beneficial effect on health outcomes.

E-Z Derm (Mölnlycke Health Care US, LLC) is a porcine-derived, biosynthetic xenograft that is intended for use on partial-thickness skin loss, donor sites, and skin ulcerations and abrasions.

### *FlowerAmnioFlo*

There are few published studies that address the use of FlowerAmnioFlo for wound treatment. Therefore, it is not possible to determine whether FlowerAmnioFlo has a beneficial effect on health outcomes.

FlowerAmnioFlo, also known as FlowerFlo (Flower Orthopedics Corporation), is a 100% acellular, liquid amniotic fluid allograft that is injected on or in the wound site. It is intended for the treatment of nonhealing wounds and burn injuries. According to the manufacturer, FlowerAmnioFlo delivers cytokines, proteins, and growth factors to help generate soft tissue.

### *FlowerAmnioPatch*

There are few published studies that address the use of FlowerAmnioPatch for wound treatment. Therefore, it is not possible to determine whether FlowerAmnioPatch has a beneficial effect on health outcomes.

FlowerAmnioPatch, also known as FlowerPatch (Flower Orthopedics Corporation), is a dehydrated (human) amniotic membrane allograft used for the treatment of nonhealing wounds and burn injuries. According to the manufacturer, FlowerAmnioPatch delivers cytokines, proteins, and growth factors to help generate soft tissue.

### *FlowerDerm*

There are few published studies that address the use of FlowerDerm. Therefore, it is not possible to determine whether FlowerDerm has a beneficial effect on health outcomes.

FlowerDerm (Flower Orthopedics Corporation) is a hydrated acellular (human) dermal allograft matrix that is used for the treatment of nonhealing wounds and burn injuries. According to the manufacturer, FlowerDerm contains extracellular matrix that provides a scaffold for cellular ingrowth vascularization, tissue regeneration, and formation of granulation tissue.

### *Fluid Flow and Fluid GF*

There are few published studies that address the use of Fluid Flow and Fluid GF. Therefore, it is not possible to determine whether these products have a beneficial effect on health outcomes.

Fluid Flow and Fluid GF (BioLab Sciences, Inc.) are human amniotic flowable allografts. These products are intended for treating acute or chronic wounds, soft tissue injury, degenerative tissue disorders, and inflammatory conditions such as tendonitis and fasciitis.

### *Foundation Dermal Regeneration Scaffold (DRS) Solo*

Studies are lacking regarding the use of Foundation DRS Solo for wound treatment. Therefore, it is not possible to determine whether Foundation DRS Solo has a beneficial effect on health outcomes.

Foundation DRS Solo (Bionova Medical, Inc.) is an advanced wound care device that features a biodegradable, porous matrix made from chitosan (derived from shellfish) and sodium chondroitin sulfate. This matrix acts as a scaffold for cellular invasion and capillary growth, promoting healing by maintaining a moist wound environment. It can be replaced or left in place to support cellular infiltration and capillary growth as it degrades. Foundation DRS Solo is suitable for managing various wounds, including full- and partial-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, partial-thickness burns, donor sites, abrasions, trauma wounds, dehisced wounds, and surgical wounds.

### *G4Derm Plus*

Due to a lack of sufficient studies on G4Derm Plus for wound treatment, it is not currently possible to determine whether G4Derm Plus has a beneficial effect on health outcomes.

G4Derm Plus (Gel4Med) is intended for the local management of partial- and full-thickness wounds, including pressure and diabetic ulcers; lower extremity ulcers of venous, arterial, or mixed origin; surgical wounds; and first-degree or partial-thickness burns. It also supports healing of abrasions and burns from dermabrasion or laser resurfacing.

### *GammaGraft*

There are limited studies related to GammaGraft for acute and chronic surface wounds. Therefore, it is not possible to determine whether GammaGraft has a beneficial effect on health outcomes.

GammaGraft (Promethean LifeSciences, Inc.) is an irradiated human skin allograft that is intended for surface wounds, both chronic and traumatic.

### *Genesis Amniotic Membrane*

There are few published studies that address the use of Genesis Amniotic Membrane. Therefore, it is not possible to determine whether Genesis Amniotic Membrane has a beneficial effect on health outcomes.

Genesis Amniotic Membrane (Genesis Biologics, Inc.) is a dehydrated, collagenous human tissue allograft that is intended for the treatment of acute and chronic wounds, soft tissue injuries, and surgical wounds and infection prevention.

### *GRAFIX, GRAFIX PRIME, and GRAFIX PL PRIME*

GRAFIX (Osiris Therapeutics, Inc.) is a cryopreserved placental membrane that comprises an extracellular matrix that contains collagen, growth factors, fibroblasts, mesenchymal stem cells, and epithelial cells that are native to the tissue.

Refer to the above section titled Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes for additional articles/reports that evaluate GRAFIX.

## Diabetic Foot Ulcers

An ECRI Clinical Evidence Assessment for GRAFIX Cellular Repair Matrix for Treating Chronic Wounds indicated that evidence from two RCTs (Ananian et al., 2018; Lavery et al., 2014), three retrospective studies, and seven prospective studies suggests that GRAFIX is safe, may be more effective than EPIFIX dressing, and may be noninferior to Dermagraft® at promoting chronic wound healing. Evidence from 12 studies of varied designs and quality indicates that GRAFIX is safe and may aid in the healing of wounds that failed to heal with standard care alone. GRAFIX may be noninferior to Dermagraft and more effective than EPIFIX, but the available evidence is insufficient to draw firm conclusions regarding comparative effectiveness. Additional independent RCTs would be useful to understand GRAFIX wound closure rate, healing time, and the likelihood of wound reoccurrence; other studies that compare GRAFIX with other active dressings and autologous skin grafts are also needed. [ECRI, GRAFIX Cellular Repair Matrix (Osiris Therapeutics, Inc.) for Treating Chronic Wounds, 2021.]

A Hayes Health Technology Assessment for GRAFIX Cryopreserved Placental Membrane concluded that a low-quality body of evidence provided consistent evidence that suggests that adjunctive treatment with GRAFIX Cryopreserved Placental Membrane may improve healing of chronic, diabetes-related foot ulcers. Evidence that compares GRAFIX with other skin substitutes is insufficient. Significant uncertainty exists because of the low number of comparative studies, variability in wound characteristics across studies, and limited follow-up. Additional well-designed, comparative trials are needed to confirm that GRAFIX is more effective than SWC alone. Studies that address appropriate individual selection criteria are also needed to establish which individuals and wound types would most benefit from GRAFIX [Hayes, GRAFIX Cryopreserved Placental Membrane (Osiris Technologies Inc.) for Treatment of Chronic Foot Ulcers in Individuals with Diabetes Mellitus, 2019; updated October 2022].

In a prospective, single-center, open-label, single-arm study, Farivar et al. (2019) enrolled participants with active venous leg ulcers that had failed to heal after a trial of standard therapy of at least 12 weeks, which included weekly multilayer compression therapy, along with local wound care. The same participants subsequently received application of human viable wound matrix (hVWM) (GRAFIX) every 1 to 2 weeks, in addition to standard therapy. Healing with hVWM therapy was then compared with that with standard therapy, with each participant serving as their own control. Overall, 30 venous leg ulcers were observed in 21 consecutive eligible participants who were enrolled in the study. All participants were men with an average age of 67 years, and the average area of venous ulcers before hVWM initiation was 12.2 $cm^2$. Complete ulcer healing was achieved in 53% (16/30) of venous leg ulcers that were refractory to standard therapy after application of hVWM. There was a mean reduction in wound surface area by 79% after a mean treatment time of 10.9 weeks. Overall 80% of venous leg ulcers were reduced in size by half compared with 25% with standard therapy. The mean rate of reduction in ulcer area after hVWM applications was 1.69% per day vs. 0.73% per day with standard therapy. It was concluded that cryopreserved placental tissue improves healing processes and helps achieve complete wound closure in a significant proportion of chronic venous leg ulcers that are refractory to standard therapy; additionally, adjunctive therapy with hVWM provides superior healing rates in refractory venous leg ulcers. According to the authors, large, randomized trials are needed to confirm these preliminary results.

Raspovic et al. (2018) conducted a real-world, retrospective analysis, using electronic health records, to evaluate the effectiveness of viable cryopreserved placental membrane (vCPM; GRAFIX) for the management of DFUs. The primary end point was the proportion of DFUs that achieved complete closure. Deidentified electronic health record data for 360 patients with 441 wounds treated with vCPM were extracted from the database. The average patient age was 63.7 years, with a mean wound size of 5.1 $cm^2$ and an average wound duration of 102 days prior to vCPM treatment. For evaluation of clinical outcomes, 350 DFUs larger than 0.25 $cm^2$ at baseline were analyzed. Closure at the end of treatment was achieved in 59.4% of wounds, with a median treatment duration of 42.0 days and four applications of vCPM. The probability of wound closure at week 12 was 71%, and the number of amputations and wound-related infections was 13 (3.0%) and nine (2.0%), respectively. Data also demonstrated a correlation between wound size and closure rate as well as a correlation between > 50% wound area reduction by week 4 and wound closure by week 12. The authors indicated that the results of this study support the benefits of vCPM for DFU management. Study limitations include the retrospective nature of the study and absence of a control cohort.

Lavery et al. (2018) conducted a single-arm, open-label extension phase of the GRAFIX (cryopreserved placental membrane) multicenter, blinded RCT for chronic DFUs that was previously reported by Lavery and colleagues in 2014. In the extension phase, 26 participants in the SWC arm with DFUs that did not close in the blinded phase chose to receive weekly applications of GRAFIX in an open-label extension phase. Seventeen participants (65.4%) experienced wound closure in a median of 34 days and three visits. There were fewer total adverse events (24 cryopreserved placental membrane vs. 52 SWC) and index wound-related infections (five cryopreserved placental membrane vs. 12 SWC) during GRAFIX application compared with the number of adverse events in the same participants during SWC treatment in the blinded phase of the trial. According to the authors, these results corroborate the benefits with this cryopreserved

placental membrane combined with SWC over SWC alone for chronic DFUs that were previously reported for the blinded, randomized phase of the trial. This study is limited by its small sample size.

Ananian et al. (2018; included in the ECRI report above) analyzed clinical outcomes between a vCPM (GRAFIX) and human fibroblast–derived dermal substitute (hFDS), Dermagraft, for the treatment of chronic DFUs in a prospective, multicenter, randomized, single-blinded study. The outcomes in 62 participants were analyzed: 31 participants in the vCPM treatment group and 31 participants in the hFDS treatment group. Using a noninferiority trial design and the established treatment regimen of eight applications of hFDS, the authors demonstrated that vCPM was not inferior to hFDS for the proportion of participants who achieved complete wound closure. However, preliminary findings showed that vCPM may have better outcomes for wounds of ≤ 5 $cm^2$: 81.3% (13/16) of wounds in the vCPM group vs. 37.5% (6/16) of wounds in the hFDS group reached complete closure at the end of treatment. Future studies will be needed to confirm these preliminary results. According to the authors, study limitations include the single-blinded design of the study, lack of stratification by wound location and size for analyses, lack of a follow-up period after the treatment phase of the trial, and lack of specificity regarding wound location.

Paggiaro et al. (2018) performed a systematic review to analyze the scientific evidence found in the literature on the use of the amniotic membrane to stimulate DFU healing. Following the inclusion and exclusion criteria, RCTs were identified, and the risk of bias was analyzed according to the Cochrane Risk of Bias Tool. The authors conducted a meta-analysis of the two outcomes to evaluate the level of evidence. Six clinical trials were identified, with a total of 331 individuals. For examination of the wound healing outcome, five studies (Zelen et al., 2016; Zelen et al., 2013b; Snyder et al., 2016; Lavery et al., 2014; DiDomenic et al., 2016) could be used for the meta-analysis. However, for wound healing time, only three studies (Zelen et al., 2016; Lavery et al., 2014; DiDomenic et al., 2016) could be used. The most common risks of bias in the studies were selection, attrition, and detection biases. From the meta-analysis, although the result difference of the intervention group (amnion) in relation to the control group was not statistically significant, it was found that wound healing in the group that was treated with amniotic membrane occurred 2.32 times more often and was 32 days faster compared with that in the group that used conventional dressings. The authors concluded that there is no statistical evidence to support the effectiveness of amniotic membrane compared with other conventional dressings. However, there is a clear trend that shows that amniotic membrane treatment results in a larger number of DFUs healing at a quicker rate. According to the authors, the main limitations of this study are the small number of RCTs found and the flaws found in the results that are published in these studies. The authors indicated that these two conditions impaired the statistical analysis and prevented the development of definitive evidence for the use of amniotic membrane in the treatment of DFUs.

Haugh et al. (2017) performed a meta-analysis that examined RCTs that compared amniotic tissue products with SOC for nonhealing DFUs. A search of three databases identified 596 potentially relevant articles. Application of selection criteria led to the selection of five RCTs. The five selected RCTs represented a total of 311 individuals. Three of the trials that were included compared EPIFIX, a dehydrated amniotic membrane product, with SOC (Zelen et al., 2013b; Zelen et al., 2015; Zelen et al., 2016). One trial compared the use of DAMA, which is also a dehydrated amniotic membrane product, and SOC with SOC alone (Snyder et al., 2016). One trial compared GRAFIX, a cryopreserved amniotic product, with SOC (Lavery et al., 2014). The pooled relative risk of healing with amniotic products compared with the control was 2.7496. The authors concluded that the current meta-analysis indicates that the treatment of DFUs with amniotic membrane improves healing rates in DFUs. The authors stated that further studies are necessary to confirm the findings that were identified in these five trials and to determine whether amniotic products have the same impact on all individuals with diabetes seen in clinical practice. The authors also stated that although this analysis indicates that amniotic membrane has great potential for use in DFUs in clinical practice, individuals in all five of the included trials had to have adequate tissue perfusion and a lack of any signs of infection to enroll. Many individuals who develop DFUs do not have adequate tissue perfusion and are often have chronic infections; therefore, it is unclear how these products would translate into the everyday clinical care of individuals with diabetes. According to the authors, the lack of follow-up in individuals is a significant limitation of the identified studies and their review.

In a systematic review and meta-analysis, Laurent et al. (2017) assessed the efficacy and time sensitivity of human amnion/chorion membrane treatment in individuals with chronic DFUs. All RCTs that compared human amnion/chorion membrane plus standard therapy and standard therapy alone in individuals with DFUs were included in the analysis. Eligible studies were reviewed, and data were extracted into standard form. The Cochrane Risk of Bias Tool was used. Review manager version 5.3 software was used for statistical analysis. Data were analyzed using a random-effects model. Overall, the initial search of the four databases identified 352 published studies; of these, seven RCTS were ultimately included in the meta-analysis (Zelen et al., 2013b; Zelen et al., 2015; Zelen et al., 2016; DiDomenico et al., 2016; Snyder et al., 2016; Lavery et al., 2014; Mohajeri-Tehrani et al., 2016). The analysis results showed that individuals who received amniotic membrane plus standard therapy had far fewer incomplete healing wounds than those receiving SOC alone. Assessment of the wound healing state at 4 and 6 weeks revealed that the wound healing state was almost the same, but there was a net difference of wound healing state at 12 weeks. The authors concluded that human

amnion/chorion membrane plus SOC treatment heals DFUs significantly faster than SOC alone. When using the amnion in individuals with DFUs, the optimal times to assess progress in wound healing should be 4 and 12 weeks. According to the authors, the number of studies and the sample sizes were not sufficiently large, which can increase biases. The authors stated that further large studies or RCTs are still needed to verify the findings and assess healing in infected DFUs.

Johnson et al. (2017) reported on the clinical outcomes in two nonrandomized (but statistically equal), homogeneous individual cohorts, which received either an intact vCPM or dHACM, for the management of wounds at a single center. A total of 79 individuals, with 101 wounds, were analyzed: 40 individuals with 46 wounds received vCPM (GRAFIX), and 39 individuals with 55 wounds received dHACM (EPIFIX). The proportion of wounds that achieved complete closure was 63.0% (29/46) with vCPM and 18.2% (10/55) with dHACM for all treated wounds combined. According to the authors, the retrospective and nonrandomized nature of this single-center study presents significant limitations.

In an RCT, Lavery et al. (2014; reviewed in the Paggiaro et al., 2018, Haugh et al., 2017, and Laurent et al., 2017 systematic reviews and meta-analyses above) compared the efficacy of GRAFIX, an hVWM (n = 50), with SWC (n = 47) to heal DFUs. Standard care included offloading and nonadherent dressings (Adaptic) and either saline-moistened gauze or ALLEVYN for moderately draining wounds. The primary end point was the proportion of participants with complete wound closure by 12 weeks. Secondary end points included the time to wound closure, adverse events, and wound closure in the crossover phase. The proportion of participants who achieved complete wound closure was significantly higher among those who received GRAFIX (62%) than controls (21%). The median time to healing was 42 days in GRAFIX participants compared with 69.5 days in controls. There were fewer GRAFIX participants with adverse events (44% vs. 66%) and fewer GRAFIX participants with wound-related infections (18% vs. 36%). Among the study participants who healed, ulcers remained closed in 82% (23 of 28 participants) in the GRAFIX group vs. 70% (7 of 10 participants) in the control group. The authors concluded that treatment with GRAFIX significantly improved DFU healing compared with standard wound therapy. According to the authors, the results of this well-controlled study show that GRAFIX is a safe and more effective therapy for treating DFUs than standard wound therapy. These findings require confirmation in a larger study.

## Venous Stasis Ulcers

There is limited evidence related to the safety of and long-term outcomes with GRAFIX products for treating venous leg ulcers.

Dhillon et al. (2025) conducted a multicenter RCT to evaluate the effectiveness of GRAFIX PL, a lyopreserved amniotic membrane (LPM), in treating venous leg ulcers. The study enrolled 200 participants across 30 U.S. sites and compared weekly applications of LPM plus SOC against SOC alone in a 12-week period. Results showed that LPM significantly accelerated wound size reduction and improved healing rates, with a 72% higher probability of wound closure in the LPM group for wounds with an initial size of 3 to 25 $cm^2$. Additionally, participants receiving LPM reported a five-fold improvement in quality of life, and the graft was particularly effective in closing larger wounds. However, the study has limitations, including its open-label design, which may introduce bias, and the lack of long-term follow-up to assess sustained healing and recurrence. These limitations highlight the importance of conducting further research, particularly blinded, long-term studies that can more reliably assess the sustained effectiveness and broader clinical applicability of LPMs in chronic wound care.

## *GRAFIX CORE*

There are few published studies that address the use of GRAFIX CORE. Therefore, it is not possible to determine whether GRAFIX CORE has a beneficial effect on health outcomes.

GRAFIX CORE (Smith+Nephew) is a cryopreserved chorion matrix with limited product information.

## *GRAFIX Duo*

Due to a lack of sufficient studies on GRAFIX Duo for wound treatment, it is not currently possible to determine whether GRAFIX Duo has a beneficial effect on health outcomes.

GRAFIX Duo (Smith+Nephew) is a dual-layer, dehydrated, amniotic membrane–based skin substitute that is indicated for the management of acute and chronic wounds. It serves as a protective barrier to support healing.

