Skin and Soft Tissue Substitutes (for Nebraska Only)

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➲ Instructions for Use

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Related Policies

- Breast Reconstruction (for Nebraska Only)
- Prolotherapy and Platelet Rich Plasma Therapies

Application

This Medical Policy only applies to the State of Nebraska.

Coverage Rationale

EpiFix or Grafix® (GrafixPL, GrafixPRIME, and GrafixPL PRIME) (Non-Injectable)

EpiFix or Grafix is proven and medically necessary for treating diabetic foot ulcer when all of the following criteria are met:

- Adequate circulation to the affected extremity as indicated by one or more of the following:
  - Pedal pulses palpable
  - Ankle-brachial index (ABI) between 0.7 and 1.2
  - Dorsum transcutaneous oxygen test (TcPO2) ≥ 30 mm Hg within the last 60 days
  - Triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg
- Optimal glucose control glycated hemoglobin test (HgA1c) < 12% (within the last 90 days)
- Individual has a diagnosis of Type 1 or Type 2 diabetes
- Ulcer size ≥ 1 cm^2 and < 25 cm^2
- Ulcer has failed to demonstrate Measurable Signs of 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
- Individual does not have active Charcot deformity or major structural abnormalities of the affected foot
- Individual does not have a known or suspected malignancy of the current ulcer being treated
- Standard wound care continues
- Ulcer being treated does not extend to tendon, muscle, capsule, or bone

EpiFix and Grafix Application Limitations

- EpiFix is limited to one application per week for up to 12 weeks
- Grafix is limited to one application per week for up to 12 weeks

Due to insufficient evidence of efficacy, EpiFix and/or Grafix are unproven and not medically necessary for all other indications including but not limited to:

- EpiFix application more frequently than once a week or beyond 12 weeks
- Grafix application more frequently than once a week or beyond 12 weeks

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:

- Acesso DL
- Acesso TL
- Activate Matrix
- Affinity®
- AlloGen™
- AlloSkin™
- AlloWrap®
- Altiply®
- AmniCore Pro
- AmniCore Pro+
- Amnio Quad-Core
- Amnio Tri-Core Amniotic
- Amnio Wound™
- Amnio Wrap2™
- AmnioAMP-MP™
- AmnioArmor™
- AmnioBand®
- AmnioBind or DermaBind TL
- AmnioCore™
- Amniocyte Plus™
- AMNIOEXCEL®, AMNIOEXCEL Plus, or BioDExcel™
- AmnioFix®
- AMNIOMATRIX® or BioDMatrix™
- Amnio-Maxx™ or Amnio-Maxx™ Lite
- Amniorepair
- Amniotext
- Amniotext patch
- Amnion Bio™
- AMNIPLY™
- Apis
- Architect®
- Artacent® Cord
- Artacent Wound or Artacent AC
- ArthroFLEX®
- Ascent™
- AxoBioMembrane™
- Axolotl™ Ambient or Axolotl Cryo
- Axolotl Graft or Axolotl DualGraft
- Barrera SL or Barrera DL, per sq cm
- BellaCell HD™
- bio-ConneKt®
- BioDfence™ or BioDFence DryFlex™
- Bioskin™
- Bioskin Flow
- Biovance® Biovance Tri-Layer or Biovance 3L
- BioWound™, BioWound Plus, or BioWound Xplus
- CarePATCH™
- Celera Dual Layer or Celera Dual Membrane
- Cellesta™ or Cellesta Duo
- Cellesta Cord
- Cellesta Flowable Amnion
- CLARIX®
- CLARIX FLO®
- Cocoon membrane
- Cogenex (amniotic membrane and flowable amnion)
- Coll-e-Derm™
- Complete AA
- Complete ACA
- Complete™ FT, Complete™ SL
- Conexa™
- Corecyte™
- Coretext™ or Protext™
- CorMatrix®
- Corplex™
- Corplex p
- Cryo-Cord™
- Cygnus™ Cygnus Dual or Cygnus matrix
- Cymetra™
- Cytal™
- DermaBind CH, DermaBind DL, or DermaBind SL
- DermACELL®*, DermACELL AWM®, or DermACELL AWM Porous (*refer to asterisked note below when DermACELL is used during breast reconstruction*)
- Dermacyte® Amniotic Membrane Allograft®
- Derma-Gide™
- DermaPure™
- DermaSpan™
- Dermavest® or Plurivest®
- Derm-Maxx
- Dual Layer Impax™
- Emerge Matrix
- Enverse
- EpiCord®
- EPIEFFECT

- EpiFix®, injectable
- Esano A, Esano AAA, Esano AC, or Esano ACA
- Excellagen®
- E-Z Derm®
- FlowerAmnioFlo™ or FlowerFlo™
- FlowerAmnioPatch™ or FlowerPatch™
- FlowerDerm™
- Fluid Flow™
- Fluid GF™
- GammaGraft™
- Genesis Amniotic Membrane
- Grafix Core
- Grafix Plus
- Guardian
- Helicoll™
- hMatrix®
- Human Health Factor 10 Amniotic Patch (HHF10-P)
- Hyalomatrix®
- InnovaMatrix AC or Innovamatrix FS
- Integra® Flowable Wound Matrix
- InteguPly®
- Interfyl™
- Keramatrix®
- Kerasorb®
- Kerecis™ Omega3, Kerecis® Omega3 MariGen® Shield
- Keroxx™
- Lamellas and Lamellas XT
- Matrion™
- MatriStem MicroMatrix®
- Mediskin™
- Membrane Graft™
- Membrane Wrap-Hydro or Membrane Wrap™
- MemoDerm™
- Microlyte Matrix
- Mirragen Advanced Wound Matrix
- MIRODERM™
- MLG-Complete
- MyOwn Skin™
- NeoMatriX
- NeoPatch™
- NEOX®
- NeoStim Membrane, NeoStim TL Membrane, NeoStimDL
- NEOX FLO®
- Novachor™
- Novafix™
- Novafix™ DL
- NovoSorb SynPath
- NuDYN™
- NuShield®
- Omeza Collagen Matrix
- ORION
- PalinGen® Amniotic Tissue Allograft and PalinGen Flow Products
- PermeaDerm B
- PermeaDerm glove
- PermeaDerm C
- Phoenix Wound Matrix®
- Polycyte™
- PriMatrix®
- Procenta®
- ProgenaMatrix™
- ProMatrX™
- PuraPly®, PuraPly AM, or PuraPly XT
- Rebound Matrix
- REGUaRD™
- Relese
- Repriza®
- Restorigin™
- Restrata
- Revita™
- Revitalon®
- RevoShield+ Amniotic Barrier
- Signature APatch
- SkinTE™
- STRATTICE™
- Stravix™ or StravixPL™
- Supra SDRM
- Suprathel
- Surederm™
- Surfactor®
- SurGraft® SurGraft® FT, SurGraft® TL, SurGraft® XT
- SurgiCORD™
- SurgiGRAFT™
- SurgiGRAFT-DUAL
- Symphony
- TAG
- Talymed®
- TenSIX®
- TheraGenesis
- TheraSkin®
- Therion™
- TranZgraft®
- TruSkin™
- Vendaje
- Vendaje A
- Vim
- WoundEx®
- WoundEx™ Flow
- WoundFix™, WoundFix Plus, or WoundFix Xplus
- WoundPlus membrane or E-Graft
- Xcell Amnio Matrix
- XCelliStem
- XCellerate™
- XCM BIOLOGIC® Tissue Matrix
- XWRAP™
- Zenith Amniotic Membrane

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

Definitions

Acellular Matrix: A Matrix that is derived from sources other than human skin. Acellular Matrices are the most frequently used skin substitute. Acellular Matrices are composed of allogeneic or xenogeneic derived collagen, membrane, or cellular remnants (Debels et al., 2015; Ferreira et al., 2011; Nicholas et al., 2016; Vig et al., 2017).