## *GRAFIX Plus*

Studies are lacking regarding the use of GRAFIX Plus for wound treatment. Therefore, it is not possible to determine whether GRAFIX Plus has a beneficial effect on health outcomes.

GRAFIX Plus (Smith+Nephew) is a lyophilized, human placental chorionic membrane-based skin substitute product. GRAFIX Plus is indicated for use in the treatment of acute and chronic wounds. The product acts as a wound cover, wrap, and barrier, including for surgically created wounds.

### *Helicoll*

There are limited studies related to Helicoll for wound treatments, second-degree burns, and chronic ulcers. Therefore, it is not possible to determine whether Helicoll has a beneficial effect on health outcomes.

Helicoll (MCT Medical Solutions LLC) is a semiocclusive, self-adhering collagen sheet that is used for wound treatments, second-degree burns, and chronic ulcers. This biodegradable skin substitute is made from animal tissues.

In an evidence-based review, McNamara et al. (2020) discussed the principles of pediatric wound management and new treatments that were published in the literature to date. Databases were searched for relevant sources, including PubMed, Embase, Web of Science, and DynaMed. The findings noted that amniotic membrane living skin equivalent is a cellular matrix that has been reportedly successful in treating pediatric wounds and is currently under investigation in randomized clinical trials. The authors indicated that Helicoll, an acellular matrix, shows promise in children with recessive dystrophic epidermolysis bullosa. According to the authors, there have been promising results in many studies to date, but RCTs that involve larger sample sizes are necessary to (1) determine the specific role that these advanced products play in pediatric wounds and (2) identify their safety and efficacy.

Dhanraj (2015) conducted a prospective RCT to compare Helicoll, a type I pure collagen dressing, with OPSITE dressing and with scarlet red dressing in the treatment of standardized STSG donor sites. Overall, 30 participants, over a 3-month period, underwent various reconstructive procedures, necessitating the use of STSGs. Following a simple randomized clinical protocol, the analysis of data included donor site pain, the healing time of the donor site, the initial absorption of the applied dressing, and the rate of infection with the three different dressings. Compared with the OPSITE and scarlet red dressing groups, participants in the Helicoll group reported significantly less pain and a decreased infection rate, and they required no dressing change. The healing time of the donor site in the Helicoll group was shorter than that in the scarlet red group; however, it was comparable to that in the OPSITE group. The authors concluded that Helicoll, as a donor site dressing, is successful in providing pain-free mobility, with a measurable healing rate. Study limitations include a small study population and the fact that only one wound type (STSG donor site) was evaluated.

### *hMatrix*

There are few published studies that address the use of hMatrix. Therefore, it is not possible to determine whether hMatrix has a beneficial effect on health outcomes.

hMatrix PR ADM (Bacterin International, Inc.) is an ADM allograft that is derived from donated human skin. It is indicated to provide appropriate support and reinforcement for hernia and abdominal wall repairs.

### *Human Health Factor 10 Amniotic Patch (HHF10P)*

There are few published studies that address the use of Human Health Factor 10 Amniotic Patch (HHF10P) for wound treatment. Therefore, it is not possible to determine whether HHF10P has a beneficial effect on health outcomes.

HHF10P (Wolver and Poole Distribution, LLC) is a single-layer amniotic allograft that is derived from donated and screened, full-term human birth tissue, specifically the immunoprivileged amnion layer. It is a semitransparent, minimally manipulated, terminally sterilized membrane allograft. HHF10P is intended for homologous use; it acts as a covering and barrier and offers protection from the surrounding environment in clinical applications.

### *Hyalomatrix*

Several noncomparative, published studies address the use of Hyalomatrix, and all have limitations. Therefore, it is not possible to determine whether Hyalomatrix has a beneficial effect on health outcomes.

Hyalomatrix (Medline Industries, Inc.) is a nonwoven pad comprising a wound contact layer that is made of a derivative of hyaluronic acid in fibrous form; the outer layer comprises a semipermeable silicone membrane. It is indicated for the management of a variety of wounds.

The ECRI reports for Hyalomatrix Tissue Reconstruction Matrix for Treating Burns and Chronic Wounds both indicated that the evidence for these products is inconclusive because there is limited evidence. No data are available to determine how Hyalomatrix compares with other wound dressings for healing any type of chronic wound (ECRI Hyalomatrix Tissue

Reconstruction Matrix for Treating Burns, 2018; ECRI Hyalomatrix Tissue Reconstruction Matrix for Treating Chronic Wounds, 2018' updated April 2021; Simman et al., 2018).

In a 2018 prospective, noncomparative clinical case series, Simman et al. (reviewed in the ECRI report above) analyzed the efficacy of a hyaluronic acid–based matrix (Hyalomatrix) in the treatment of lesions in which the extracellular matrix was lost. Twelve participants, with 12 serious surgical wounds of different etiologies, participated. Many defects showed exposed muscle, tendons, and/or bone. After thorough debridement, a hyaluronic acid-based matrix, with a removable, semipermeable silicone top layer, was applied for the purpose of generating a neodermis. In a number of cases, the matrix was combined with negative-pressure wound therapy. All wounds developed granulation tissue. Nine wounds were subsequently closed with a split-skin autograft. No graft failure occurred. Three wounds healed by secondary intention. All wounds showed complete reepithelialization. The authors concluded that in this case series, the use of a hyaluronic acid-based matrix provided a granulation tissue, and all lesions healed completely; additionally, the case series showed a strong trend for Hyalomatrix to play an important role in supporting wound healing in complex, surgical wounds. Limitations include a lack of a control group and small number of participants.

## *InnovaMatrix AC, InnovaMatrix FD, or InnovaMatrix FS*

There are few published studies that address the use of InnovaMatrix AC, InnovaMatrix FD, and InnovaMatrix FS. Therefore, it is not possible to determine whether InnovaMatrix AC, InnovaMatrix FD, or InnovaMatrix FS has a beneficial effect on health outcomes.

InnovaMatrix AC (Convatec Triad Life Sciences, LLC) is a skin substitute that is created from extracellular matrix that is found in porcine placenta for the treatment of acute, traumatic, and chronic wound care.

InnovaMatrix FD (Convatec Triad Life Sciences, LLC) is a wound matrix that is made from porcine placental extracellular matrix that contains collagen, elastin, laminin, fibronectin, hyaluronic acid, and sulfated glycosaminoglycans. It is intended for various wound types, including pressure, diabetic, vascular, surgical, and trauma wounds.

InnovaMatrix FS (Convatec Triad Life Sciences, LLC) is a decellularized extracellular matrix topical wound covering that is derived from porcine placental tissue.

## *Integra Flowable Wound Matrix*

There are several published studies that address the use of Integra Flowable Wound Matrix, and all the studies have limitations. Therefore, it is not possible to determine whether Integra Flowable Wound Matrix has a beneficial effect on health outcomes.

Integra Flowable Wound Matrix (Integra LifeSciences Corporation) is an advanced wound care product that comprises granulated, cross-linked bovine tendon collagen and glycosaminoglycan. It is intended for the management of deep and tunneling wounds.

Campitiello et al. (2017) conducted a randomized clinical trial, with the aim to evaluate the efficacy of an advanced wound matrix (Integra Flowable Wound Matrix) for treating wounds with irregular geometries vs. a wet dressing in participants with DFUs. The study was conducted in the General Surgery Unit and Geriatric of the Second University of Naples, Italy, for 12 months. Overall, 46 cases of DFUs (grade 3 Wagner) were equally and randomly divided into control and test groups. The first group was treated with Integra Flowable Wound Matrix, while the control group received a wet dressing. Both groups were evaluated once per week for 6 weeks to value the degree of epithelialization and granulation tissue of the wound. The complete healing rate in the whole study population was 69.56% (Integra Flowable Wound Matrix group, 86.95%; control group, 52.17%). Amputation and rehospitalization rates were higher in the control group than the treatment group; therefore, the difference was statistically significant. The Integra Flowable Wound Matrix was significantly superior, compared with the wet dressing, by promoting the complete healing of DFUs. The authors concluded that this product is appropriate in the management of DFUs, but additional research is needed and will highlight the promising advantages of this material in healing DFUs. This study was excluded from the AHRQ report (Snyder et al., 2020) because it did not meet the criteria for using adequate SOC.

An ECRI report for Integra Flowable Wound Matrix concluded that the available evidence is inconclusive due to too few data on outcomes and comparisons of interest to determine whether Integra Flowable Wound Matrix is effective and safe for treating DFUs. Only one RCT that compared treatment with Integra Flowable Wound Dressing with treatment with a wet dressing was identified. This RCT has several limitations, including a small sample size and no blinding; additionally, it was conducted in a single medical center in a single country, and the need for longer follow-up results in a risk of bias (ECRI, 2019).

## *IntéguPly*

There are few published studies that address the use of IntéguPly. Therefore, it is not possible to determine whether this product has a beneficial effect on health outcomes.

IntéguPly (Aziyo Biologics) is a human ADM that is intended for the treatment of chronic DFUs, venous leg ulcers, and pressure wounds. It is also intended for the support, protection, reinforcement, and covering of a tendon, ligament, and rotator cuff.

## *Interfyl*

There are few published studies that address the use of Interfyl. Therefore, it is not possible to determine whether Interfyl has a beneficial effect on health outcomes.

Interfyl (Celularity Inc.) is a decellularized and dehydrated placental disc (chorionic plate)-derived extracellular matrix. Interfyl is intended for treating deep dermal wounds, irregularly shaped and tunneling wounds, and augmentation of deficient/inadequate soft tissue, and it also repairs small surgical defects.

## *Keramatrix*

There are several studies that are related to Keramatrix, and all the studies have limitations. Therefore, it is not possible to determine whether Keramatrix has a beneficial effect on health outcomes.

Keramatrix (Keraplast Technologies LLC) is an absorbable, keratin-rich dressing that is indicated for full- and partial-thickness wounds with low to high exudate. It comprises freeze-dried, acellular, animal-derived keratin protein.

Loan et al. (2016) conducted a controlled study that included 40 individuals with superficial or partial-thickness burn injuries that were treated with Keramatrix and compared them with 40 historical controls who received SOC treatment. The results indicated a significantly faster mean healing time in the Keramatrix group than in the control group (8.7 days vs. 14.4 days). This was a small, nonrandomized trial.

Davidson et al. (2013) conducted an RCT using a standard care alginate (ALGISITE) dressing side by side with an experimental dressing (Keramatrix) in 26 participants with partial-thickness donor site wounds. The proximal/distal placement of the control and treatment were randomized. Percentage epithelialization after approximately 7 days was estimated from which the time to fully epithelialize could be inferred. Participants were grouped into young (age ≤ 50 years) and old (age > 50 years). For the old participants (n = 15), the median epithelialization percentage at 7 days was 5% and was significantly greater with the experimental dressing. For the young participants (n = 11), the median epithelialization percentage at 7 days was 80%; no significant difference between the experimental and standard care control dressings was observed. The authors concluded that the Keramatrix dressing significantly increases the rate of epithelialization in acute, traumatic, partial-thickness wounds in older individuals. This study was limited by a small sample size and short follow-up time.

## *Kerasorb*

There are few published studies that address the use of Kerasorb. Therefore, it is not possible to determine whether Kerasorb has a beneficial effect on health outcomes.

Kerasorb (Keraplast Technologies LLC) is a keratin protein–based topical wound and surgical dressing for treating skin wounds.

## *Kerecis Omega3 and Kerecis Omega3 MariGen Shield*

Several studies have examined Kerecis Omega3 products and Kerecis Omega3 MariGen Shield, each with notable limitations. Although the evidence is somewhat favorable, it remains limited regarding the safety of and long-term outcomes with these products.

Kerecis develops and manufactures products that are made from decellularized North Atlantic cod that is processed to maintain the fish skin's natural components like omega-3 fatty acids, collagen, and elastin, which are intended to facilitate growth in the wound bed and tissue regeneration. It is intended to treat diabetic, venous, pressure, and vascular ulcers and partial- and full-thickness wounds, including trauma and surgical wounds.

A Hayes (2024) Evolving Evidence Review for Kerecis Omega3 Wound (Kerecis) Fish Skin Grafts for the management of burns indicated minimal support in both clinical studies and a systematic review. No guidelines were found at the time of

this review. One very-poor-quality, retrospective comparison study suggested that deep, partial-thickness burns treated with Kerecis Omega3 Wound had statistically significantly shorter 95% reepithelialization time and better scar quality at 12 months of follow-up vs. deep, partial-thickness burns treated with an STSG. Pain and itchiness levels were low with both Kerecis Omega3 Wound and the STSG.

A 2024 Hayes Evolving Evidence Review for Kerecis Omega3 Wound Fish Skin Grafts indicated that there is a minimal level of support based on clinical studies and systematic reviews, with no clear guidelines for the use of Kerecis in the management of diabetic ulcers. One fair-quality comparative study indicated that approximately 60% of individuals experienced complete wound healing and a shorter time to healing compared with those receiving collagen alginate therapy (CAT), although the difference in time was small. Two systematic reviews included two or three comparative or noncomparative studies, with small sample sizes and short follow-up durations, that evaluated Kerecis. One of the RCTs showed a higher rate of full healing in DFUs treated with Kerecis vs. those treated with a collagen alginate dressing alone; no other product comparisons were identified. Additional RCTs are needed to compare how Kerecis performs compared with SOC and other products. Studies, with longer-term follow-up, are also needed to detect the rate of recurrence (Lantis et al., 2023, included below).

A Hayes Evolving Evidence Review for Kerecis Omega3 Wound (Kerecis) for the management of chronic lower extremity wounds includes three poor-quality and one fair-quality study that describe the clinical benefits of wound healing. One RCT found better healing outcomes with Kerecis compared with the collagen alginate dressing. Additional RCTs are needed to determine if Kerecis Omega3 Wound is better, worse, or the same as opposing alternatives, such as other animal-derived grafts. Kerecis Omega3 Wound has been suggested and tested for use in additional applications; however, the focus of this report was restricted to its use in chronic wounds of the lower leg. Based on these current studies and the large number of identified ongoing studies, this technology's evidence base should be regarded as evolving and monitored for new publications (Hayes, 2022).

An ECRI report for Omega3 Wound Matrix (Kerecis) for Treating Acute Wounds indicated that the evidence is inconclusive due to too few data on outcomes and comparisons of interest. A single-center study and a single-center case study were identified, with major limitations and a high risk of bias (ECRI, 2020).

A 2024 revised ECRI report for Omega3 Wound Matrix (Kerecis) for Treating Chronic Wounds found that one systematic review and two RCTs demonstrated its safety and efficacy in enhancing DFU healing compared with standard care and collagen/alginate dressings. A small RCT also suggested potential benefits for ischemic wounds, although further research is needed. No evidence currently supports its use for pressure ulcers. (ECRI; updated 2023).

Karhana and Khan (2025) conducted a systematic review to assess the efficacy and safety of omega-3 acellular fish skin grafts (AFSGs) in treating chronic and complicated wounds. Analyzing nine studies, they found that AFSGs promoted faster healing, reduced pain, and lowered the need for antibiotics, with no autoimmune reactions reported. Healing times varied by wound type, with DFUs healing in approximately 15 weeks and biopsy wounds healing in under 4 weeks. AFSGs generally outperformed standard treatments like collagen alginate dressings and porcine submucosa. However, the study faced limitations, including a small number of included studies, heterogeneity in the design and outcomes, a lack of RCTs, and some reported adverse effects such as rashes and hypergranulation. Additionally, potential publication bias may have influenced the findings due to the exclusion of non-English and unpublished studies. While the study found promising results regarding accelerated healing, pain reduction, and safety, the evidence base remains limited. The review included only nine studies, many of which varied in design, wound types, and outcome measures, making it difficult to draw definitive conclusions. Moreover, the lack of RCTs and reports of adverse effects, in some cases, emphasize the need for more robust, large-scale clinical research to validate efficacy, assess long-term outcomes, and better understand potential risks.

Dardari et al. (2024) conducted a multicenter RCT to evaluate the effectiveness of intact fish skin grafts (FSGs; Kerecis Omega3 Wound) in treating deep DFUs below the malleolus that penetrate to bone, joint, or tendon (University of Texas diabetic wound classification system, grade 2 or 3). This study included 255 participants across 15 centers in Europe and the United States and compared outcomes between those treated with FSGs and those receiving SOC. At 16 weeks, 44% of participants in the fish skin group achieved complete wound closure compared with 26% in the SOC group. By 24 weeks, healing rates increased to 55% and 38%, respectively. The fish skin group also experienced a faster median time to healing by approximately 2 weeks. Primary wound infections occurred in 30.2% of the fish skin group and 29.3% of the SOC group (corrected in 2025 from the initial publication). Despite its strengths, the study has several limitations: (1) it was open label, which introduces potential bias; (2) it was partially funded by the manufacturer; (3) site heterogeneity across countries may have affected consistency; and (4) the follow-up period was limited to 24 weeks, leaving long-term outcomes unassessed. Additionally, the need for a published correction raises concerns about the initial accuracy of the study. The authors concluded that intact FSGs are a promising therapeutic option, with the potential to heal more DFUs

than SOC, and were associated with faster times to heal, especially wounds that were deep and penetrating. Additional research would benefit from blinded designs, standardized wound care protocols, and head-to-head comparisons with other advanced therapies.

Gao et al. (2023) conducted a systematic review and meta-analysis that evaluated the effectiveness of FSGs as an adjuvant treatment to SOC for chronic ulcer treatment. Chronic wounds are wounds that fail to heal with a timely and orderly SOC treatment. SOC treatment has been commonly applied for the management of chronic wounds, but SOC alone may not be adequate to heal all ulcers effectively. An FSG is a xenogenic skin substitute that is made from the skin of North Atlantic cod, which could be used for accelerating skin healing. Several RCTs have identified the efficacy of FSG, with rather small sample sizes. No high-level evidence has been published to integrate the current available evidence on the clinical efficacy of FSG for treating chronic wounds. A total of eight studies were included in a qualitative synthesis and meta-analysis, with 145 individuals treated with SOC and 245 individuals treated with SOC plus FSG. No significant difference was observed between the two groups in time to healing (MD, 1.99; 95% CI, -3.70 to 7.67; p = 0.493). The complete healing rate was significantly higher in the FSG group compared with SOC alone (OR, 3.44; 95% CI, 2.03-5.82; p < 0.001). The mean PAR was reported in six studies, with a range of 71.6% to 97.3%. However, many of these studies did not report the value of SD, so the data could not be pooled. No significantly different ulcer recurrence rate (RR, 0.60; 95% CI, 0.07-5.27; p = 0.645) and severe adverse event risk (RR, 1.67; 95% CI, 0.42 to 6.61; p = 0.467) were found between the two groups. Study limitations include the different points of follow-up; additionally, the data that resulted from the final follow-up may have caused a risk of bias on the pooling results, the included studies were lacking regarding the safety of FSG, and the studies had small sample sizes. This study was designed to evaluate the efficacy of FSG in the management of chronic ulcers, including DFUs, peripheral artery disease ulcers, venous ulcers, and other complicated, chronic wounds. Conducting subgroup analyses on diverse types of wounds could possibly provide more reliable conclusions. The authors noted that the application of FSG treatment for individuals with chronic ulcers that do not respond well to SOC management could significantly increase the complete healing rate compared with SOC alone, without increased recurrence rate and serious adverse event risk. Additional studies are needed, with larger sample sizes and a focus on individual wound types, to provide higher-quality evidence.