Allogeneic Matrix: A Matrix that is derived from human tissue such as neonatal fibroblasts of the foreskin (Debels et al., 2015; Ferreira et al., 2011; Nicholas et al., 2016; Vig et al., 2017).

Composite Matrix: A Matrix that is derived from human keratinocytes and fibroblasts supported by a scaffold of synthetic mesh or xenogeneic collagen. These Matrices contain active cellular components that continue to generate compounds and protein that may accelerate wound healing (Debels et al., 2015; Ferreira et al., 2011; Nicholas et al., 2016; Vig et al., 2017).

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

Human Skin Allograft: An Allograft that is derived from donated human skin (e.g., cadavers) that has been processed to remove the cellular components (Debels et al., 2015; Ferreira et al., 2011; Nicholas et al., 2016; Vig et al., 2017).

Measurable Signs of Healing: Wound is diminishing in size (either surface or depth) and there is decreased amount of exudate and necrotic tissue (Gould et al., 2016).

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).

Xenograft: Skin from another species (e.g., cows, pigs, horses, fish, etc.).

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

HCPCS Code	Description
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
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 InteguPly, 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

HCPCS Code	Description
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
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

HCPCS Code	Description
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
Q4206	Fluid Flow or Fluid GF, 1 cc
Q4208	Novafix, per sq cm
Q4209	SurGraft, per sq cm
Q4210	Axolotl Graft or Axolotl DualGraft, per sq cm
Q4211	Amnion Bio or AxoBioMembrane, per sq cm
Q4212	AlloGen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta Cord, per sq cm
Q4215	Axolotl Ambient or Axolotl Cryo, 0.1 mg
Q4216	Artacent Cord, per sq cm
Q4217	WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm
Q4218	SurgiCORD, per sq cm
Q4219	SurgiGRAFT-DUAL, per sq cm
Q4220	BellaCell HD or Surederm, per sq cm
Q4221	Amnio Wrap2, per sq cm
Q4222	ProgenaMatrix, per sq cm
Q4224	Human Health Factor 10 Amniotic Patch (HHF10-P), per sq cm
Q4225	AmnioBind, per sq cm or DermBind 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
Q4231	Corplex p, per cc
Q4232	Corplex, per sq cm
Q4233	Surfactor or nudyn, per 0.5 cc
Q4234	Xcellerate, per sq cm
Q4235	AMNIOREPAIR or AltiPly, per sq cm
Q4236	carePATCH per sq cm
Q4237	Cryo-cord, per sq cm
Q4238	Derm-maxx, per sq cm
Q4239	Amnio-maxx or amnio-maxx lite, per sq cm
Q4240	Corecyte, for topical use only, per 0.5 cc
Q4241	Polycyte, for topical use only, per 0.5 cc
Q4242	Amniocyte plus, per 0.5 cc
Q4244	Procenta, per 200 mg
Q4245	Amniotext, per cc
Q4246	Coretext or protext, per cc
Q4247	Amniotext patch, per sq cm
Q4248	Dermacyte Amniotic Membrane Allograft, per sq cm
Q4249	AMNIPLY, for topical use only, per sq cm

HCPCS Code	Description
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
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
Q4277	WoundPlus membrane or E-Graft, 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

HCPCS Code	Description
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

Description of Services

Skin substitutes also known as bioengineered, tissue-engineered, or artificial skin, are a mixed group of biologic, 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.