In 2023, Lantis et al. (included in the ECRI report on chronic wounds above) reported the final results of a prospective, multicenter RCT that evaluated the efficacy of an omega-3–rich, acellular FSG, Kerecis Omega3 MariGen, compared with that of CAT, Fibracol Plus Collagen Wound Dressing with Alginate, in the management of chronic DFUs. Previous results were reported in 2021 (Lullove et al., 2021). Overall, 102 participants were recruited and randomized 1:1 to the study arm and control arm. The primary end point was the absolute percentage of participants who achieved wound closure at 12 weeks. Secondary outcomes included the effect of FSG, healing rate, and PAR. Of the 102 participants, 77 comprised the per-protocol cohort; 25 ITT participants were excluded from the per-protocol analysis due to protocol deviations, or they were not on track to achieve healing. Although all 102 participants were included in the ITT analysis, these participants were excluded from time to healing and wound area reduction calculations. The primary end point results showed that in the ITT analysis, 56.9% of index ulcers (29 of 51) healed in the FSG arm compared with 31.4% (16 of 51) in the CAT arm, and this difference began to show at 4 weeks. Secondary end points were assessed at 6 and 12 weeks in the ITT and per-protocol groups and showed the same healing time for both, with a mean time to healing of 7.31 weeks in the CAT arm and 7.17 weeks in the FSG arm. The mean PAR at 6 weeks was 51.6% in 32 participants in the CAT group and 71.6% in 36 participants in the FSG group; in both the ITT and per-protocol analyses, the mean PAR at 12 weeks was 64% in 27 participants in the CAT group and 86.3% in 38 individuals in the FSG group. At the 6- to 12-month follow-up, one ulcer recurrence was reported in the CAT arm, and three ulcer recurrences were recorded in the FSG arm, which may be related to three of the four participants not having appropriate offloading footwear. The authors concluded that the use of FSG resulted in significantly more healed DFUs in 12 weeks than CAT. This RCT is limited by a small group of participants; additionally, it only assessed DFUs. This RCT was also impacted by the COVID-19 pandemic, which resulted in a 24.5% dropout rate. Further high-quality research, with larger participant populations and different types of wounds, is necessary to validate these findings. (This study is included in the systematic review by Gao et al., 2023.)

Luze et al. (2022) conducted a systematic review that summarized the current published evidence on the use of acellular fish skin in the treatment of burn injuries. Acellular fish skin acts as a skin substitute, decreasing the inflammatory response and promoting proinflammatory cytokines that help wound healing. These properties might represent an effective treatment approach in burn wound management. A systematic review of the literature, up to March 2022, which resulted in 14 trials that investigated the effects of acellular fish skin in burn wounds or split-thickness donor sites, were determined to be eligible and included in the present review. Nile tilapia were evaluated in seven of the trials, and Kerecis Omega3 (North Atlantic cod) was evaluated in five trials. The present evidence on the use of acellular fish skin shows an acceleration of wound healing, reduction in pain and necessary dressing changes, and improved aesthetic and functional outcomes compared with conventional treatment options. Study limitations include the following: (1) the study cohorts were small; (2) the results cannot be pooled; (3) the studies were geographically limited based on the availability of xenografts; and (4) comparison studies are needed between products. Acellular fish skin xenografts may be an effective

treatment for superficial and partial-thickness burns. Larger cohort studies are needed to clarify the full potential of this promising approach. (This study is included in the systematic review by Gao et al., 2025.)

Lullove et al. (2021; included in the ECRI report above) conducted an RCT to evaluate FSGs with SOC using a collagen alginate dressing in the management of treatment-resistant DFUs that do not involve the tendon capsule or bone. Participants with DFUs who were first treated with SOC (offloading, appropriate debridement, and moist wound care) for a 2-week screening period were then randomized to either receive SOC or SOC plus an FSG applied weekly for up to 12 weeks. The main end-point was the percentage of wounds closed at 12 weeks. Overall, 49 participants were included in the final study. At 12 weeks, DFUs in 16 of 24 participants (67%) in the fish skin arm were completely closed compared with DFUs in 8 of 25 participants (32%) in the SOC arm [$p = 0.0152$ ($n = 49$); significant at $p < 0.047$]. At 6 weeks, the PAR was 41.2% in the SOC arm and 72.8% in the fish skin arm. The application of an FSG to previously nonresponsive DFUs resulted in significantly more fully healed wounds at 12 weeks than SOC alone. Study limitations include a small study population and intrinsic blinding, in which the participant and member applying the product were aware that the FSG was being applied. The study findings show favorable results for the use of FSGs for chronic DFUs that do not heal with SOC treatment. These findings need to be confirmed in a larger study population.

In a prospective RCT, Kirsner et al. (2020) compared FSGs with human amnion/chorion membrane allografts in acute would healing. Grafts can come from an individual's own skin (autograft), a human donor (allograft), or from a different species (xenograft). A fish skin xenograft from cold-water fish (Atlantic cod, Gadus morhua) is a relatively new option that shows promising preclinical and clinical results in wound healing. Chronic wounds vary greatly in etiology and nature, requiring large cohorts for effective comparison between therapeutic alternatives. In this study, they attempted to imitate the status of a freshly debrided, chronic wound by creating acute full-thickness wounds, which were 4 mm in diameter, on healthy volunteers to compare two materials that are frequently used to treat chronic wounds: fish skin and dHACM. The purpose was to give an indication of the efficacy of the two therapeutic alternatives in the treatment of chronic wounds in a simple, standardized, randomized controlled, double-blinded study. All volunteers were given two identical punch biopsy wounds, one of which was treated with an FSG and the other with a dHACM allograft. In the study, 170 wounds were treated (85 wounds per group). The primary end point was defined as the time to heal (full epithelialization) by blinded assessment at days 14, 18, 21, 25, and 28. The superiority hypothesis was that the FSGs would heal the wounds faster than the dHACM. To evaluate the superiority hypothesis, a mixed Cox proportional hazards model was used. Wounds treated with fish skin healed significantly faster (hazard ratio, 2.37; 95% CI, 1.75-3.22; $p = 0.0014$) compared with wounds treated with dHACM. The results showed that acute biopsy wounds that are treated with FSGs heal faster than wounds treated with dHACM. Limitations of this study include the use of acute wounds from a punch biopsy rather than chronic, nonhealing wounds. Larger studies are needed to include participants with chronic, unhealing wounds. (This study is included in the systematic review by Karhana and Khan, 2025, and Gao et al., 2022.)

### *Keroxx*

There are few published studies that address the use of Keroxx. Therefore, it is not possible to determine whether Keroxx has a beneficial effect on health outcomes.

Keroxx Flowable Wound Matrix (Molecular Biologicals, Inc.) is a wound matrix that comprises keratin-enriched proteins and is intended to aid in the growth of new tissue in wounds. These keratin proteins are extracted from sheep wool and are placed in an open-celled, injectable gel format.

### *Lamellas and Lamellas XT*

Studies are lacking regarding the use of Lamellas and Lamellas XT for wound treatment. Therefore, it is not possible to determine whether Lamellas and/or Lamellas XT has a beneficial effect on health outcomes.

Lamellas and Lamellas XT (Keyport Management) are intended for use as a protective wound covering and barrier in acute and chronic wounds.

### *Mantle DL Matrix*

Studies are lacking regarding the use of Mantle DL Matrix for wound treatment. Therefore, it is not possible to determine whether Mantle DL Matrix has a beneficial effect on health outcomes.

Mantle DL Matrix (Sequence LifeScience, Inc.) is a dual-layer, minimally manipulated HAM product that is derived from placental tissue that retains the structural and functional characteristics of the tissue. The product is typically used for individuals with full-thickness, acute and chronic wounds for which a biological barrier or wound cover is required.

## *MariGen Pacto*

Due to a lack of sufficient studies on MariGen Pacto for wound treatment, it is not currently possible to determine whether MariGen Pacto has a beneficial effect on health outcomes.

MariGen Pacto (Kerecis) is an FSG that is derived from North Atlantic cod. It is created by assembling smaller pieces of fish skin into a larger, stable sheet that is designed to maintain integrity in the wound bed. It is indicated for the management of partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, trauma wounds, and certain surgical or draining wounds.

## *MatriDerm*

There are several studies that are related to MatriDerm, and all the studies have limitations. Therefore, it is not possible to determine whether MatriDerm has a beneficial effect on health outcomes.

MatriDerm (MedSkin Solutions Dr. Suwelack AG) is a single-use, 3D ADM that is composed of bovine collagen fibers and bovine elastin. MatriDerm is indicated for the management of wounds, including full-thickness and partial-thickness wounds, chronic wounds (e.g., pressure ulcers, venous ulcers, diabetic ulcers, chronic ulcers), surgical wounds (e.g., donor sites/grafts, post Mohs surgery, post laser surgery, podiatric, wound dehiscence), partial-thickness burns, trauma wounds (e.g., abrasions, lacerations, skin tears), and draining wounds.

In a 2023 ECRI Clinical Evidence Assessment for treating burns, one RCT (Vana et al., 2020) and two nonrandomized comparison studies suggested that MatriDerm is safe and works as intended for the healing of burns and burn scar reconstruction in conjunction with STSGs; however, the studies provided very-low-quality evidence and assessed too few individuals to be conclusive.

In a 2023 ECRI Clinical Evidence Assessment for managing wounds following otorhinolaryngology surgery, evidence from four low-quality studies (three nonrandomized comparison studies and one case series) suggests that MatriDerm is safe and works as intended in managing and repairing otorhinolaryngology defects, both as a stand-alone treatment and in conjunction with skin grafts and stromal vascular cells; however, the studies have a high a risk of bias and evaluate too few individuals to be conclusive.

## *Matrion*

There are few published studies that address the use of Matrion. Therefore, it is not possible to determine whether Matrion has a beneficial effect on health outcomes.

Matrion (LifeNet Health) is a regenerative human placental allograft that is procured and processed from donated human tissue. The resulting decellularized placental membrane is available in membrane, injectable, and sponge configurations for use in wound, tendon, and nerve application. Matrion is intended to modulate inflammation in surgical sites, enhance healing, and act as a barrier.

## *MatriStem MicroMatrix*

There are several studies related to MatriStem MicroMatrix, and all the studies have limitations. Therefore, it is not possible to determine whether MatriStem MicroMatrix has a beneficial effect on health outcomes.

MatriStem (ACell Inc.) products consist of collagens, carbohydrates, and proteins that are derived from the urinary bladder tissue of pigs. MatriStem is intended for surgical wound care, pelvic floor support or reconstruction, burns, and wound healing.

Refer to the above section titled Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes for additional articles/reports that evaluate MatriStem.

Frykberg et al. (2016) conducted a prospective, randomized clinical study at 13 centers throughout the United States to assess the application of MatriStem MicroMatrix and MatriStem Wound Matrix (porcine urinary bladder-derived extracellular matrix) compared with that of Dermagraft (hFDS) for the management of nonhealing DFUs. There were 95 participants who entered into the SOC 4-week screening phase of the trial, and 56 of them were randomized into the treatment phase. This study was developed to evaluate the hypothesis that the wound outcomes observed after wound management with MatriStem were noninferior to those with Dermagraft after 8 weeks. The authors presented the planned interim results of this study after half of the projected enrollment was completed. At the planned interim analysis, there was significant improvement in quality of life in the participants treated with MatriStem compared with those managed with Dermagraft. However, there was not a statistically significant difference found during the analysis of the interim data

between the two study groups for rate of wound healing or number of participants with complete wound closure. This study reports only interim results.

### *Matrix HD Allograft Dermis*

There are few published studies that address the use of Matrix HD Allograft Dermis. Therefore, it is not possible to determine whether Matrix HD Allograft Dermis has a beneficial effect on health outcomes.

Matrix HD Allograft Dermis (Royal Wound-X) is an acellular human dermis matrix that is intended as a wound cover to help repair, replace, reconstruct, and supplement damaged soft tissue in acute and chronic wounds, including DFUs and burns.

### *Mediskin*

There is limited evidence related to the efficacy of and long-term outcomes with Mediskin for treating wounds. Therefore, it is not possible to determine whether Mediskin has a beneficial effect on health outcomes.

Mediskin (Brennen Medical, Inc.) is a porcine-derived decellularized fetal skin product.

In a prospective, randomized, three-arm clinical study, Karlsson et al. (2014) compared Aquacel®, ALLEVYN, and Mediskin I in the treatment of STSG donor sites in 67 adults. Participants were randomly assigned to treatment with Aquacel, ALLEVYN, or Mediskin I. The donor site was assessed on postoperative days 3, 14, and 21 for healing, infection, pain, impact on everyday life, and ease of use. The obtained results demonstrate significantly faster reepithelialization in participants treated with Aquacel or Mediskin I compared with ALLEVYN. Regarding infections, there were no significant differences between the groups. Participants wearing Aquacel experienced significantly less pain when changing the dressing and less impact on everyday life than those wearing ALLEVYN. According to the authors, Aquacel was shown to be significantly easier for the caregiver to use than ALLEVYN and Mediskin I. These findings require confirmation in a larger, controlled trial.

### *Membrane Graft, Membrane Wrap, Membrane Wrap-Hydro, or Membrane Wrap-Lite*

There are few published studies that address the use of Membrane Graft, Membrane Wrap, Membrane Wrap-Hydro, and Membrane Wrap-Lite. Therefore, it is not possible to determine whether these products have a beneficial effect on health outcomes.

Membrane Graft and Membrane Wrap (BioLab Sciences, Inc.) are human amniotic allograft membranes that are intended to be used to repair tissue deficits and to reduce healing time for chronic wounds and postsurgical wounds.

Membrane Wrap-Hydro (BioLab Sciences, Inc.) is a hydrated human amnion membrane that is indicated for chronic and acute wounds. The product serves as a protective covering from the surrounding environment for acute and chronic wounds.

Membrane Wrap-Lite (BioLab Sciences, Inc.) is a human amnion single-layer allograft that is indicated for acute and chronic wounds.

### *MemoDerm*

There are few published studies that address the use of MemoDerm. Therefore, it is not possible to determine whether this product has a beneficial effect on health outcomes.

MemoDerm (Stryker) is an ADM that is derived from human allograft tissue. It is manufactured using a proprietary gamma irradiation sterilization process. It is marketed for use for joint surgeries and chronic DFUs.

### *Miro3D Fibers*

Studies are lacking regarding the use of Miro3D Fibers for wound treatment. Therefore, it is not possible to determine whether Miro3D Fibers has a beneficial effect on health outcomes.

The Miro3D Fibers Wound Matrix is a sterile, single-use, acellular wound dressing that is made from porcine liver tissue. The liver undergoes perfusion decellularization to create a collagen matrix, which is then dried, cut into fibers, and sterilized using e-beam irradiation. The Miro3D Fibers Wound Matrix is intended for the management of wounds, including partial- and full-thickness wounds; pressure ulcers; venous ulcers; chronic vascular ulcers; diabetic ulcers; tunneled,

undermined wounds; trauma wounds (abrasions, lacerations, partial-thickness burns, and skin tears); draining wounds; and surgical wounds (donor sites/grafts, post Mohs surgery, post laser surgery, podiatric, and wound dehiscence).

## *MiroDry Wound Matrix*

Studies are lacking regarding the use of MiroDry Wound Matrix for wound treatment. Therefore, it is not possible to determine whether MiroDry Wound Matrix has a beneficial effect on health outcomes.

The MiroDry Wound Matrix is a sterile, single-use, acellular wound dressing that is made from porcine liver tissue. The liver is perfusion-decellularized to create a collagen matrix, which is then dried and cut to specific sizes. The MiroDry Wound Matrix is intended for the management of wounds, including partial- and full-thickness wounds; pressure ulcers; venous ulcers; chronic vascular ulcers; diabetic ulcers; tunneled, undermined wounds; trauma wounds (abrasions, lacerations, partial thickness burns, and skin tears); draining wounds; and surgical wounds (donor sites/grafts, post Mohs surgery, post laser surgery, podiatric, and wound dehiscence).

## *Microlyte Matrix*

There are few published studies that address the use of Microlyte Matrix for wound treatment. Therefore, it is not possible to determine whether Microlyte Matrix has a beneficial effect on health outcomes.

Microlyte Matrix (Imbed Biosciences) comprises a polyelectrolyte multilayer nanofilm of cationic and anionic polymers, which together act as a functional molecular template to facilitate the granulation in the wound bed. Microlyte Matrix provides just the right combination of a synthetic wound matrix and moisture management to facilitate healing in acute and chronic wounds.

## *MicroMatrix Flex*

There are few published studies that address the use of MicroMatrix Flex for wound treatment. Therefore, it is not possible to determine whether MicroMatrix Flex has a beneficial effect on health outcomes.

MicroMatrix Flex (Acell Inc.) is a dual-syringe system that is designed to enable convenient mixing and delivery of MicroMatrix paste to hard-to-reach wound areas. It is intended for the management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post Mohs surgery, post laser surgery, podiatric, and wound dehiscence), trauma wounds (abrasions, lacerations, partial-thickness burns, and skin tears), and draining wounds. The device is intended for one-time use.

## *MIRODERM*

There are few published studies that address the use of MIRODERM for wound treatment. Therefore, it is not possible to determine whether MIRODERM has a beneficial effect on health outcomes.

MIRODERM (Miromatrix Medical Inc.) is a non-crosslinked, acellular wound matrix that is derived from porcine liver and is processed and stored in a phosphate-buffered aqueous solution. It is intended for the management of wounds.

## *MiroTract Wound Matrix*

There are few published studies that address the use of MiroTract Wound Matrix for wound treatment. Therefore, it is not possible to determine whether MiroTract Wound Matrix has a beneficial effect on health outcomes.

MiroTract Wound Matrix (Reprise Biomedical) is a single-use, non-crosslinked, acellular wound dressing that is derived from porcine liver tissue. The porcine liver is perfusion-decellularized, resulting in a collagen matrix that is dried, cut to size, and radially compressed onto the guidewire of the MiroTract delivery system. The delivery system includes a guidewire and tamp tube to manually push the MiroTract Wound Matrix off the guidewire into a wound. The MiroTract Wound Matrix is intended for the management of wounds, including partial- and full-thickness wounds; pressure ulcers; venous ulcers; chronic vascular ulcers; diabetic ulcers; tunneled, undermined wounds; trauma wounds (abrasions, lacerations, partial-thickness burns, and skin tears); draining wounds; and surgical wounds (donor sites/grafts, post Mohs surgery, post laser surgery, podiatric, and wound dehiscence).

## *Mirragen*

There are few published studies that address the use of Mirragen. Therefore, it is not possible to determine whether Mirragen has a beneficial effect on health outcomes.

Mirragen Advanced Wound Matrix (ETS Tech Holdings, LLC) is a synthetic, resorbable skin substitute that is made of biocompatible and resorbable borate-based glass fibers and particulates. The material covers the wound, absorbs exudate, and provides a matrix or scaffold material that the body uses for revascularization and soft tissue regeneration. It is intended to be used to treat a variety of acute and chronic wounds, including diabetic ulcers, pressure ulcers, vascular ulcers, trauma wounds, surgical incisions, and first- and second-degree burns.