There is no universal classification system that allows for simple categorization of all the products that are currently commercially available. Davison-Kotler's (2018) most recent system organized skin substitutes according to cellularity (cellular, acellular), layering (single layer, bilayer), replaced region (i.e., epidermis, dermis, or both), materials used (biologic, synthetic, or both), and permanence (temporary, permanent). 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 include 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. Patients 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 debridement of necrotic tissue, maintaining moisture balance, preventing, and treating infection, correct ischemia, and 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, as well as 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 over another. There is currently an ongoing clinical trial being conducted by St. Luke's Wound Care Clinic in Texas to develop a Cellular and Tissue Based Therapy Registry (CTPR) for Wounds. It is sponsored in collaboration with the U.S. Wound Registry. Data is submitted by hospital outpatient departments regarding all cellular and tissue-based products currently reimbursed in the

hospital-based outpatient department. Additional information can be found at: https://clinicaltrials.gov/ct2/show/NCT02322554. (Accessed August 24, 2022)

Many skin and tissue substitutes are included in and ongoing clinical trials. Refer to the following for more information: www.clinicaltrials.gov.

Clinical Evidence

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

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 suggesting 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 it a 'C' rating for use of acellular or cellular skin substitutes as an adjunct to standard wound care (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 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 2021).

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 suggesting that acellular skin substitutes appear to heal more chronic DFU than standard wound care (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 and time to healing, and possibly quality of life, no definitive conclusions can be drawn as to comparative effectiveness and safety of these products due to the limited number of studies overall, and on the individual skin substitutes. Questions remain about the effect of acellular skin substitutes on the incidence of amputation and on ulcer recurrence due to the limited number of studies on these outcomes. Evidence directly comparing different acellular skin substitutes or comparing acellular with cellular skin substitutes is extremely limited and of very low quality to determine whether any 1 product or product type is superior. The acellular skin substitutes that were part of the evidence base for this report included Epifix, EpiCord, AmnioBand, and AmnioExcel, MatriStem MicroMatrix, DermCell (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 assessing the comparative effectiveness and safety of cellular skin substitutes incremental to SWC alone for treatment of DFUs in patients 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 both very low. While cellular skin substitutes appear to benefit DFU healing over SWC alone, there is insufficient evidence on individual products to assess whether any particular cellular skin substitute is more effective than the others. 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 part of the evidence base for this report included 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, randomized controlled trials (RCTs), and prospective nonrandomized comparative studies examining commercially available skin substitutes in individuals with diabetic foot ulcers, venous leg ulcers, pressure ulcers, and arterial leg ulcers were included in the review. Seventy-six commercially available skin substitutes were identified and categorized based on the Davison-Kotler classification system. Sixty-eight (89%) were categorized as acellular dermal substitutes, mostly replacements from human placental membranes and animal tissue sources. Three systematic reviews and 22 RCTs examined use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Twenty-one ongoing clinical trials (all RCTs) examined an additional nine skin substitutes with comparable classifications. EpiFix was reviewed in five studies. Grafix/GrafixPrime, 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 percent of studies examining acellular dermal substitutes described the experimental intervention as favorable over standard of care for wound healing and shorter time to heal, 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 standard of care. 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 or carcinogenic effects are not known. Information on amputations and hospitalizations due to infections is also missing. Before findings can be relied upon, more data are needed on hospitalization, pain reduction, need for amputation, exudate and 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 reporting wound size inclusion criterion. Sizes ranged from as small as 0.5 cm^2 to 100 cm^2. One 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 industry funded 20 of 22 RCTs included in this report, which raises significant concerns about possible publication bias or selective outcome reporting in that results unfavorable to industry may not be reported or published

According to the investigators, the lack of studies examining the efficacy of most skin substitute products and the need for better designed studies providing more clinically relevant data are this Technical Brief's clearest implications. 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 6-month follow-up.

Gordon et al. (2019) conducted a systematic review to determine the efficacy of biologic skin substitutes for healing diabetic foot ulcers. 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 mean time to healing. Biologic skin substitutes were organized both very specifically into product brand and more broadly by 4 main groups based on product composition: allografts/xenografts, cultured skin grafts, dermal substitutes, and biosynthetic dressings. Twenty-five studies were identified that assessed the proportion of complete wound closure by 12 weeks. Wounds treated with biologic dressings were 1.67 times more likely to heal by 12 weeks than those treated with standard of care (SOC) dressings ($p < 0.00001$). Five studies assessed the proportion of complete wound closure by 6 weeks. Wounds treated with biologic 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 biologic 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 biologic skin substitutes are more effective than SOC dressings at healing diabetic foot ulcers by 12 weeks. This review had several study limitations, one being 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 within that time periods was not assessed. Finally, adverse effects of the skin products were not mentioned. Future studies must address the relative benefits of different skin substitutes as well as the long-term implications of these products.

Skin and Soft Tissue Substitutes

Acesso DL

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

Acesso DL (Dynamic Medical Services LLC, Surgenex) is a dehydrated dual layered human amniotic membrane allograft intended to serve as a barrier or cover for acute and chronic wounds.

Acesso TL

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

Acesso TL(Dynamic Medical Services LLC, Surgenex) is a dehydrated allograft 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.

Activate Matrix

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

Activate Matrix consists of all three layers of the placental membranes including amnion, intermediate layer, and chorion. It is a minimally manipulated human placental membrane product 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 that serves as a natural, biological barrier or wound cover.

Affinity

There are few published studies addressing the use of Affinity. Therefore, it is not possible to conclude 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.

Serena et al. (2020) conducted a multicenter, prospective, randomized, controlled, clinical trial across 14 centers to assess clinical outcomes associated with the use of HSAM plus standard of care (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). 76 subjects with DFUs were treated with either Affinity plus standard care (n = 38) or standard care alone (n = 38). Wound closure for the Affinity group was significantly greater than 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 subjects vs. 48% of control subjects (p = 0.04). The authors reported that the probability of wound closure with Affinity vs. standard care increased by 75% (HR, 1.75). Limitations included the lack of binding and 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, HSAM significantly reduced baseline ulcer area, depth, and volume. Additional data from well-designed trials are needed to support these conclusions.

AlloGen

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

AlloGen (Vivex Biomedical, Inc.) is an amniotic fluid product derived from donated birth tissue. AlloGen is intended for treatment of non-healing wounds and burn injuries.

AlloSkin

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

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

Moravvej et al. (2016) evaluated allogeneic fibroblasts on meshed split thickness skin grafts (STSGs) in 14 patients. After debridement and wound excision, 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 patients. Alloskin demonstrated good properties compared to petroleum jelly-impregnated gauze. The average healing time and hypertrophic scar formation were significantly different between the two groups. In addition,

the skin pigmentation score in the Alloskin group was closer to normal. The authors concluded that Alloskin grafting, including fibroblasts on meshed STSG, may be a useful method to reduce healing time and scar size and may require less autologous STSG in extensive burns where a high percentage of skin is burned and there is a lack of available donor sites. Larger prospective, controlled clinical studies are needed to compare the effectiveness, of human skin allograft to standard care.

AlloWrap

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

AlloWrap (AlloSource) is a human amniotic membrane designed to provide a biologic barrier following surgical repair.

AmniCore Pro

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

AmniCore Pro (Stability Biologics) is comprised of donated human tissue that has been screened, recovered, and serologically/microbiologically tested at Certified Laboratory Improvement Amendments (CLIA) certified labs in adherence with Food and Drug Administration (FDA), State and American Association of Tissue Banks (AATB) requirements. AmnioCore Pro is a significantly different allograft compared to all other AmnioCore brands. AmnioCore Pro is unique in that it is comprised of amniotic membrane and chorionic membrane, whereas all other AmnioCore brands are comprised of 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 conclude whether AmniCore Pro+ has a beneficial effect on health outcomes.