An ECRI report for Mirragen Advanced Wound Matrix (ETS Tech Holdings, LLC) for Treating Diabetic Foot Ulcers indicates that the evidence for Mirragen is inconclusive. There was one small RCT that indicated that Mirragen is safe and works as intended. This study had a very small sample size to be conclusive. Additional RCTs are needed to validate these findings, and RCTs comparing Mirragen with other advanced wound care products are necessary to assess Mirragen's comparative safety and effectiveness for treating DFUs (ECRI, 2024).

In an RCT, Armstrong et al. (2022a) investigated the healing potential of Mirragen Advanced Wound Matrix (BBGFM) in participants with chronic DFUs, comparing the healing rate with that with SOC treatment (collagen alginate dressing) alone at 12 weeks. Both groups received standard diabetic foot care, including glucose monitoring, weekly debridement when needed, and an offloading device. The primary end point was percentage of full-thickness, noninfected, nonischemic wounds healed at 12 weeks, with secondary end points including PAR and changes in Semmes-Weinstein monofilament testing. The result that was illustrated in the ITT analysis at 12 weeks showed that 70% (14/20) of the BBGFM-treated DFUs healed compared with 25% (5/20) treated with SOC alone (adjusted $p = 0.006$). The mean PAR at 12 weeks was 79% in the BBGFM group compared with 37% in the SOC group (adjusted $p = 0.027$). The mean change in neuropathic score between baseline and up to 12 weeks of treatment was 2.0 in the BBGFM group compared with -0.6 in the SOC group, where positive improvement in scores is better (adjusted $p = 0.008$). The mean number of BBGFM applications was 6.0. In conclusion, adding BBGFM to SOC significantly improved wound healing, with no adverse events related to treatment, compared with SOC alone. While the design was robust, the study had weaknesses. The main weakness is the lack of investigator blinding and failure to withdraw participants who were not responding and provide them with a different treatment. In conclusion, this trial has established that the addition of a bioactive glass microfiber matrix that contains boron to SOC results in suggestively improved wound healing in Wagner 1 DFUs compared with SOC alone, with hopeful results regarding infection and neuropathy. Additional studies are needed to confirm these findings.

## *MLG-Complete*

There are few published studies that address the use of MLG-Complete for wound treatment. Therefore, it is not possible to determine whether MLG-Complete has a beneficial effect on health outcomes.

MLG-Complete (Samaritan Biologics, LLC) is a full-thickness, amnion-chorion–derived allograft for the management of wounds and burn injuries. MLG-Complete is a sterile, single-use, dehydrated allograft that is derived from donated human amnion-chorion membrane that acts as a cover and a barrier that offers protection from the surrounding environment. The intended use of MLG-Complete includes the management of wounds, such as partial- and full-thickness wounds, pressure sores/ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor site/grafts, post laser surgery, post Mohs surgery, podiatric wounds, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, partial-thickness burns, skin tears), and draining wounds.

## *MOST*

There are few published studies that address the use of MOST for wound treatment. Therefore, it is not possible to determine whether MOST has a beneficial effect on health outcomes.

MOST (Samaritan Biologics, LLC) is a perforated, three-layer, amnion-chorion-amnion–derived allograft that serves as a barrier and provides protective coverage from the surrounding environment for acute and chronic wounds.

## *MyOwn Skin*

There are few published studies that address the use of MyOwn Skin. Therefore, it is not possible to determine whether MyOwn Skin has a beneficial effect on health outcomes.

MyOwn Skin (BioLab Sciences, Inc.) is an autologous, homologous skin product. This product is composed of an individual's own viable skin cells and is intended to support cellular attachment and proliferation for tissue and skin repair.

## *Myriad Matrix*

Studies are lacking regarding the use of Myriad Matrix for wound treatment. Therefore, it is not possible to determine whether Myriad Matrix has a beneficial effect on health outcomes.

Myriad (Aroa Biosurgery Ltd.) is an advanced collagen matrix that is made from over 70% natural, nonreconstituted collagen that is derived from sheep forestomach extracellular matrix. It serves as a porous scaffold for cell infiltration and vascular ingrowth during wound healing. Myriad is used to treat various acute and chronic wounds and to reinforce soft tissue in plastic and reconstructive surgery. It is indicated for partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining wounds.

### *Myriad Morcells*

Studies are lacking regarding the use of Myriad Morcells for wound treatment. Therefore, it is not possible to determine whether Myriad Morcells has a beneficial effect on health outcomes.

Myriad Morcells (Aroa Biosurgery Ltd.) is an extracellular matrix that is primarily composed of ovine (sheep)-derived collagen Ovine and associated extracellular matrix components collagen I and collagen III. Myriad Morcells is the proprietary (brand) name of the technology, which was cleared under the device name “Myriad Particles.” Morcells functions as a porous scaffold for cell infiltration and vascular ingrowth during wound healing and is used for the treatment of certain acute and chronic wounds, consistent with its US Food and Drug Administration indication for use.

### *Natalin*

Due to a lack of sufficient studies on Natalin for wound treatment, it is currently not possible to determine whether Natalin has a beneficial effect on health outcomes.

Natalin (RMBB Health) is a trilayer DDHAM allograft that is terminally sterilized via e-beam irradiation. It serves as a biological barrier and wound covering to protect surgical sites and support healing in acute and chronic wounds, including ulcers and burns.

### *NeoMatriX*

There are few published studies that address the use of NeoMatriX. Therefore, it is not possible to determine whether NeoMatriX has a beneficial effect on health outcomes.

NeoMatriX (NeXtGen™ Biologics) is fabricated from the dermal extracellular matrix of axolotl. This device is derived from an amphibian farm-raised hybrid axolotl source from a closed herd in a dedicated facility. NeoMatriX wound matrix provides an adherent covering that protects the wound from the environment.

### *NeoPatch*

There are few published studies that address the use of NeoPatch for wound treatment. Therefore, it is not possible to determine whether this product has a beneficial effect on health outcomes.

NeoPatch (CryoLife, Inc.) is a wound covering that is derived from terminally sterilized, dehydrated human placental membrane tissue that comprises both amnion and chorion.

### *NeoThelium FT, NeoThelium 4L, and NeoThelium 4L Plus*

Due to a lack of sufficient studies on NeoThelium FT, NeoThelium 4L, and NeoThelium 4L Plus for wound treatment, it is currently not possible to determine whether NeoThelium FT, NeoThelium 4L, or NeoThelium 4L Plus have that is derived from donated human placental tissue. It is intended for use as a protective wound covering and barrier for both acute and chronic wounds.

NeoThelium 4L Plus (Neostim, LLC) is a full-thickness quad-layer amnion/chorion/chorion/amnion allograft that is derived from donated human placental tissue. It is intended for use as a protective wound covering and barrier for both acute and chronic wounds.

### *NEOX*

There are few published studies that address the use of NEOX for wound treatment. Therefore, it is not possible to determine whether NEOX has a beneficial effect on health outcomes.

NEOX Wound Allografts (Amniox Medical, Inc.) comprise two products: NEOX CORD 1K Wound Allograft, which is a cryopreserved human umbilical cord and amniotic membrane, and NEOX 100 Wound Allograft, which is a cryopreserved HAM that is indicated for minor and superficial dermal wounds. Both are indicated as wound coverings for dermal ulcers and defects.

### *NEOX FLO*

There are few published studies that address the use of NEOX FLO for wound treatment. Therefore, it is not possible to determine whether this product has a beneficial effect on health outcomes.

NEOX FLO (Amniox Medical, Inc.) is a particulate form of NEOX that comprises amniotic membrane and umbilical cord products that are derived from human placental tissue. It is intended to be used as a wound covering for dermal ulcers and defects such as diabetic ulcers.

A 2021 ECRI Clinical Evidence Assessment did not identify any published studies regarding NEOX FLO's safety and efficacy for treating chronic wounds.

### *NeoStim Membrane, NeoStim DL Membrane, and NeoStim TL*

There are few published studies that address the use of NeoStim products. Therefore, it is not possible to determine whether these products have a beneficial effect on health outcomes.

NeoStim products include NeoStim Membrane (single layer), NeoStim DL (double layer), and NeoStim TL (triple layer) dehydrated amnion membrane allografts that are derived from donated HAM; NeoStim products serve as a barrier or provide a protective coverage from the surrounding environment for acute and chronic wounds such as partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, and trauma wounds.

### *Novachor*

There are few published studies that address the use of Novachor. Therefore, it is not possible to determine whether Novachor has a beneficial effect on health outcomes.

Novachor (Organogenesis Inc.) comprises the chorion layer of the placental membranes. It is intended to be applied as a graft to protect the wound and support healing for acute and chronic wounds, including neuropathic ulcers, venous stasis ulcers, pressure ulcers, burns, posttraumatic wounds, and postsurgical wounds.

### *Novafix*

There are few published studies that address the use of Novafix. Therefore, it is not possible to determine whether Novafix has a beneficial effect on health outcomes.

Novafix (Triad Life Sciences, LLC) is a dehydrated HAM allograft that is indicated for use in the management of wounds.

### *Novafix DL*

There are few published studies that address the use of Novafix DL. Therefore, it is not possible to determine whether Novafix DL has a beneficial effect on health outcomes.

Novafix DL (Triad Life Sciences, LLC) is an amnion-chorion membrane that is composed of placental extracellular matrix, which is donated by prescreened mothers who elected cesarean birth, that is used to offer protection in the treatment of superficial and traumatic injuries.

### *NovoSorb SynPath*

There are few published studies that address the use of NovoSorb SynPath. Therefore, it is not possible to determine whether NovoSorb SynPath has a beneficial effect on health outcomes.

NovoSorb SynPath is a synthetic dermal matrix that comprises a porous network of nontoxic, biodegradable synthetic polymers that acts as a scaffold to support the proliferation of cells involved in cellular repair. NovoSorb Biodegradable Temporizing Matrix may be used to temporarily close the wound and aid the body in generating new tissue.

### *NuDYN*

There are few published studies that address the use of NuDYN for wound treatment. Therefore, it is not possible to determine whether NuDYN has a beneficial effect on health outcomes.

NuDYN (Fidia Pharma USA Inc.) is an injectable, flowable amniotic membrane–derived allograft that is packaged in sterile vials and is intended for topical application to the wound surface; it supports wound healing and soft tissue repair. It is a

nonsurgical alternative for health care providers to offer their patients and complements products such as Hyalgen. Its properties include hyaluronic acid, collagen, and growth factors, which protect, lubricate, and support the tissue.

## *NuShield*

There are limited studies that address the use of NuShield. Therefore, it is not possible to determine whether NuShield has a beneficial effect on health outcomes.

NuShield (NuTech) is a protective patch that is derived from amniotic membrane; it is indicated as an adhesion barrier and wound covering and acts as an adjunct to soft tissue healing. It is intended for use in spinal surgery and as a protective barrier for tendons and nerves following tendon repair.

Cazzell et al. (2024) conducted a multicenter, prospective RCT to assess the clinical effectiveness of dehydrated amnion chorion membrane (dACM) for DFUs. Participants with a DFU extending into dermis, subcutaneous tissue, tendon, capsule, bone, or joint were enrolled in a 12-week trial. They were divided equally between a dACM (plus SOC) group and an SOC-alone group. The central end point was frequency of wound closure, decided by a Cox analysis that varied for duration and wound area. A Kaplan-Meier analysis was used to determine the average time to complete wound closure. The study included 218 participants, who were split equally between a dACM (plus SOC) group and an SOC-alone group (109 participants in each). A Cox analysis showed that the estimated frequency of wound closure in the dACM plus SOC group was statistically superior to that in the SOC-alone group at week 4 (12% vs .8%), week 6 (22% vs. 11%), week 8 (31% vs. 21%), week 10 (42% vs. 27%), and week 12 (50% vs. 35%), respectively ($p = 0.04$). The computed hazard ratio (1.48; CI, 0.95-2.29) showed a 48% greater probability of wound closure in favor of the dACM group. The median time to wound closure for dACM-treated ulcers was 84 days compared with “not achieved” in the SOC-treated group (i.e., ≥ 50% of SOC-treated DFUs failed to heal by week 12; $p = 0.04$). Limitations include the following: blinding was lacking; the investigator and participants were not aware of group assignments; both groups included offloading, but there was no standardization; the study was conducted under highly controlled conditions; and there was high internal validity, with an attentive selection of participants as well as a standardized treatment protocol. The authors indicated that to their knowledge, this is the first RCT of dACM; while RCTs are considered level 1 evidence, future real-world, comparative effectiveness research studies may be necessary to demonstrate clinical outcomes in a variety of wound care settings and in broader participant populations. Additional RCTs are needed to strengthen these promising results.

## *Omeza Collagen Matrix*

There are few published studies that address the use of Omeza Collagen Matrix. Therefore, it is not possible to determine whether Omeza Collagen Matrix has a beneficial effect on health outcomes.

Omeza Collagen Matrix (Omeza®) is a wound care matrix that comprises hydrolyzed fish collagen that is infused with cod liver oil, which acts as an anhydrous skin protectant. When applied to a wound surface, the matrix is naturally incorporated into the wound over time. Omeza Collagen Matrix is designed for intimate contact with both regular and irregular wound beds to provide a conducive environment for the individual’s natural wound healing process. It is indicated for the management of wounds, including partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post Mohs surgery, post laser surgery, podiatric, and wound dehiscence), trauma wounds (abrasions, lacerations, superficial partial-thickness burns, and skin tears), and draining wounds.

## *Orion*

There are few published studies that address the use of Orion. Therefore, it is not possible to determine whether Orion has a beneficial effect on health outcomes.

Orion (Legacy Medical Consultants) is a sterile, dehydrated, dual-layered HAM allograft. Orion Amniotic Membrane is intended to serve as a barrier or cover for acute and chronic wounds and for use as a barrier to protect wounds from the surrounding environment.

## *Overlay SL Matrix*

Studies are lacking regarding the use of Overlay SL Matrix for wound treatment. Therefore, it is not possible to determine whether Overlay SL Matrix has a beneficial effect on health outcomes.

Overlay SL Matrix (Sequence LifeScience, Inc.) is a single-layer, minimally manipulated HAM product that is derived from placental tissue that retains the structural and functional characteristics of the tissue. Overlay SL Matrix consists of extracellular matrix proteins and is designed to be applied over wounds, serving as a barrier or protective covering for

both acute and chronic wounds. It is commonly used for individuals with full-thickness acute and chronic wounds that need a biological barrier or wound cover.

## *PalinGen*

There are several studies related to PalinGen, and all the studies have limitations. Therefore, it is not possible to determine whether PalinGen has a beneficial effect on health outcomes.

PalinGen Membrane (Amnio Technology) is a human allograft that comprises amniotic membrane. It is intended to repair or replace soft tissue defects, soft trauma defects, tendinitis, tendinosis, chronic wound repair, and localized inflammation. PalinGen Flow and SportFlow (Amnio Technology) are human allografts that comprise amnion and amniotic fluid components, providing a liquid allograft to aid in the healing and repair of chronic wounds. These products are marketed for use in the following orthopedic clinical conditions: chronic pain; joint pain; localized inflammation; tendon, fasciae, ligament, and capsule repair; synovial injuries; injured chondral surfaces; chronic tendinopathies; and tendinosis.

A Hayes report for Human Amniotic Membrane (HAM) Injections for Treatment of Chronic Plantar Fasciitis indicates that a low-quality body of evidence suggests that HAM injections may result in pain relief and improved function. None of the studies reviewed by Hayes evaluated the comparative effectiveness of amniotic tissue–derived treatments compared with other types of injections such as platelet-rich plasma or botulinum toxin, extracorporeal shockwave therapy, or surgery. Substantial uncertainty remains regarding the comparative effectiveness. The studies included for review had limited follow-up of 12 weeks or less, making it difficult to assess the long-term effects of this treatment. Double-blinded RCTs, with active treatment comparators (injectables, surgery, or extracorporeal shockwave therapy), are needed to evaluate the effectiveness and safety of amniotic tissue-derived allograft treatments for plantar fasciitis. The products evaluated in this report included PalinGen SportFlow, CLARIX FLO, and AMNIOFIX (Hayes, Human Amniotic Membrane Injections for Treatment of Chronic Plantar Fasciitis, 2021).

Hanselman et al. (2015) compared a novel treatment, cryopreserved human amniotic membrane (c-HAM), with a traditional treatment, a corticosteroid. The hypothesis was that c-HAM would be safe and comparable to corticosteroids for plantar fasciitis regarding individual outcomes. A randomized controlled, double-blinded, single-center pilot study was completed. Participants were randomized into one of two treatment groups: c-HAM or corticosteroid. Participants received an injection at their initial baseline visit, with an option for a second injection at their first 6-week follow-up. Total follow-up was obtained for 12 weeks after the most recent injection. The primary outcome measurement was the Foot Health Status Questionnaire (FHSQ). The secondary outcome measurements were the VAS and verbally reported percentage improvement. Data were analyzed between groups for the two different cohorts (one injection vs. two injections). Overall, 23 participants had complete follow-up. Fourteen were randomized to receive a corticosteroid, and nine were randomized to receive c-HAM. Three participants in each group received second injections. With the numbers available, the majority of outcome measurements showed no statistical difference between groups. However, the corticosteroid had greater FHSQ shoe fit improvement at 6 weeks, FHSQ general health improvement at 6 weeks, and verbally reported improvement at 12 weeks in the one-injection cohort. c-HAM had greater FHSQ foot pain improvement at 18 weeks in the two-injection cohort. The authors concluded that c-HAM injection may be safe and comparable to corticosteroid injection for the treatment of plantar fasciitis. According to the authors, this is a pilot study that requires further investigation. This study was not sufficiently powered to detect between-group differences; therefore, no definitive conclusions can be made regarding the comparative effectiveness of c-HAM and corticosteroid treatment for individuals with chronic plantar fasciitis. Study limitations include a small sample size, no comparison of baseline characteristics, a limited follow-up, and a lack of power analysis.

Zelen et al. (2013) reported the results of a randomized clinical trial that examined the efficacy of mDHACM injection as a treatment for chronic, refractory plantar fasciitis. An institutional review board-approved, prospective, randomized, single-center clinical trial was performed. Overall, 45 participants were randomized to receive an injection of 2 cc 0.5% Marcaine plain, then either 1.25 cc saline (controls), 0.5 cc mDHACM, or 1.25 cc mDHACM. Follow-up visits occurred over 8 weeks to measure function, pain, and functional health and well-being. Significant improvement in plantar fasciitis symptoms was observed in participants receiving 0.5 cc or 1.25 cc mDHACM vs. controls within 1 week of treatment and throughout the study period. At 1 week, American Orthopaedic Foot and Ankle Society Hindfoot scores increased by a mean of 2.2 ±17.4 points for controls vs. 38.7 ±11.4 points for those receiving 0.5 cc mDHACM and 33.7 ±14.0 points for those receiving 1.25 cc mDHACM. By week 8, American Orthopaedic Foot and Ankle Society Hindfoot scores increased by a mean of 12.9 ±16.9 points for controls vs.51.6 ±10.1 and 53.3 ±9.4 for those receiving 0.5 cc and 1.25 cc mDHACM, respectively. No significant difference in treatment response was observed in participants receiving 0.5 cc vs. 1.25 cc mDHACM. The authors concluded that in individuals with refractory plantar fasciitis, mDHACM is a viable treatment option. Study limitations include a lack of a power analysis, small sample size, limited follow-up, lack of an active comparator, and lack of blinding of outcome assessors.

## *PalinGen Dual-Layer Membrane*

Studies are lacking regarding the use of PalinGen Dual-Layer Membrane for wound treatment. Therefore, it is not possible to determine whether PalinGen Dual-Layer Membrane has a beneficial effect on health outcomes.

PalinGen Dual-Layer Membrane (Amnio Technology) is a dehydrated human allograft that is derived from the placenta that uses two layers of amniotic tissue to provide twice the growth factor, offering a protective barrier and an extracellular matrix scaffold to support wound healing.

## *Palisade DM Matrix*

Studies are lacking regarding the use of Palisade DM Matrix for wound treatment. Therefore, it is not possible to determine whether Palisade DM Matrix has a beneficial effect on health outcomes.

Palisade DM Matrix (Sequence LifeScience, Inc.) is a dual-membrane, minimally manipulated human amniotic and chorionic membrane product that is derived from placental tissue that retains the structural and functional characteristics of the tissue. Palisade DM Matrix is made up of extracellular matrix proteins and is designed to be applied over wounds, providing a barrier or protective covering for both acute and chronic wounds. It is generally used for individuals with full-thickness acute and chronic wounds that require a biological barrier or wound cover.

## *PelloGraft*

Studies are lacking regarding the use of PelloGraft for wound treatment. Therefore, it is not possible to determine whether PelloGraft has a beneficial effect on health outcomes.

PelloGraft (Surgenex) is a dual-layer amniotic/chorionic membrane allograft. PelloGraft functions as a barrier and provides protective coverage for acute and chronic wounds.

## *PermeaDerm B, PermeaDerm Glove, or PermeaDerm C*

There are few published studies that address the use of PermeaDerm B, PermeaDerm Glove, or PermeaDerm C for any other indications. Therefore, it is not possible to determine whether PermeaDerm B, PermeaDerm Glove, or PermeaDerm C have a beneficial effect on health outcomes.

PermeaDerm B, PermeaDerm C, and PermeaDerm Glove (Stedical Scientific, Inc.) are identical in chemical composition and 3D structure. They are all composed of a monofilament nylon knitted fabric that is bonded to a thin, slitted silicone membrane. The nylon side of this dressing is coated with a mixture of hypoallergenic porcine gelatin and a pure fraction of aloe vera. The physical differences in the two configurations (PermeaDerm B vs. PermeaDerm C and PermeaDerm Glove) are in the number and orientations of slits per unit area.

- PermeaDerm B is indicated for partial-thickness burn wounds, donor sites, and coverage of meshed autograft.
- PermeaDerm C is indicated for partial thickness wounds, pressure sores, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post Mohs, post laser surgery, podiatric, and wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds.
- PermeaDerm Glove is indicated for debrided partial-thickness hand burns.

## *Phoenix Wound Matrix*

There are few published studies that address the use of Phoenix Wound Matrix for any other indications. Therefore, it is not possible to determine whether Phoenix Wound Matrix has a beneficial effect on health outcomes.

The Phoenix Wound Matrix (Nanofiber Solutions) is a sterile, single-use device that is intended for the management of wounds. The Phoenix Wound Matrix is a conformable, nonwoven, fibrous, 3D matrix. The Phoenix Wound Matrix is made from two types of polymer fibers, poly(lactide-co-caprolactone) and polyglycolic acid, which are bioabsorbed after degrading via hydrolysis. It is intended for use in the management of wounds. Wound types include partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post Mohs surgery, post laser surgery, podiatric, and wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds.

## *Polycyte*

There are few published studies that address the use of Polycyte for any other indications. Therefore, it is not possible to determine whether Polycyte has a beneficial effect on health outcomes.

Polycyte (Predictive Biotech) is a minimally manipulated human tissue allograft that is derived from the Wharton jelly of the umbilical cord. It is intended for use in repair, reconstruction, replacement, and supplementation of cells or tissue.

## *PriMatrix*

There are several studies related to PriMatrix, and all the studies have limitations. Although the evidence for this product is somewhat favorable, there is limited evidence related to the safety of and long-term outcomes with this product.

PriMatrix (Integra LifeSciences Corporation) is a bovine-derived ADM that is indicated for the treatment of a variety of wounds.

An ECRI report for PriMatrix Dermal Repair Scaffold for treating a variety of wounds (partial- and full-thickness wounds; pressure, diabetic, and venous ulcers; second-degree burns; surgical, trauma, and draining wounds; and tunneled/undermined wounds) indicated that evidence is inconclusive based on two small, nonrandomized studies and four case series. One small study indicated that PriMatrix resulted in faster healing than Apligraf, but there are limited data and too high of a risk of bias to draw conclusions. All studies need validation in larger, randomized trials that report more long-term effects (ECRI, 2019).

Lantis et al. (2021) conducted an RCT to evaluate the safety and efficacy of a fetal bovine acellular dermal matrix (FBADM) plus SOC for treating hard-to-heal DFUs. A prospective, multicenter RCT was conducted. The study included a 2-week run-in period, 12-week treatment phase, and 4-week follow-up phase. The primary end point was complete wound closure at 12 weeks. Overall, 21 US sites enrolled and randomized 226 participants with hard-to-heal DFUs. The study was terminated early due to the COVID-19 pandemic, which led to a modified ITT population of 207 participants, with 103 in the FBADM group and 104 in the SOC group. Of these participants, 161 completed the study per protocol (modified per-protocol population), with 79 receiving FBADM and 82 without. At the first analysis point, participants treated with FBADM were found to be significantly more likely to achieve complete wound closure than those receiving SOC alone (modified ITT: 45.6% vs. 27.9%, p = 0.008; modified per protocol: 59.5% vs. 35.6%, p = 0.002). The difference in outcome yielded an OR of 2.2 (95% CI, 1.2-3.9; p = 0.008). The median time to closure within 12 weeks was 43 days in the FBADM group compared with 57 days in the SOC group (p = 0.36). The median number of applications of FBADM to achieve closure was one. Adverse events were similar between groups, and no product-related serious adverse events occurred. Study limitations include the early termination of the study and lack of blinding for both the investigator and the participant; additionally, participants were only studied for 4 weeks post wound closure, and there may have been selection bias since the participants were healthier than most individuals with a DFU. Although these results include somewhat favorable results, additional studies are needed for validation in larger, randomized trials that report more long-term effects.

Sabolinski and Gibbons (2018) compared the effectiveness of bilayered living cellular construct (Apligraf) and an acellular fetal bovine collagen dressing (FBCD; PriMatrix) for the treatment of venous leg ulcers. Data from an EMR database were used to analyze 1,021 refractory venous leg ulcers that were treated at 177 facilities. Kaplan-Meier analyses showed that bilayered living cellular construct (893 wounds) was superior to FBCD (128 wounds) for wound closure by weeks 12 (31% vs. 25%), 24 (55% vs. 43%), and 36 (68% vs. 53%); reduction in time to wound closure of 37% (19 vs. 30 weeks); and improvement in the probability of healing by 45%. The authors concluded that bilayered living cellular construct vs. FBCD showed significant differences in both times to and frequency of healing. A limitation of this study is that the use of EMR databases to collect data may introduce some reporting differences between or within centers. Information made available from all participating centers may not reflect uniform standards of individual assessments and standardization of general wound care practices.

## *Procenta*

There are few published studies that address the use of Procenta for wound treatment. Therefore, it is not possible to determine whether Procenta has a beneficial effect on health outcomes.

Procenta (Lucina BioSciences, LLC) is an acellular, sterile, human placental-derived allograft. It is indicated to treat chronic, nonhealing wounds, such as venous stasis and DFUs, to assist in the wound healing process.

## *ProgenaMatrix*

There are few published studies that address the use of ProgenaMatrix. Therefore, it is not possible to determine whether ProgenaMatrix has a beneficial effect on health outcomes.

ProgenaMatrix (Cell Constructs I, LLC) is a graft matrix that is composed of human keratin proteins that are selectively extracted from human hair. This product is intended for the treatment of dry and exuding partial- and full-thickness wounds.

## *ProMatrX*

There are few published studies that address the use of ProMatrX for wound treatment. Therefore, it is not possible to determine whether ProMatrX has a beneficial effect on health outcomes.

ProMatrX ACF (Amnio Technology) is a human allograft that comprises amnion and amniotic fluid that is intended to provide a liquid allograft to aid in the healing and repair of chronic wounds.

## *PuraPly, PuraPly AM (Formerly Called FortaDerm), or PuraPly XT*

There are several studies that are related to PuraPly, PuraPly AM (formerly called FortaDerm), or PuraPly XT, and all the studies have limitations. Therefore, it is not possible to determine whether PuraPly, PuraPly AM (formerly called FortaDerm), or PuraPly XT has a beneficial effect on health outcomes.

PuraPly (Organogenesis Inc.) is a dressing made of porcine intestinal collagen matrix that is coated with polyhexamethylene biguanide hydrochloride antimicrobial agent. It is intended for wound care management.

Bain et al. (2020) evaluated the effectiveness of purified native type I collagen matrix plus polyhexamethylene biguanide antimicrobial (PCMP; PuraPly AM) for cutaneous wounds by conducting a prospective cohort study in 307 participants (67 venous leg ulcers, 62 DFUs, 45 pressure ulcers, 54 postsurgical wounds, and 79 other wounds). Cox wound closure for PCMP was 73% at week 32. The median time to wound closure was 17 weeks (Kaplan-Meier). The incidence of PCMP-treated wounds showing > 60% reductions in areas, depths, and volumes was 81%, 71%, and 85%, respectively. The authors concluded that PCMP demonstrated clinically meaningful benefits in participants with various types of cutaneous wounds. This study is limited because no comparator treatment group was included.

A Hayes report on PuraPly indicated that the quantity of published peer-reviewed clinical data is insufficient to evaluate PuraPly AM for chronic lower extremity ulcers in a full assessment [Hayes, PuraPly Antimicrobial (AM) Wound Matrix (Organogenesis Inc.) for Treatment of Wounds, 2022].

A 2022 ECRI report for PuraPly AM Antimicrobial Wound Matrix for treating chronic wounds indicates that evidence is inconclusive. Three small cases series, with a high risk of bias, noted that PuraPly AM with SWC achieved complete wound closure in approximately one-third to two-thirds of chronic wounds with different etiologies within 5 to 7 weeks. The studies are at a very high risk of bias due to small sample sizes; single-center designs; and a lack of controls, blinding, and randomization. The studies are lacking in long-term outcomes and individual-oriented outcomes. Large multicenter RCTs are needed that address long-term and cosmetic outcomes as well as complications.

## *Rampart DL Matrix*

Studies are lacking regarding the use of Rampart DL Matrix for wound treatment. Therefore, it is not possible to determine whether Rampart DL Matrix has a beneficial effect on health outcomes.

Rampart DL Matrix (Sequence LifeScience, Inc.) is a dual-layer, minimally manipulated HAM product that is derived from placental tissue that retains the structural and functional characteristics of the tissue. The final product is dehydrated, packaged in different-sized sheets, and terminally sterilized by irradiation. Rampart DL Matrix consists of extracellular matrix proteins and is designed to be applied over wounds, serving as a barrier or protective covering for both acute and chronic wounds. It is commonly used for individuals with full-thickness acute and chronic wounds that need a biological barrier or wound cover.

## *Rebound Matrix*

Studies are lacking regarding the use of Rebound Matrix for wound treatment. Therefore, it is not possible to determine whether Rebound Matrix has a beneficial effect on health outcomes.

Rebound Matrix (Sequence LifeScience, Inc.) is a full-thickness, minimally manipulated human placental membrane product that is derived from donated placental tissues that retain the structural and functional characteristics of the tissues. Rebound Matrix is composed of extracellular matrix proteins and serves as a natural, biological barrier or wound cover. The typical population of individuals includes those with chronic, full-thickness ulcers and other skin defects for which a biological barrier or cover is required.

### *Reeva FT*

Studies are lacking regarding the use of Reeva FT for wound treatment. Therefore, it is not possible to determine whether Reeva FT has a beneficial effect on health outcomes.

Reeva FT (Legacy Medical Consultants) is a dehydrated, resorbable allograft that is derived from donated human placental birth tissue and applied over the wound; it serves as a barrier and protective covering from the surrounding environment for acute and chronic wounds.

### *RegeneLink Amniotic Membrane Allograft*

Studies are lacking regarding the use of RegeneLink Amniotic Membrane Allograft for wound treatment. Therefore, it is not possible to determine whether RegeneLink Amniotic Membrane Allograft has a beneficial effect on health outcomes.

RegeneLink Amniotic Membrane Allograft (LifeLink Foundation, Inc.) is a sterile, lyophilized, gamma-irradiated, full-thickness allograft that includes amnion and chorion that is derived from donated human placenta. RegeneLink Amniotic Membrane Allograft is intended for use as a protective covering or barrier for internal and external tissue defects.

### *REGUaRD*

There are few published studies that address the use of REGUaRD. Therefore, it is not possible to determine whether REGUaRD has a beneficial effect on health outcomes.

REGUaRD (New Life Medical, LLC) is a hydrated acellular (human) dermal allograft matrix that is used for the treatment of nonhealing wounds and burn injuries. It contains extracellular matrix that provides a scaffold for cellular ingrowth vascularization, tissue regeneration, and formation of granulation tissue.

### *Relese*

There are few published studies that address the use of Relese for wound treatment. Therefore, it is not possible to determine whether Relese has a beneficial effect on health outcomes.

Relese is a sheet skin substitute product that contains nonviable cells and is intended for use as a selective barrier; it protects wounds from the surrounding environment, including chronic and acute wounds such as dermal ulcers and other defects.

### *Renew FT Matrix*

Studies that address the use of Renew FT Matrix are lacking. Therefore, it is not possible to determine whether Renew FT Matrix has a beneficial effect on health outcomes.

Renew FT Matrix (Sequence LifeScience, Inc.) is a full-thickness, minimally manipulated placental membrane that is derived from donated tissue, preserving its natural structure and function. It is intended to be used in chronic, full-thickness ulcers and wounds.

### *RenoGraft*

Studies that address the use of RenoGraft are lacking. Therefore, it is not possible to determine whether RenoGraft has a beneficial effect on health outcomes.

RenoGraft (Surgenex) is a triple-layer amniotic/chorionic membrane allograft. RenoGraft functions as a barrier and provides protective coverage for acute and chronic wounds.

### *Repriza*

There are few published studies that address the use of Repriza. Therefore, it is not possible to determine whether Repriza has a beneficial effect on health outcomes.

Repriza (Promethean LifeSciences, Inc.) is an ADM that is prepared from a human skin allograft. Repriza is intended for implantation for reconstructive surgery wherever an ADM may be used [i.e., in abdominal wall reconstruction (AWR) or augmentation of soft tissue irregularities].

Cockcroft and Markelov (2018) followed up 11 patients in a retrospective cohort study for a minimum of 6 weeks (mean, 12 weeks). The patients had undergone a trapeziectomy with interpositional arthroplasty using Repriza ADM to treat primary and secondary carpometacarpal joint arthritis. Subjective and objective data were collected to assess pain,

subjective improvement of symptoms, radiographic measurements of first metacarpal subsidence, key pinch strength, grip strength, and range of motion. Early outcomes compared favorably to other treatment series. On average, patients received a significant pain reduction of 63%, with 36% of patients reporting complete pain resolution. All patients had an overall subjective improvement in symptoms. Overall, 91% of patients achieved postoperative opposition of the thumb and fifth digit. Comparison with preoperative x-rays showed a mean thumb metacarpal subsidence of 27%. Zigzag deformity and extra-articular ADM migration, due to lack of patient adherence to the splint, were observed complications. The authors concluded that this technique is safe and effective for Eaton grades III and IV thumb carpometacarpal arthritis. A long-term study, with a larger sample size, is needed to investigate this technique further.

## *Restorigin*

There are few published studies that address the use of Restorigin. Therefore, it is not possible to determine whether Restorigin has a beneficial effect on health outcomes.

The Restorigin Amnion Patch (Parametrics Medical) is derived from the amnion layer of fetal membranes in the umbilical cord. It is intended to provide protection as well as a tissue matrix to reduce inflammation and scarring in individuals with chronic, nonhealing wounds and burns.

## *Restrata or Restrata MiniMatrix*

There are limited studies that address the use of Restrata and/or Restrata MiniMatrix. Therefore, it is not possible to determine whether Restrata or Restrata MiniMatrix have a beneficial effect on health outcomes.

Restrata is a synthetic, resorbable fiber matrix that resembles human extracellular matrix and acts as a scaffold material that the body uses for revascularization and soft tissue regeneration. It is intended to treat wounds such as diabetic, venous, and pressure ulcers as well as second-degree burns and other traumatic wounds.

Restrata MiniMatrix (Acera Surgical Inc.) comprises a micronized electrospun fiber matrix (particulate less than 3.15 mm in diameter), offering a dispersible form factor of Restrata that may be applied to soft tissue areas with irregular or complex topography. It is intended for use in the management of wounds, including partial- and full-thickness wounds, pressure sores/ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor site/grafts, post laser surgery, post Mohs surgery, podiatric wounds, dehisced wounds), trauma wounds (e.g., abrasions, lacerations, partial-thickness burns, skin tears), and draining wounds.

An ECRI report for Restrata Resorbable Wound Matrix (Acera Surgical Inc.) for Treating Acute and Surgical Wounds for Treating Complex and Chronic Wounds indicates that the evidence for Restrata is inconclusive. There is very-low-quality evidence that Restrata promotes wound healing of chronic DFUs. The studies have a very small sample size to be conclusive, and there is a high risk of bias. RCTs are needed to validate these findings that compare Restrata with other advanced wound care products (ECRI, 2024).

Regulski and MacEwan (2018) conducted a retrospective review in a single center to evaluate the efficacy and utility of the implantable nanomedical scaffold in the treatment of chronic, nonhealing lower extremity wounds in patients with multiple comorbidities. Data were retrospectively collected via chart review by the treating physician. A total of 82 wounds were included in this study; wound types consisted of 34 DFUs, 34 venous leg ulcers, and 14 other wounds. Overall, treated wounds demonstrated progressive and sustained wound area reduction over the course of treatment, with 85% achieving complete closure at 12 weeks. Limitations include (1) the fact that this was an initial review of the implantable nanomedical scaffold and (2) the lack of a control group and randomization, which limits the ability to draw conclusions about the effectiveness of the scaffold. Additional research is needed, along with large RCTs to further predict efficacy and safety.

## *Revita*

There are few published studies that address the use of Revita. Therefore, it is not possible to determine whether Revita has a beneficial effect on health outcomes.

Revita (StimLabs LLC) is a sterilized, dehydrated human placental allograft. It is intended to be used as a wound covering or barrier membrane over chronic and acute wounds, including dermal ulcers. It also has clinical applications in dentistry, ophthalmology, and orthopedics.