AmniCore Pro+ (Stability Biologics) is comprised of donated human tissue that has been screened, recovered, and serologically/microbiologically tested at Certified Laboratory Improvement Amendments (CLIA) certified labs in adherence with Food and Drug Administration (FDA), State and American Association of Tissue Banks (AATB) requirements. AmnioCore Pro+ is an exclusive and bioactive allograft different from AmnioCore Pro and other AmnioCore brands. The AmnioCore Pro+ is a three-layer allograft comprised of amniotic membrane and chorionic membrane, whereas AmnioCore Pro is a dual layer amnion/chorion graft all the other AmnioCore brands are comprised of only amnionic membranes. The AmnioCore Pro+ is a three-layer allograft with an amnion inferior surface, chorion inner layer, and an amnion superior surface.

Amnio Quad-Core

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

Amnio Quad-Core (Stability Biologics is comprised of donated human tissue that has been screened, recovered, and serologically/microbiologically tested at Certified Laboratory Improvement Amendments (CLIA) certified labs in adherence with Food and Drug Administration (FDA), State and American Association of Tissue Banks (AATB) requirements. Amnio Quad-Core is a four-layer allogeneic amniotic membrane allograft for use as a barrier and 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 conclude 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 applied as a covering.

AmnioAmp-MP

There are few published studies addressing the use of AmnioAmp-MP. Therefore, it is not possible to conclude 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 intended for homologous use to cover and protect a recipient's tissue to be used for acute and chronic wounds, barrier to enhance soft tissue healing after a primary surgical repair and general reconstructive surgery to reduce scar tissue formation and enhance soft tissue healing.

Amnio Wound

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

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

AmnioWrap2

There are few published studies addressing the use of Amnio Wrap2. Therefore, it is not possible to conclude whether Amnio Wrap2 has a beneficial effect on health outcomes.

AmnioWrap2 (Direct Biologics™) is a placental-based allograft comprised of 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 (ECM), growth factors and cytokines.

AmnioArmor

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

AmnioArmor (Bone Bank Allografts, a subsidiary of Globus Medical, Inc.) is a dehydrated human amniotic membrane allograft 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 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 randomized controlled trials and one case series suggest Amnioband may improve wound healing compared with Apligraf® and when added to standard care in patients with diabetic foot ulcers, the studies include too few patients to be conclusive, and the studies do not validate each other, because each on addressed a different comparison. Larger, double-blind 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.

Alvaro-Afonso et al. (2020) reviewed the recent advances in dermo epidermal skin substitutes (DSS) for the treatment of diabetic foot ulcers (DFUs). PubMed and Cochrane databases were systematically searched for systematic reviews published after 2013 and for randomized controlled trials (RCTs). A retrospective evaluation of 28 RCTs was performed. Rates of complete wound closure and time to healing were examined for 17 commonly available DSS. Healing rates after 12 weeks and time to complete closure in DFUs were heterogeneous among the 28 RCT. The best healing rates at 12 weeks were accomplished with dermal cellular substitutes (Epifix, 100% and Amnioband, 85%). The authors concluded that based on these studies, DSS used in conjunction with standard care appear to improve the healing rates of DFUs, as 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 DSS. According to the authors, future RCTs should include patients with severe comorbidities, in order to be more representative of clinical reality.

Glat et al. (2019; reviewed in the ECRI report above) conducted a randomized controlled trial in which dehydrated human amnion and chorion allograft (dHACA) (AmnioBand) was compared to one of the earliest and most commonly accepted