## *Revitalon*

There are few published studies that address the use of Revitalon for wound treatment. Therefore, it is not possible to determine whether Revitalon has a beneficial effect on health outcomes.

Revitalon (Medline Industries, Inc.) is a minimally processed amniotic membrane that is proposed for the treatment of chronic, nonhealing wounds.

### *RevoShield+ Amniotic Barrier*

Studies are lacking regarding the use of RevoShield+ Amniotic Barrier for wound treatment. Therefore, it is not possible to determine whether RevoShield+ Amniotic Barrier has a beneficial effect on health outcomes.

RevoShield+ Amniotic Barrier (4Front Strategic Partners, Surgenex) is a minimally manipulated, dual-layer, tissue-based product that is derived from the amniotic membrane of the human placenta. Following preparation of the wound (i.e., excision and debridement), the RevoShield+ Amniotic Barrier is applied over the wound. The intended use of the RevoShield+ Amniotic Barrier is to serve as a barrier and to provide protective coverage from the surrounding environment for acute and chronic wounds.

### *SanoGraft*

Studies that address the use of SanoGraft are lacking. Therefore, it is not possible to determine whether SanoGraft has a beneficial effect on health outcomes.

SanoGraft (Surgenex) is a dehydrated, single-layer amnion membrane allograft that is intended to function as a barrier and provides protective coverage for acute and chronic wounds.

### *Sanopellis*

Studies that address the use of Sanopellis are lacking. Therefore, it is not possible to determine whether Sanopellis has a beneficial effect on health outcomes.

Sanopellis (ReNu LLC) is an amniotic membrane product that is used as a wound covering and acts as a barrier for full- and partial-thickness, chronic and acute wounds.

### *Sentry SL Matrix*

Studies are lacking regarding the use of Sentry SL Matrix for wound treatment. Therefore, it is not possible to determine whether Sentry SL Matrix has a beneficial effect on health outcomes.

Sentry SL Matrix (Sequence LifeScience, Inc.) is a single-layer, minimally manipulated HAM product that is derived from placental tissue that retains the structural and functional characteristics of the tissue. The final product is dehydrated, packaged in different-sized sheets, and terminally sterilized by irradiation. Sentry SL Matrix is composed of extracellular matrix proteins and is intended for use over wounds and as a barrier and protective coverage for acute and chronic wounds. The product is typically used for individuals with full-thickness acute and chronic wounds for which a biological barrier or wound cover is required.

### *Shelter DM Matrix*

Studies are lacking regarding the use of Shelter DM Matrix for wound treatment. Therefore, it is not possible to determine whether Shelter DM Matrix has a beneficial effect on health outcomes.

Shelter DM Matrix (Sequence LifeScience, Inc.) is a dual-membrane, minimally manipulated human amniotic and chorionic membrane product that is derived from placental tissue that retains the structural and functional characteristics of the tissue. The final product is dehydrated, packaged in different-sized sheets, and terminally sterilized by irradiation. Shelter DM Matrix is composed of extracellular matrix proteins and is intended for use over wounds and as a barrier and protective coverage for acute and chronic wounds.

### *Signature APatch*

There are few published studies that address the use of Signature APatch for wound treatment. Therefore, it is not possible to determine whether Signature APatch has a beneficial effect on health outcomes.

Signature APatch (Signature Biologics, LLC) is a cryopreserved tissue that is derived from amniotic membrane for homologous use as a wound covering. Signature APatch can separate the underlying tissue from the external environment.

## *SimpliGraft or SimpliMax*

Studies are lacking regarding the use of SimpliGraft or SimpliMax for wound treatment. Therefore, it is not possible to determine whether SimpliGraft or SimpliMax has a beneficial effect on health outcomes.

SimpliGraft (Xtant Medical) is a single-layer amniotic membrane that is obtained from healthy deliveries following informed consent that is intended to serve as a barrier and provide protective coverage from the surrounding environment when it is topically applied to chronic and acute wounds.

SimpliMax (Xtant Medical) is a dual-layer amniotic membrane that is obtained from healthy deliveries following informed consent. SimpliMax is intended to serve as a barrier and provide protective coverage from the surrounding environment when topically applied to chronic and acute wounds.

## *Singlay*

Studies are lacking regarding the use of Singlay for wound treatment. Therefore, it is not possible to determine whether Singlay has a beneficial effect on health outcomes.

Singlay (Samaritan Biologics, LLC) is a perforated, single-layer, amnion-derived allograft that serves as a barrier and provides protective coverage from the surrounding environment for acute and chronic wounds.

## *SkinTE*

There are few published studies that address the use of SkinTE for wound treatment. Therefore, it is not possible to determine whether SkinTE has a beneficial effect on health outcomes.

SkinTE (PolarityTE, Inc.) is a fully autologous, homologous skin product that is intended to be used for the repair, reconstruction, replacement, supplementation, or regeneration of defects or functional losses of the skin. SkinTE is manufactured from a harvested sample of an individual's full-thickness skin, composed of viable skin cells and an organized extracellular matrix, with no additional cell or tissue source from another human (allogeneic) or different species (xenogeneic). The product is intended for the treatment of acute burns that require excision or grafting and chronic wounds.

An ECRI report for SkinTE for Treating Acute and Chronic Wounds indicated that the evidence for SkinTE is inconclusive because no evidence is available (ECRI, 2018).

## *STRATTICE*

There are several studies related to STRATTICE, and all the studies have limitations. Therefore, it is not possible to determine whether STRATTICE has a beneficial effect on health outcomes.

STRATTICE (Allergan) is a porcine-derived acellular dermal biological mesh that is intended for use as a soft tissue patch to reinforce soft tissue where weakness exists and for the surgical repair of damaged or ruptured soft tissue membranes. It is intended for the repair of hernias and/or body wall defects that require the use of reinforcing or bridging material to obtain the desired surgical outcome.

An ECRI 2023 Clinical Evidence Assessment for STRATTICE Reconstructive Tissue Matrix for hernia repair indicates that the current evidence on STRATTICE for abdominal hernia repair is of very low quality and does not allow conclusions about its comparative safety and effectiveness vs. other mesh types. The available studies, including one systematic review, four RCTs, and four nonrandomized, comparative studies, are limited by small sample sizes, a high risk of bias, mixed results, and short follow-up durations. The systematic review includes mostly single-arm studies, with fewer STRATTICE-treated individuals, and excludes RCTs. The RCTs are small, with some including individuals with contaminated defects, which may affect outcomes and limit generalizability. Nonrandomized studies suffer from a retrospective design and lack of randomization. No studies report outcomes beyond 2.5 years, which is insufficient for assessing long-term complications like infection or recurrence. Additionally, all studies focus on abdominal, incisional, or ventral hernias, so findings may not apply to other hernia types. Large, multicenter RCTs, with a > 5-year follow-up, are needed to better evaluate STRATTICE's performance.

Jakob et al. (2020) conducted a two-arm, randomized study to compare the outcome after prophylactic, intraperitoneal implantation of a biological STRATTICE mesh with that with standard abdominal closure in participants undergoing emergency abdominal surgery. Participants were randomly assigned to prophylactic implantation of a biological intraperitoneal mesh using STRATTICE (mesh group) or standard abdominal closure using a single, continuous running suture (no-mesh group). Because of safety concerns, participant enrollment had to be closed prematurely. Eligibility for

inclusion was assessed in 61 participants. A total of 48 participants were randomized (21 in the mesh group; 28 in the no-mesh group). No differences in baseline characteristics were found. Abdominal wall complications that required reoperations were more frequent in the mesh group than the no-mesh group [five of 13 (83.3%) vs. one of 13 (14.3%) individuals; p = 0.026]. Mesh-associated abdominal wall complications included nonintegration of the mesh into the abdominal wall, dissolution of the mesh, and mesh-related infections. The investigators concluded that in individuals undergoing emergency abdominal surgery, intraperitoneal biological STRATTICE mesh implantation is associated with significantly more frequent abdominal wall complications requiring reoperation. Therefore, the use of such meshes cannot be recommended in the contaminated environment of emergency abdominal surgery.

In a cohort study, Kaufmann et al. (2020) evaluated clinical efficacy and participant satisfaction following STRATTICE placement in complex abdominal wall hernia repair. The aim of this study was to evaluate clinical efficacy and participant satisfaction following STRATTICE placement in participants treated for complex abdominal wall hernia repair in three academic and peripheral hospitals in Germany. Participants underwent abdominal examination, an ultrasound was performed, and participants completed quality-of-life questionnaires. Overall, 27 participants were assessed (14 male; age, 67.5 years; follow-up, 42.4 months). The most frequent postoperative complication was wound infection (39.1%). STRATTICE did not have to be removed in any of the participants. Four participants died. During outpatient clinic visits, six of 23 participants (26.1%) had a recurrence of hernia, and one participant had undergone reoperation. Five participants (21.7%) had bulging of the abdominal wall. Quality-of-life questionnaires revealed that participants judged their scar with a median 3.5 out of 10 points (0 = best) and judged their restrictions during daily activities with a median of 0 out of 10.0 (0 = no restriction). The investigators indicated that despite a high rate of wound infection, no biological mesh had to be removed. According to the authors, in some cases, the biological meshes provided a safe way out of desperate clinical situations. Both the recurrence rate and the amount of bulging were high (failure rate, 47.8%). Since the design of this study was a cross-sectional cohort study, data were partly retrospective and partly prospectively collected. This could have led to a bias in the study results.

Maxwell et al. (2019) used a prospectively maintained database to compare Fortiva, STRATTICE, and AlloDerm ADMs in AWR. Hernia recurrence and surgical site occurrence (SSO) were the primary and secondary end points. Kaplan-Meier survival curves and logistic regression models were used to evaluate risks for hernia recurrence and SSO. A total of 229 individuals underwent AWR with one of three ADMs. The median follow-up time was 20.9 months (1-60 months). Cumulative recurrence rates for each mesh were 6.9%, 11.2%, and 22.0% for the Fortiva, STRATTICE, and Alloderm Groups, respectively. Surgical site occurrence for each mesh was 56.9%, 49.0%, and 49.2%. Seroma was significantly lower in the Fortiva group (1.4%). Independent risk factors for hernia recurrence included a body mass index of 30 $kg/m^2$ or higher and hypertension. Adjusted risk factors included oncological resection for hernia recurrence and a wound class of contaminated or dirty/infected for SSO. The authors concluded that ADMs provide durable repair, with a low overall rate of recurrence and complications in AWR. The study found that the recurrence and complication profiles differ between brands. These results need to be confirmed by prospective, randomized trials. The limitation of this study is the absence of a control arm to compare biological mesh reconstruction with other techniques of AWR (included in the ECRI 2023 report).

Trippoli et al. (2018) conducted a meta-analysis to evaluate the treatment of primary and incisional ventral hernia using biological meshes. The study consisted of the following phases: (1) identification of the biological meshes available on the market; (2) performance of a literature search focused on the efficacy and safety of these meshes; and (3) analysis of the findings derived from the literature search. The information was reviewed and presented according to standard meta-analysis. The main end points of the analysis included infection of the surgical wound at 1 month and recurrence at 12 months. Eleven trials that evaluated five biological meshes were identified: Permacol™ (706 individuals), STRATTICE (324 individuals), Surgisis (44 individuals), Tutomesh (38 individuals), and XenMatrix™ (22 individuals). These studies generally showed a poor methodological quality, and surgical wound infection showed wide range between study variability. A significantly lower rate of recurrence at 12 months was found with Permacol compared with STRATTICE. The authors concluded that the different types of meshes showed a marked statistical variability in the clinical outcomes, and nearly all comparisons between different meshes in the two clinical end points did not reach statistical significance. These findings are in line with those of a recent consensus review from a European working group (Köckerling et al., 2018) that does not recommend the routine use of biological meshes for AWR. The study conducted by Huntington et al. (2016), which was previously cited in this policy, is included in the Trippoli et al. (2018) meta-analysis. (Included in the ECRI 2023 report.)

### *STRAVIX and STRAVIX PL*

There are few published studies related to STRAVIX and STRAVIX PL, and all the studies have limitations. Therefore, it is not possible to determine whether STRAVIX and/or STRAVIX PL has a beneficial effect on health outcomes.

STRAVIX and STRAVIX PL (Osiris Therapeutics, Inc.) are thicker versions of GRAFIX PRIME and GRAFIX PL PRIME. These products use umbilical amnion and Wharton Jelly to support wound repair. STRAVIX and STRAVIX PL are intended for treating ulcers, burns, pyoderma gangrenosum, epidermolysis bullosa, and other types of wounds.

A 2021 ECRI report for STRAVIX Cryopreserved Placental Tissue (Osiris Therapeutics, Inc.) states that STRAVIX is a ready-to-use, cryopreserved amniotic membrane graft that is derived from human placenta and is intended for treating wounds and repairing connective tissue defects. The graft is purported to be minimally processed to retain the amnion's native cells and extracellular matrix. STRAVIX is intended as a substitute for skin autografts when harvesting skin is infeasible, impractical, or risky to the individual. This report indicates that there is a single, small case series that provides too little evidence to determine how well STRAVIX works to treat surgical wounds or how it compares with other skin substitutes.

### *Summit AAA*

Due to a lack of sufficient studies on Summit AAA for wound treatment, it is currently not possible to determine whether Summit AAA has a beneficial effect on health outcomes.

Summit AAA (Legacy Medical Consultants) is a triple-layer amnion allograft that is derived from donated human placental tissue. It provides an extracellular matrix scaffold, serving as a protective barrier for acute and chronic wounds.

### *Supra SDRM*

There are few published studies that address the use of Supra SDRM for wound treatment. Therefore, it is not possible to determine whether Supra SDRM has a beneficial effect on health outcomes.

Supra SDRM is a novel, synthetic, guided wound closure matrix that is built as a bimodal foam membrane structure for the management of chronic wounds.

### *SUPRATHEL*

There are several studies related to SUPRATHEL, and all the studies have limitations. Therefore, it is not possible to determine whether SUPRATHEL has a beneficial effect on health outcomes.

SUPRATHEL (PolyMedics Innovations) is indicated in superficial (2a°) and deep dermal/partial-thickness (2b°) skin loss diseases, such as burn wounds, STSG donor sites, and trauma and surgical wounds.

An ECRI 2023 Clinical Evidence Assessment for SUPRATHEL for Treating Burns suggests that SUPRATHEL is safe, yet the studies are at a high risk for bias, and there are too few individuals per comparison to make the findings conclusive about the comparative effectiveness.

An ECRI 2021 Clinical Evidence Assessment for SUPRATHEL Skin Substitute (PolyMedics Innovations) for Treating Donor Site Wounds suggests that SUPRATHEL is safe, but whether it improves individual outcomes compared with other dressings cannot be determined because available studies are at a high risk of bias and assess too few individuals per comparison. There was one RCT and two comparison studies. Comparison multicenter RCTs comparing SUPRATHEL with other donor site wound treatments that report on pain, infection rates, and wound healing are needed to assess comparative effectiveness, but none are ongoing. (Schwarze et al., 2007, and Markl et al., 2010, included in this report).

In a retrospective chart review from a single-center burn center, Blome-Eberwein et al. (2021) reviewed SUPRATHEL, a new, biodegradable synthetic membrane that was recently introduced to treat second-degree burns in adults and pediatric patients. There were 229 burn patients [141 male and 88 female (138 pediatric)], with a mean age of 18 years (9 weeks to 73 years), included in the study. Overall, 474 sheets of the synthetic membrane were applied to second-degree burns (superficial and deep). The average burn size was 8.9% (range, 1%-60% total body surface area). The wound bed was prepped with either rough debridement or dermabrasion. After hemostasis, the membrane was applied to the wound with an outer dressing of fatty gauze, bridal veil, and absorptive gauze followed by an ACE® wrap. The outer dressing was removed every 1 to 4 days, depending on exudate, to closely follow the wound through the translucent membrane and fatty gauze layers. After epithelialization, the dressing separated and could be removed. The study focused on the need for subsequent grafting, healing time, individual pain level, hypertrophic scarring, and rate of infection. All wounds in this study that were treated with SUPRATHEL healed without grafting. The average total body surface area was 8.9% (1%-60%). The average time to healing was 13.7 days for ≥ 90% epithelialization, with 11.9 days for pediatric patients vs. 14.7 days for adults. Throughout the treatment period, the average pain level was 1.9 on a 10-point scale. Overall, 27 patients developed hypertrophic scarring in some areas (11.7%). The average length of stay was 6.9 days. The rate of infection was 3.8% (8/229). Failure or progression to full thickness in part of the wounds was 5.2% (12/229). Limitations include

those of any retrospective study as well as a lack of a control group. The authors noted that SUPRATHEL is a good treatment option when treating second-degree burns. It is a basic treatment that provides a physiological healing environment, with good outcomes and less pain than options previously used by the providers at the same institution. The authors indicated that a prospective, long-term outcome study, with a control group, is in preparation to confirm these preliminary findings.

In a prospective, single-center RCT, Hundeshagen et al. (2018) compared Mepilex Ag, a silver-impregnated foam dressing, with SUPRATHEL, a DL-lactic acid polymer, in the outpatient treatment of partial-thickness burns in pediatric and adult participants. Reepithelialization, wound pain, and discomfort during dressing changes were observed. Objective scar characteristics (elasticity, transepidermal water loss, hydration, and pigmentation) and subjective assessments (Patient and Observer Scar Assessment Scale) were measured at 1 month post burn. Data are presented as mean ±SEM, and significance was accepted at $p < 0.05$. Overall, 62 participants (SUPRATHEL, n = 32; Mepilex Ag, n = 30) were enrolled; age, sex, and burn size were comparable between the groups. Time to reepithelialization was not different between the groups (12 days; $p = 0.75$). Pain ratings were significantly reduced during the first 5 days after the burn in the SUPRATHEL group in all participants ($p = 0.03$) and a pediatric subgroup ($p < 0.001$). Viscoelasticity of burned skin was elevated compared with unburned skin in the Mepilex Ag group at 1 month post burn. Participants treated with SUPRATHEL reported better overall scar quality (SUPRATHEL: 2; Mepilex Ag: 4.5; $p < 0.001$). Both dressings are feasible and useful for the outpatient treatment of minor and selected moderate partial-thickness burns. Study limitations include results that were assessed by clinical judgement rather than objective assessment tools such as Doppler; additionally, there were a number of participants who did not report at later points of the study, and there was no blinding to the study personnel. Further studies on this treatment are warranted.

In an open-label, single-center RCT, Markl et al. (2010) evaluated three different synthetic wound dressings for treating STSG donor sites. Overall, 77 participants were randomly assigned to three study groups: SUPRATHEL, Biatain® Ibu, and Mepitel. Wounds were inspected daily until complete reepithelization. Ease of care and scar development after a 6-month follow-up were evaluated. SUPRATHEL showed significant ($p \leq 0.001$) pain reduction after 24 hours but increasing pain scores on the fifth day of treatment. Biatain Ibu showed significant pain relief immediately after application and during the entire treatment period ($p < 0.05$). Mepitel did not show any significant pain reduction. There were no significant differences in the reepithelization period of the three dressing materials. Further studies are warranted.

Schwarze et al. (2007) conducted a prospective, randomized, two-center clinical study to evaluate the impact on wound healing of SUPRATHEL in donor sites of STSGs. SUPRATHEL represents an absorbable, synthetic wound dressing, with properties of natural epithelium. Overall, 22 burn participants who were treated with STSGs, with a mean age of 39.6 years, were included in the study. Donor sites of skin grafts were randomly selected, partly treated with Jelonet, and partly treated with SUPRATHEL. The first gauze change was conducted on the fifth day post operation, followed by regular wound inspection until complete reepithelization. The study focused on individual pain score, healing time, analysis of wound bed, and ease of care. No significant difference in healing time of the graft donor sites was detected between SUPRATHEL and Jelonet. The mean 10-day pain score was 0.92 (median, 1.0; range, 0.2-1.8) in the SUPRATHEL group and 2.1 (median, 2.8; range, 0.4-3.0) in the Jelonet group. These scores were statistically significant ($p = 0.0002$). There was a significantly lower pain score in participants treated with SUPRATHEL ($p = 0.0002$). SUPRATHEL became transparent when applied and allowed close monitoring of wound healing. In contrast to Jelonet, SUPRATHEL showed excellent plasticity, with better attachment and adherence to wound surfaces. Throughout the healing process, it detached from wounds, without damaging the new epithelial surface. In addition, wound areas treated with SUPRATHEL required less frequent dressing changes. It also demonstrated ease of care. Limitations include a small sample size and lack of blinding; additionally, participants were their own control group (both dressings applied to different areas of the same wound), and the reporting outcomes were subjective. While these results are promising, larger, robust studies are needed.

## *SureDerm*

There are few published studies that address the use of SureDerm. Therefore, it is not possible to determine whether SureDerm has a beneficial effect on health outcomes.

SureDerm (HansBioMed) is a human ADM. It is intended to be used as skin reconstruction to repair skin loss from burns, wounds, congenital diseases, urinary incontinence, and ulcers or malformations.

## *Surfactor*

There are few published studies that address the use of Surfactor for wound treatment. Therefore, it is not possible to determine whether Surfactor has a beneficial effect on health outcomes.

Surfactor (Surgenex) is an injectable amniotic membrane allograft that is packaged in sterile vials and intended for injection to the wound surface; it supports wound healing and soft tissue repair.

### *SurgiCORD*

There are few published studies that address the use of SurgiCORD. Therefore, it is not possible to determine whether SurgiCORD has a beneficial effect on health outcomes.

SurgiCORD (Synergy Biologics) is a human umbilical tissue membrane allograft that is intended to treat neuropathic ulcers, venous stasis ulcers, and posttraumatic and pressure ulcers.

### *SurgiGRAFT Dual*

There are few published studies that address the use of SurgiGRAFT Dual. Therefore, it is not possible to determine whether SurgiGRAFT Dual has a beneficial effect on health outcomes.

SurgiGRAFT Dual (Synergy Biologics) is a bilayer human amniotic tissue allograft that is intended to be used to treat chronic, nonhealing wounds, including neuropathic ulcers and posttraumatic and pressure ulcers.

### *SurgiGRAFT*

There are few published studies that address the use of SurgiGRAFT. Therefore, it is not possible to determine whether SurgiGRAFT has a beneficial effect on health outcomes.

SurgiGRAFT (Synergy Biologics) is a minimally manipulated, human amnion–only regenerative extracellular tissue matrix that is derived from human placental tissue. It is intended for use in the following conditions: neuropathic ulcers, venous stasis ulcers, posttraumatic wounds, pre- and postsurgical wounds and pressure ulcers, diabetic wounds, burn wounds, scar tissue, scarring, and adhesion barrier up to and including nerve bundle and peripheral wrap as a wound covering.

### *SurGraft, SurGraft AC, SurGraft ACA, SurGraft FT, SurGraft TL, or SurGraft XT*

There are few published studies that address the use of SurGraft products. Therefore, it is not possible to determine whether these SurGraft products have a beneficial effect on health outcomes:

- SurGraft
- SurGraft AC
- SurGraft ACA
- SurGraft FT
- SurGraft TL
- SurGraft XT

SurGraft (Surgenex) is a family of HAM allografts that are used as wound coverings and intended to treat nonhealing foot ulcers, including diabetic, pressure and venous ulcers:

- SurGraft – Single-layer, amnion-derived allograft
- SurGraft AC – Dual layer, amnion/chorion derived
- SurGraft ACA – Triple layer, amnion/chorion/amnion derived
- SurGraft FT – Full-thickness placental allograft retaining the intermediary layer between amnion and chorion
- SurGraft TL – Triple-layer, amnion-derived allograft
- SurGraft XT– Dual layer, amnion derived

### *Symphony*

There are few published studies that address the use of Symphony. Therefore, it is not possible to determine whether Symphony has a beneficial effect on health outcomes.

Symphony (Aroa Biosurgery Ltd.) is a bioengineered skin substitute that is composed of extracellular matrix and hyaluronic acid. It consists of three layers, with more than 150 extracellular matrix proteins that aid in the wound healing process. It is intended for use in acute and chronic wounds.

### *TAG*

There are few published studies that address the use of TAG for wound treatment. Therefore, it is not possible to determine whether TAG has a beneficial effect on health outcomes.

TAG (Conventus Flower Orthopedics) is a sterile, dehydrated, triple-layer amniotic allograft composed solely from the amniotic membrane of donated human placental tissue. TAG is intended to serve as a barrier and provide protective coverage from the surrounding environment for acute and chronic wounds.

### *Talymed*

There are few published studies that address the use of Talymed. Therefore, it is not possible to determine whether Talymed has a beneficial effect on health outcomes.

Talymed (Marine Polymer Technologies, Inc.) is a wound care management product composed of shortened fibers of poly-N-acetyl glucosamine (pGlcNAc) that are isolated from microalgae. It is indicated for the management of a range of serious, complex wounds.

Refer to the above section titled Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes for additional articles/reports that evaluate Talymed.

Kelechi et al. (2012) conducted a randomized controlled, investigator-blinded pilot study to evaluate the efficacy, safety, and tolerability of an advanced, pGlcNAc, nanofiber-derived, wound-healing technology (Talymed) among participants with venous leg ulcers compared with treatment with standard care plus pGlcNAc (applied only once, every other week, or every 3 weeks) or with standard care alone. The results showed that among the 82 randomized participants, 71 completed the study, with seven lost to follow-up, and four discontinued because of systemic infection. There were no significant group differences regarding baseline demographics, illness, and venous leg ulcer characteristics. At 20 weeks, the proportion of participants with completely healed venous leg ulcers was 45.0% (9 of 20), 86.4% (19 of 22), and 65.0% (13 of 20) for groups receiving standard care plus pGlcNAc only once, every other week, and every 3 weeks, respectively, vs. 45.0% (9 of 20) for those receiving standard care alone. The advanced wound-healing technology was well tolerated and safe. The authors concluded that the results of this pilot study suggest that the pGlcNAc advanced wound-healing technology is well tolerated and effective. This study was limited by the small sample size and participants unblinded to treatment allocation. Further research, with RCTs, is needed to validate these findings.

### *TenSix*

There are few published studies that address the use of TenSix. Therefore, it is not possible to determine whether TenSix has a beneficial effect on health outcomes.

The product information on TenSix is not currently available.

### *TheraGenesis*

There are few published studies that address the use of TheraGenesis. Therefore, it is not possible to determine whether TheraGenesis has a beneficial effect on health outcomes.

TheraGenesis is a bilayer wound matrix that comprises a biodegradable porcine tendon-derived atelocollagen layer and a silicone film layer. The collagen matrix acts as a scaffold material that the body uses for revascularization and soft tissue regeneration. The silicone layer contains a nonadhesive mesh that helps better adhere the matrix and chosen fixation to the wound. It is intended to treat wounds such as diabetic, venous, and pressure ulcers as well as second-degree burns and other traumatic wounds.

An ECRI report for TheraGenesis Bilayer Wound Matrix (marketed as Pelnac outside the United States) for treating partial- and full-thickness wounds indicated that the evidence for this product is inconclusive due to too few data on outcomes of interest. While there was one blinded RCT, the study was small and heterogeneous in the etiology of the wound. Larger studies are needed (ECRI, 2023).

### *TheraMend*

There are few published studies that address the use of TheraMend for wound treatment. Therefore, it is not possible to determine whether TheraMend has a beneficial effect on health outcomes.

TheraMend (LUX Therapeutics) is a patch product that is made from minimally processed, dehydrated amniotic membrane obtained from donated human tissue and is sterilized via gamma irradiation.

## *TheraSkin*

There are several studies related to TheraSkin, and all the studies have limitations. Although the evidence for this product is somewhat favorable, larger, more robust studies are needed.

TheraSkin (Solsys™ Medical) is an extracellular dermal matrix proposed for multiple healing indications. It contains human collagen, fibroblasts, growth factors, keratinocytes, and cytokines.

Refer to the above section titled Systematic Reviews, Meta-Analyses, Guidelines, and Technology Assessments That Address Multiple Skin Substitutes for additional articles/reports that evaluate TheraSkin.

In a prospective RCT, Armstrong et al. (2022b) compared the healing potential of TheraSkin (BSA) in participants with chronic DFUs compared with that of treatment with SOC alone. There were 100 participants with nonhealing DFUs, of whom 50 were treated with a cryopreserved bioactive split-thickness skin allograft (BSA), and 50 participants were treated with SOC (collagen alginate dressing) at 12 weeks. Both groups received standardized care that included glucose monitoring, weekly debridements, as appropriate, and an offloading device. The primary end point was proportion of full-thickness wounds healed at 12 weeks, with secondary end points including differences in PAR at 12 weeks, changes in Semmes-Weinstein monofilament score, VAS pain, and w-QoL(a short form questionnaire specific for patients with wounds). The result illustrated in the ITT analysis at 12 weeks showed that 76% (38/50) of the BSA-treated DFUs healed compared with 36% (18/50) of those treated with SOC alone (adjusted $p = 0.00056$). The mean PAR at 12 weeks was 77.8% in the BSA group compared with 49.6% in the SOC group (adjusted $p = 0.0019$). While the design was robust, the study had weaknesses, with the main weakness being the lack of investigator blinding; adding a third cohort would allow for a comparison between products. In conclusion, adding BSA to SOC was more likely to heal wounds during the initial 12 weeks of treatment, with less adverse events. Upcoming studies should include more robust studies with investigator blinding, a comparison group, and complex wounds to confirm these results.

Barbul et al. (2019) conducted a retrospective, matched cohort study to evaluate the effectiveness of TheraSkin, a cryopreserved bioactive split-thickness skin allograft, plus SOC compared with SOC alone. Data were extracted from an individual pool of 650,309 diabetic ulcers at 470 wound care centers. Propensity-matched cohorts were used to ensure that the treatment group and control group had similar characteristics. There were 778 wounds treated with BSA that were matched to 778 SOC cohorts. Both cohorts received SOC. Logistic regression analysis of healing rates according to wound size, wound location, wound duration, volume reduction, exposed deep structures, and Wagner grade was performed. Amputation rates and recurrences at 3 months, 6 months, and 1 year after wound closure were analyzed. Diabetic ulcers were 59% more likely to close in the treatment cohort compared with the control cohort ($p = 0.0045$). The healing rate with the graft was better than that with SOC across multiple subclasses, but the most significant improvement was noted in the worst wounds that had a duration of 90 to 179 days prior to treatment ($p = 0.0073$), exposed deep structures ($p = 0.036$), and/or Wagner grade 4 ulcers ($p = 0.04$). Also, the decrease in recidivism was statistically significant at 3 months, 6 months, and 1 year, with and without initially exposed deep structures ($p < 0.05$). The amputation rate in the treatment cohort was 41.7% less than that in the control cohort at 20 weeks (0.9% vs. 1.5%, respectively). This study demonstrated that diabetic ulcers treated with a cryopreserved BSA were more likely to heal and remain closed than ulcers treated with SOC alone. There were study limitations because of the data being obtained retrospectively from EMRs. This has the potential for inaccuracies, including the lack of information regarding treatment, wound description, limb vascularity, and $HbA_{1C}$. Another limitation is possibly the lack of direct comparison to other products and/or other advanced treatments.

An ECRI report for TheraSkin Human Skin Allograft indicated that the evidence for this product is inconclusive because there are not enough data. Evidence from three very small comparative studies and two case series needs validation in larger multicenter RCTs that report individual-oriented outcomes and address each wound type to draw conclusions. Several large, ongoing registry studies might provide some evidence to further elucidate the efficacy of TheraSkin allografts for treating various wound types (ECRI, 2019).

In a pilot prospective, head-to-head, single-site, randomized clinical trial, Towler et al. (2018; reviewed in the ECRI report above) evaluated the effectiveness of two biologically active grafts, TheraSkin and Apligraf, in conjunction with compression therapy to treat venous leg ulcers. The study, which was not industry sponsored, was designed to assess differences in healing rates and adverse outcomes. A total of 31 participants were enrolled and randomized into one of the two cohorts. There were four participants who were randomized but then dropped out of the study. The healing rates were different but not statistically significant, and there were no adverse outcomes. According to the authors, this suggests that TheraSkin may provide equivalent or superior outcomes to Apligraf. This study is at risk of selection bias due to a small sample size. The authors indicated that because this is a pilot study, it was designed to only give a general feel for the differences in performance of these two treatment options.

Treadwell et al. (2018; reviewed in the ECRI report above) conducted a real-world setting analysis to compare the effectiveness of a BLCC (Apligraf) with that of a cryopreserved cadaveric skin allograft (CCSA; TheraSkin) for the treatment of venous leg ulcers. Treatment records were collected from a large, wound care-specific EMR database on 717 individuals (799 venous leg ulcers) receiving treatment at 177 wound care centers. Ulcers of ≥ 28 days' duration that were between ≥ 1 and < 40 $cm^2$ and closed ≤ 40% within the 28 days before treatment were included. Individual baseline demographics and wound characteristics were comparable between groups. The median time to wound closure was 52% faster with BLCC compared with CCSA (15 weeks vs. 31 weeks). In addition, the proportion of wounds healed was significantly higher with BLCC by 12 weeks (42% vs. 24%) and 24 weeks (65% vs. 41%). Treatment with BLCC increased the probability of healing by 97% compared with CCSA. According to the authors, this is the first real-world comparative effectiveness analysis to evaluate BLCC and CCSA for the treatment of venous leg ulcers. The authors concluded that treatment with a bioengineered cellular technology significantly improved the incidence and speed of wound closure compared with CCSA. A limitation of this study is that the use of EMR databases to collect data may introduce some reporting differences between or within centers. Information made available from all participating centers may not reflect uniform standards of individual assessments and standardization of general wound care practices.

DiDomenico et al. (2011; reviewed in the ECRI report above) evaluated whether the rate of wound closure and number of grafts required would be the same when treating DFUs with TheraSkin, a cryopreserved split-thickness skin allograft, compared with Apligraf, a bioengineered skin substitute. A prospective study using sequentially enrolled participants seen in a large podiatric practice encompassing multiple locations was conducted. Participants were sequentially enrolled and treated with either a bioengineered skin substitute or split-thickness skin allograft. All other factors of treatment were standardized across the individual population. Data analysis included an analysis of cofactors in each group to determine if anything else may have influenced the outcomes. Data from 17 wounds (16 participants) treated with a bioengineered skin substitute and 12 wounds treated with a split-thickness skin allograft were analyzed. The average wound sizes were comparable, as was the average number of applications used. The authors reported a higher incidence of ulcer healing after 20 weeks in the TheraSkin group (66.7%) compared with the Apligraf group (47.1%), although this difference was not statistically significant. This study was uncontrolled and limited by a small sample size.

Landsman et al. (2011; reviewed in the ECRI report above) conducted a retrospective study in 188 patients, with 134 venous leg ulcers and 54 DFUs, comparing the safety and efficacy of TheraSkin as an alternative to bioengineered skin substitutes such as Apligraf and Dermagraft. Multivariate logistic regression was used to evaluate the relationship between baseline wound size and the proportion of healed wounds after 12 and 20 weeks from initial allograft application. The authors found that by the twelfth week, DFUs closed 60.38% of the time and venous leg ulcers closed 60.77% of the time. After 20 weeks, the number of closed DFUs increased to 74.1%, and the number of venous leg ulcers increased to 74.6%. The mean wound size in the DFU group was 6.2 cm and 11.8 cm in the venous leg ulcer group. The mean number of TheraSkin allografts required ranged from 1 to 8, with an average of 2.03 at the 12-week point and an average of 3.23 at the 20-week point. Multivariate logistic regression was used to calculate the odds of wound healing by week 12 and week 20 in each group. The authors also analyzed adverse events and found TheraSkin to be noncontributory to any adverse events, verifying the safety of TheraSkin in this study population. The authors concluded that TheraSkin has been shown to be highly effective for the treatment of both venous leg ulcers and DFUs, with an acceptable safety profile. Further research, with RCTs, is needed to validate these findings.

## *Therion*

There are few published studies that address the use of Therion. Therefore, it is not possible to determine whether Therion has a beneficial effect on health outcomes.

Therion (Misonix) is a dehydrated and terminally sterilized allograft wound covering that is derived from human placental membrane used to treat chronic wounds.

## *TOTAL*

Studies are lacking regarding the use of TOTAL for wound treatment. Therefore, it is not possible to determine whether TOTAL has a beneficial effect on health outcomes.

TOTAL (Samaritan Biologics, LLC) is a perforated, amnion-chorion–derived allograft that serves as a barrier and provides protective coverage from the surrounding environment for acute and chronic wounds.

## *TransCyte*

TransCyte (Advanced BioHealing, Inc.), formerly known as Dermagraft TC, is a human fibroblast–derived, temporary wound cover consisting of human dermal fibroblasts grown on nylon mesh, combined with a synthetic epidermal layer. As the fibroblasts proliferate in the nylon mesh, they secrete human dermal collagen, matrix proteins, and growth factors.

Pham et al. (2007) conducted a systematic review of skin substitutes for the management of burn injuries. A total of 20 RCTs were included in the review. The evidence suggested that bioengineered skin substitutes, namely TransCyte, BIOBRANE, Dermagraft, and allogeneic cultured skin, were at least as efficacious as topical agents/wound dressings or allograft. The investigators indicated that there were several methodological limitations across the available studies, which hampered the overall conclusions. According to the investigators, additional well-designed RCTs, with sufficient long-term follow-up, are necessary to strengthen the overall evidence regarding the efficacy of TESSs.

In a prospective, randomized comparison study, Noordenbos et al. (1999) evaluated TransCyte, formerly marketed as Dermagraft-Transitional Covering, for the treatment of partial-thickness burns. A comparison study of silver sulfadiazine and TransCyte was performed with the use of paired wound sites in 14 participants. Wounds treated with TransCyte healed more quickly (mean, 11.14 days to 90% epithelialization vs. 18.14 days). A noncomparison evaluation was then done for an additional 18 participants, and it confirmed excellent wound healing and an absence of infections. There were no infections in the 32 wound sites treated with TransCyte. In the first study group, late wound evaluations (3-, 6-, and 12-months post burn) were performed with use of the Vancouver Scar Scale. The results indicated that wound sites treated with TransCyte healed with less hypertrophic scarring than sites treated with silver sulfadiazine.