tissue-engineered skin substitutes (TESS) (Apligraf) in the treatment of nonhealing diabetic foot ulcers (DFUs) over a period of 12 weeks to assess the superiority of healing. Following a 2-week screening period during which subjects with DFUs were treated with collagen alginate dressing, 60 subjects were randomized at 5 sites to receive either dHACA or TESS applied weekly, with weekly follow-up for up to 12 weeks. The mean time to heal within 6-week time period for the dHACA group was 24 days (95% CI, 18.9-29.2) versus 39 days (95% CI, 36.4-41.9) for the TESS group; the mean time to heal at 12 weeks was 32 days (95% CI, 22.3-41.0) for dHACA-treated wounds versus 63 days (95% CI, 54.1-72.6) for TESS-treated wounds. The proportion of wounds healed at study completion (12 weeks) was 90% (27/30) for the dHACA group versus 40% (12/30) for the TESS group. It was concluded that aseptically processed dHACA heals diabetic foot wounds more reliably and statistically significantly faster than TESS. Study limitations included the lack of blinding. Withdrawing patients at 6 weeks rather than continuing through 12 weeks of treatment if their wounds were not sufficiently responding to treatment to ensure patient safety and permit other treatment pathways could also be considered a limitation. Another limitation was the insufficient follow up time needed to evaluate long-term outcomes or recurrence. Several of the study authors received research funds from MTF Biologics, the manufacturer of AmnioBand.

DiDomenico et al. (2018; reviewed in the Alvaro-Afonso systematic review and ECRI report above) conducted a prospective, randomized, multi-center clinical trial and reported on the full trial results of 80 patients where AmnioBand Membrane dehydrated human amnion and chorion allograft (dHACA) was compared with standard of care (SOC) in achieving wound closure in non-healing diabetic foot ulcers (DFUs). After a 2-week screening period, during which patients with DFUs were unsuccessfully treated with SOC, patients 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) treated with SOC alone. Mean time to heal within 12 weeks was significantly faster for the dHACA- treated group compared with SOC, 37 days vs 67 days in the SOC group. Mean number of grafts used per healed wound during the same time period was 4.0. The authors concluded that aseptically processed dHACA heals DFUs significantly faster than SOC at 12 weeks. Future studies should consider a comparative arm using an advanced skin substitute and allow wounds of greater severity or depth. The findings of the RCT need confirmation through an independently conducted RCT. MTF funded the study, and several of the study authors are consultants for MTF.

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 diabetic foot ulcers (DFU) healing. Following the inclusion and exclusion criteria, randomized controlled trials (RCT) 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 patients. 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 occurs 2.32 times more often and is 32 days faster in comparison with the group that used conventional dressings. The authors concluded that there is no statistical evidence to support the effectiveness of amniotic membrane in comparison with other conventional dressings. However, there is a clear tendency for the use of 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 the definitive evidence for the use of amniotic membrane on DFUs.

DiDomenico et al. (2017; reviewed in ECRI report above) conducted a retrospective crossover study to evaluate the effectiveness of dHACA in those patients that failed to respond to the SOC treatments and who exited the original recently published, prospective randomized controlled trial (RCT) after failing up to 12 weeks of SOC treatment. (The RCT which is referenced above, compared aseptically processed dehydrated human amnion/chorion allograft (dHACA) to standard of care (SOC), and showed 85% wound closure rates were reported in the dHACA arm while only 25% of patients in the SOC arm healed). Patients with nonhealing wounds from the SOC arm after exit from the original study were offered weekly adjunctive applications of dHACA (AmnioBand) for up to 12 weeks. The primary endpoint was the proportion of wounds completely healed at 12 weeks. Secondary endpoints included the difference in wound area from baseline to the end of study and the percentage area reduction (PAR). Eleven patients were eligible to participate and wounds for 9 of the 11 patients healed (82%). The mean wound area decreased from 1.7 cm^2 to 0.2 cm^2, with a corresponding mean PAR of 92%. Of the 2 wounds that failed to heal, 1 diabetic foot ulcer (DFU) decreased in area by 91% and the other 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 and Paggiaro systematic reviews above) compared aseptically processed dehydrated human amnion and chorion allograft (dHACA) versus standard of care (SOC) in facilitating wound closure in nonhealing diabetic foot ulcerations (DFUs). Patients with DFUs treated with SOC (off-loading, appropriate debridement, and moist wound care) after a 2-week screening period were randomized to either SOC or wound-size-specific dHACA (AmnioBand, Musculoskeletal Transplant Foundation) applied weekly for up to 12 weeks plus SOC. Primary endpoint was the percentage of wounds 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 for the dHACA group was 3.8. The mean wastage at 12 weeks was 40%. One adverse event and 1 serious adverse event occurred in the dHACA group; neither was graft related. Three adverse events and 1 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 imitations of this trial include the lack of blinding (patient 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 no published studies addressing the use of AmnioBind or DermaBind TL for wound treatment. Therefore, it is not possible to conclude 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 (PM) allograft consisting of amnion, chorion, and the associated intermediate (spongy) layer used to treat acute and chronic wounds.