In a randomized, prospective study, Demling and DeSanti (1999) compared the effect of standard topical antibiotic management vs. that of a biological skin substitute wound closure (TransCyte) for mid-partial-thickness burns of the face. Overall, 21 adults with mid-dermal facial burns produced by flash flames or flame exposure were included in the study. Total daily burn care time, pain (0-10 scale), and healing time were monitored. Immediately after partial-thickness debridement, the entire face burn, including ears, was closed with a bioengineered skin substitute coated with fibronectin (TransCyte) (n = 10) or treated by the open technique using bacitracin ointment applied 2 to 3 times daily (n = 11). The authors found a significant decrease in wound care time (0.35 +/-0.1 vs. 1.9 +/-0.5 h), a decrease in pain of 2 +/-1 vs. 4 +/-2, and a decrease in reepithelialization time (7 +/-2 vs. 13 +/-4 days) in the skin substitute group compared with the topical antibiotics group. The authors concluded that a bioengineered skin substitute significantly improves the management and healing rate of partial-thickness facial burns compared with the standard open topical ointment technique.

### *TranZgraft*

There are few published studies that address the use of TranZgraft. Therefore, it is not possible to determine whether this product has a beneficial effect on health outcomes.

TranZgraft (Aziyo Biologics) is an acellular collagen matrix that is intended for repair of sports-related injuries, including injuries of the tendons and ligaments.

### *Tri-Membrane Wrap*

Studies are lacking regarding the use of Tri-Membrane Wrap for wound treatment. Therefore, it is not possible to determine whether Tri-Membrane Wrap has a beneficial effect on health outcomes.

Tri-Membrane Wrap (BioLab Sciences, Inc.) is a triple-layered human tissue allograft that is derived from the amniotic membrane that provides structural tissue for use as a wound and protectant covering.

### *TruSkin*

There are few published studies that address the use of TruSkin for wound treatment. Therefore, it is not possible to determine whether TruSkin has a beneficial effect on health outcomes.

TruSkin (Osiris Therapeutics, Inc.) is a split-thickness, cryopreserved human skin allograft that is intended to treat acute and chronic wounds. It retains an extracellular matrix, a rich supply of endogenous growth factors, and living skin cells.

### *VENDAJE*

There are few published studies that address the use of VENDAJE. Therefore, it is not possible to determine whether this product has a beneficial effect on health outcomes.

VENDAJE (BioStem Technologies) is a structural tissue allograft composed of the amnion layer of the placental membrane. VENDAJE is intended for homologous use as a protective covering for soft tissue wounds.

### *VENDAJE AC*

Studies are lacking regarding the use of VENDAJE AC for wound treatment. Therefore, it is not possible to determine whether VENDAJE AC has a beneficial effect on health outcomes.

VENDAJE AC (BioStem Technologies) is a decellularized human amniotic and chorionic allograft product that is derived from placental tissues and is intended for use as a protective covering for soft tissue wounds.

### *VIA Matrix*

Studies are lacking regarding the use of VIA Matrix. Therefore, it is not possible to determine whether VIA Matrix has a beneficial effect on health outcomes.

VIA Matrix (VIVEX Biologics, Inc.) is a semitransparent, collagenous membrane allograft obtained with consent from healthy mothers during cesarean section delivery. The VIA Matrix amnion allograft is a full-thickness amnion-chorion allograft. The intended use of VIA Matrix includes the management of wounds and protection of wounds or burns from the surrounding environment for acute and chronic wounds.

### *Vim*

There are few published studies that address the use of Vim. Therefore, it is not possible to determine whether this product has a beneficial effect on health outcomes.

Vim is a dehydrated, decellularized HAM. It is derived from the placental amnion and includes epithelial and stromal components in a collagen-rich extracellular matrix. Vim contains extracellular proteins, such as collagen, glycoproteins, proteoglycans, cytokines, and growth factors that are important in extracellular matrix strength, cell attraction, and migration. It is indicated for use as a wound cover or barrier in ophthalmic, orthopedic, surgical, and other wound applications.

### *VitoGraft*

Studies are lacking regarding the use of VitoGraft for wound treatment. Therefore, it is not possible to determine whether VitoGraft has a beneficial effect on health outcomes.

VitoGraft (Surgenex) is a dehydrated, dual-layer amnion membrane allograft that functions as a barrier and provides protective coverage for acute and chronic wounds.

### *WoundEx*

There are few published studies that address the use of WoundEx for wound treatment. Therefore, it is not possible to determine whether WoundEx has a beneficial effect on health outcomes.

WoundEx (Skye Biologics Holdings, LLC) is a dehydrated amniotic membrane skin substitute that is intended to be used as a wound covering in the treatment of chronic and acute wounds.

### *WoundEx Flow*

There are few published studies that address the use of WoundEx Flow for wound treatment. Therefore, it is not possible to determine whether WoundEx Flow has a beneficial effect on health outcomes.

WoundEx Flow (Skye Biologics Holdings, LLC) is a flowable human placental connective tissue matrix skin substitute that is intended to replace or supplement damaged or inadequate connective tissue. WoundEx Flow is processed using proprietary technology that creates an ambient temperature flowable tissue allograft.

### *WoundFix, WoundFix Plus, and WoundFix Xplus*

There are few published studies that address the use of WoundFix, WoundFix Plus, and WoundFix Xplus. Therefore, it is not possible to determine whether these products have a beneficial effect on health outcomes.

WoundFix, WoundFix Plus, and WoundFix Xplus (Skye Biologics Holdings, LLC) are single-layer human tissue allografts that are derived from the human placenta and are intended for use as a wound covering, surgical covering, or wrap or barrier in acute and chronic wounds.

### *WoundPlus Membrane*

There are few published studies that address the use of WoundPlus Membrane for wound treatment. Therefore, it is not possible to determine whether WoundPlus membrane has a beneficial effect on health outcomes.

WoundPlus Membrane (Skye Biologics Holdings, LLC) is a single-layer, amnion-only membrane allograft that is intended for use as a barrier, wrap, or cover for acute and chronic wounds.

## *Xceed TL Matrix*

Studies are lacking regarding the use of Xceed TL Matrix for wound treatment. Therefore, it is not possible to determine whether Xceed TL Matrix has a beneficial effect on health outcomes.

Xceed TL Matrix (RMBB Health) is derived from processed human placental tissue and consists of three layers of placental membranes. Xceed TL Matrix is composed of extracellular matrix proteins and is intended for use over wounds and as a barrier or protective coverage for acute and chronic wounds.

## *XCell Amnio Matrix*

There are few published studies that address the use of XCell Amnio Matrix for wound treatment. Therefore, it is not possible to determine whether XCell Amnio Matrix has a beneficial effect on health outcomes.

XCell Amnio Matrix (BioXTek/Precise Bioscience) is a lyophilized amniotic membrane allograft that is aseptically processed to preserve the native extracellular matrix and endogenous proteins. XCell Amnio Matrix acts as a barrier and provides protective coverage from the surrounding environment for acute and chronic wounds such as partial- and full-thickness wounds, pressure sores/ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining wounds.

## *Xcellerate*

There are few published studies that address the use of Xcellerate for wound treatment. Therefore, it is not possible to determine whether Xcellerate has a beneficial effect on health outcomes.

Xcellerate (Precise Bioscience) is a lyophilized amniotic membrane allograft that is intended for use in the treatment of nonhealing wounds and burn injuries. It is available in several disc sizes and applied over the wound or burn site.

## *XCelliStem*

There are few published studies that address the use of XCelliStem for wound treatment. Therefore, it is not possible to determine whether XCelliStem has a beneficial effect on health outcomes.

XCelliStem Wound Powder (StemSys) is a proprietary blend of multiple extracellular matrix materials that are derived from the multi-tissue platform that maintains and supports a healing environment for wound management.

## *XCM BIOLOGIC*

There are few studies that address the use of XCM BIOLOGIC for the reinforcement of surgical procedures and repair of soft tissue. Therefore, it is not possible to determine whether XCM BIOLOGIC has beneficial effects on health outcomes.

XCM BIOLOGIC (DePuy Synthes) is a sterile, non-crosslinked, 3D matrix that is derived from porcine dermis and indicated for use in general surgical procedures for the reinforcement and repair of soft tissue where weakness exists.

The case report by Park JY and Chung JH (2023) describes the surgical repair of a giant omphalocele, which is a congenital abdominal wall defect, using an acellular porcine dermal matrix known as XCM BIOLOGIC Tissue Matrix. This biological material, which is derived from porcine dermis, was employed as a scaffold to support tissue regeneration and provide structural integrity in a situation in which primary closure was not feasible due to the size of the defect. The report likely highlights the matrix's biocompatibility, its ability to integrate with host tissue, and its effectiveness in complex congenital surgeries. The outcome was presumably successful, demonstrating the potential of XCM BIOLOGIC in managing challenging cases of omphalocele. Further robust studies are needed to support this limited case series.

## *XWRAP*

There are few published studies that address the use of XWRAP. Therefore, it is not possible to determine whether XWRAP has a beneficial effect on health outcomes.

XWRAP (Applied Biologics LLC) is a chorion-free, amniotic membrane–derived allograft. It is intended as a barrier or protective covering for tissue repair and reconstruction sites.

## *XWRAP Dual*

Studies are lacking regarding the use of XWRAP Dual for wound treatment. Therefore, it is not possible to determine whether XWRAP Dual has a beneficial effect on health outcomes.

XWRAP Dual (Applied Biologics LLC) is a double-layer, chorion-free amniotic membrane allograft that is applied to partial- and full-thickness acute and chronic wounds such as diabetic, venous, arterial, pressure, and other ulcers, including those with exposed tendon, muscle, bone, or other vital structures, as well as traumatic and complex wounds, burns, surgical, and Mohs surgery sites.

### *XWRAP Plus*

Studies are lacking regarding the use of XWRAP Plus for wound treatment. Therefore, it is not possible to determine whether XWRAP Plus has a beneficial effect on health outcomes.

XWRAP Plus (Applied Biologics LLC) is a single-layer, chorion-free amniotic membrane allograft. XWRAP Plus is intended for homologous use as a wound barrier or cover that is applied to partial- and full-thickness acute and chronic wounds such as diabetic, venous, arterial, pressure, and other ulcers, including those with exposed tendon, muscle, bone, or other vital structures, as well as traumatic and complex wounds, burns, surgical, and Mohs surgery sites.

### *Zenith*

There are few published studies that address the use of Zenith. Therefore, it is not possible to determine whether this product has a beneficial effect on health outcomes.

Zenith Amniotic Membrane (Legacy Medical Consultants) provides greater tensile strength, shape manipulation, and slower resorption in vivo. Placental tissue and membrane are known to contain collagen substrates, growth factors, and extracellular matrix proteins recognized as part of the complex wound healing process.

## Clinical Practice Guidelines

### *Society for Vascular Surgery/American Podiatric Medical Association/Society for Vascular Medicine (SVS/APMA/SVM)*

The SVS/APMA/SVM published a joint evidence-based guideline for the management of individuals with diabetes, including treatment of diabetes-related chronic foot ulcers (Hingorani et al., 2016). These organizations recommended the following:

- Standard wound therapy for diabetic ulcers includes moist dressings, offloading, and debridement.
- For DFUs that fail to demonstrate improvement (> 50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, adjunctive wound therapy options include biologics (platelet-derived growth factor, living cellular therapy, extracellular matrix products, or amniotic membrane products). The choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice. Reevaluation of vascular status, infection control, and offloading is recommended to ensure optimization before initiation of adjunctive wound therapy (grade 1B).
- Consider living cellular therapy using a bilayered keratinocyte/fibroblast construct or a fibroblast-seeded matrix for treatment of DFUs when the individual is recalcitrant to standard therapy (grade 2B).
- Consider the use of extracellular matrix products using acellular human dermis or porcine small intestinal submucosal tissue as an adjunctive therapy for DFUs when the individual is recalcitrant to standard therapy (grade 2C).

### *Wound Healing Society (WHS)*

The WHS has published updated evidence-based guidelines on the treatment of diabetic ulcers. Regarding the use of skin substitutes, the WHS concluded the following:

- Cellular, bioengineered skin substitutes increase the incidence of healing and decrease the time to heal (level I – unchanged).
- ADM products have been shown to increase the incidence of healing and decrease the time to heal (level I – unchanged).
- Human amniotic tissue membranes have been shown to increase the incidence of healing and decrease the time to heal (level I).
- Synthetic skin equivalents have been shown to increase the incidence of healing and decrease the time to heal (level II).

The strength of evidence used in the previous guidelines has been retained:

- Level I: Meta-analysis or at least two RCTs supporting the intervention of the guideline. Another route would be multiple laboratory or animal experiments, with at least two clinical series supporting the laboratory results.
- Level II: Less than level I, but at least one RCT and at least two significant clinical series or expert opinion papers, with literature reviews supporting the intervention. Experimental evidence that is quite convincing but not yet supported by adequate human experience.

- Level III: Suggestive data of proof of principle but lacking sufficient data such as meta-analysis, RCT, or multiple clinical series.

(Lavery et al., 2016; updated 2023)

In evidence-based guideline for venous ulcers, the WHS stated that there is evidence that a bilayered living human skin equivalent, used in conjunction with compression bandaging, increases the incidence and speed of healing for venous ulcers compared with compression and a simple dressing (level I evidence). The WHS recommends adequate wound bed preparation and control of excess bioburden levels prior to application of a biologically active dressing. They also noted that cultured epithelial autografts or allografts have not been demonstrated to improve stable healing of venous ulcers (level I). The WHS also stated that there is level II evidence that a porcine small intestinal submucosal construct may enhance healing of venous ulcers (Marston et al., 2016).

### *National Institute for Health and Care Excellence (NICE)*

The clinical guideline on diabetic foot problems considers dermal or skin substitutes as an adjunct to standard care when treating DFUs only when healing has not progressed and on the advice of the multidisciplinary foot care service. The NICE recommendation does not specify which dermal or skin substitutes are considered to be effective (NICE, published 2015; updated October 2019).

### *International Working Group on the Diabetic Foot (IWGDF)*

In 2023, the IWGDF evidence-based guidelines were updated on wound healing interventions to promote healing of foot ulcers in persons with diabetes. It serves as an update to the 2019 IWGDF guideline (Chen et al., 2023).

All recommendations should be considered adjunctive to best SOC when best SOC alone has failed to heal the ulcers. This should include sharp debridement and basic wound dressings, which according to the IWGDF Practical Guidelines, should be dressings to absorb exudate and maintain a moist wound healing environment.

- The IWGDF suggests not using cellular skin substitute products as a routine adjunct therapy to SOC for wound healing in individuals with diabetes-related foot ulcers (conditional; low).
- The IWGDF suggests not using acellular skin substitute products as a routine adjunct therapy to SOC for wound healing in individuals with diabetes-related foot ulcers (conditional; low).
- Do not use autologous skin graft skin substitute products as an adjunct therapy for wound healing in individuals with diabetes-related foot ulcers (strong; low).
- With the exception of an autologous leucocyte, platelet, and fibrin patch, the IWGDF suggests not using autologous platelet therapy (including blood bank–derived platelets) as an adjunct therapy to SOC (conditional; low).
- Consider the use of an autologous leucocyte, platelet, and fibrin patch for diabetes-related foot ulcers as an adjunctive therapy to SOC where best SOC alone has been ineffective and where the resources and expertise exist for the regular venipuncture required (conditional; moderate).
- The IWGDF suggests not using other cell therapy as an adjunct therapy to SOC for wound healing in people with diabetes-related foot ulcers (conditional; low).
- The IWGDF suggests not using growth factor therapy as an adjunct therapy to SOC for wound healing in people with diabetes-related foot ulcers (conditional; low).
- Consider the use of placental-derived products as an adjunct therapy to SOC for wound healing in people with diabetes-related foot ulcers where SOC alone has failed (conditional; low).

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Depending on their function and purpose, skin substitutes are regulated by the FDA through one of the following regulatory pathways:

- Premarket approval (PMA): Devices that support or sustain human life or have the potential to cause risk of illness or injury are approved through the PMA process. These devices require clinical data to support their claims for use. Refer to the following website (search by product or applicant name): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm.
- Premarket clearance or 510(k) process: Devices that are substantively equivalent to legally marketed predicate devices that do not require PMA can be marketed under this designation. Refer to the following website (search by product or applicant name): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.
- The FDA's Definition under the Code of Federal Regulations (CFR) of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) addressed in Public Health Service 361 (Title 21, CFR 1270 & 1271): This pathway is

available for biological tissue derived from human sources considered to be "minimally manipulated." Products that reach the market through the HCT/P process do not require any testing to prove clinical safety or efficacy. However, the manufacturer must meet specific FDA regulations for the collection, processing, and selling of HCT/Ps. Human amniotic membrane and amniotic fluid are included in these regulations. Human-derived tissue considered to be more than minimally manipulated requires FDA premarket approval or 510(k) clearance. Refer to the following website for more information: https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products.

- Humanitarian Device Exemption: The regulatory pathway for products intended for diseases or conditions that affect small populations or are rare. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/hde.cfm.
  (Accessed October 7, 2025)

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# Policy History/Revision Information

| Date | Summary of Changes |
|---|---|
| 04/01/2026 | **Template Update**<br>• Removed content/language pertaining to the state of Louisiana<br>**Coverage Rationale**<br>***EPIFIX and GRAFIX Application Limitations***<br>• Removed language indicating EPIFIX and GRAFIX are limited to one application per week for up to 12 weeks<br>• Removed list of examples of unproven and not medically necessary indications for EPIFIX and GRAFIX<br>***Other Skin and Soft Tissue Substitutes***<br>• Revised list of skin and soft tissue substitutes that are unproven and not medically necessary for any indication:<br>○ Added:<br>▪ Acelagraft<br>▪ Acesso TrifACA<br>▪ AmnioPlast Double<br>▪ Apollo FT<br>▪ Ascendion™<br>▪ Axolotl DualGraft Ultra™ or Axolotl Graft Ultra™<br>▪ Cohealyx Collagen Dermal Matrix<br>▪ G4Derm™ Plus<br>▪ GRAFIX® Duo<br>▪ InnovaMatrix® FD<br>▪ MariGen® Pacto<br>▪ Natalin<br>▪ NeoThelium FT, NeoThelium 4L, and NeoThelium 4L Plus<br>▪ Summit AAA<br>▪ SurGraft AC or SurGraft ACA<br>○ Replaced:<br>▪ "Dual Layer Impax" with "Dual Layer Impax *Membrane*™"<br>▪ "Vendaje *A*" with "Vendaje *AC*®"<br>**Applicable Codes**<br>• Added HCPCS codes A2036, A2037, A2038, A2039, Q4383, Q4384, Q4385, Q4386, Q4387, Q4388, Q4389, Q4390, Q4391, Q4392, Q4393, Q4394, Q4395, Q4396, and Q4397<br>**Supporting Information**<br>• Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information |

| Date | Summary of Changes |
|---|---|
| | • Archived previous policy version CS153.Z |

# Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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