AmnioCore TM

There are no published studies addressing the use of AmnioCore TM for wound treatment. Therefore, it is not possible to conclude whether AmnioCore TM 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 no published studies addressing the use of Amniocyte Plus for wound treatment. Therefore, it is not possible to conclude 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.

AMNIOEXCEL, AMNIOEXCEL Plus, or BioDExcel

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

AMNIOEXCEL, also marketed under trade name BioDExcel, (Integra LifeSciences, Inc.) 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) for dressing wounds and repairing soft-tissue defects indicates that the evidence for AmnioExcel is inconclusive. The studies reviewed had major limitations which resulted in a high risk of bias. Therefore, the evidence is inconclusive. (2019)

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 diabetic foot ulcers (DFU) healing. Following the inclusion and exclusion criteria, randomized controlled trials (RCT) 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 patients. 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 occurs 2.32 times more often and is 32 days faster in comparison with the group that used conventional dressings. The authors concluded that there is no statistical evidence to support the effectiveness of amniotic membrane in comparison with other conventional dressings. However, there is a clear tendency for the use of 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 the definitive evidence for the use of amniotic membrane on DFUs.

Haugh et al. (2017; reviewed in The AHRQ Technical Report above) performed a meta-analysis examining randomized controlled trials comparing amniotic tissue products with standard of care in nonhealing diabetic foot ulcers. A search of 3 databases identified 596 potentially relevant articles. Application of selection criteria led to the selection of 5 randomized controlled trials. The 5 selected randomized controlled trials represented a total of 311 patients. Three of the trials included compared EpiFix, a dehydrated amniotic membrane product, to 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 to SOC alone (Snyder et al., 2016). One trial compared Grafix, a cryopreserved amniotic product to 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 diabetic foot ulcers with amniotic membrane improves healing rates in diabetic foot ulcers. The authors state that further studies are necessary to confirm the findings identified in these 5 trials and to determine whether amniotic products have the same impact on all diabetic patients seen in clinical practice. The authors also state that although this analysis indicates that amniotic membrane has great potential for use in diabetic foot ulcers (DFUs) in clinical practice, patients in all 5 of the included trials had to demonstrate adequate tissue perfusion and a lack of any signs of infection to enroll. As many patients who develop DFUs do not demonstrate adequate tissue perfusion and are often plagued by chronic infections, it is unclear how these products would translate into every day clinical care of diabetic patients. According to the authors, the lack of follow-up of patients 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 patients with chronic diabetic foot ulcers (DFUs). All randomized controlled trials (RCTs) comparing human amnion/chorion membrane plus standard therapy and standard therapy alone in patients with DFUs were included in the analysis. Eligible studies were reviewed, and data extracted into 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 patients receiving amniotic membrane plus standard therapy had far fewer incomplete healing wounds than those receiving standard of care 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 standard of care treatment heals DFUs significantly faster than standard of care alone. When using the amnion in patients 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 randomized controlled trials (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, and Laurent et al. (2017) systematic review and meta-analysis and AHRQ Technology Report above) conducted a study to evaluate dehydrated amniotic membrane allograft (DAMA) (AMNIOEXCEL) plus standard of care (SOC) compared to SOC alone for the closure of chronic diabetic foot ulcers (DFUs).This prospective, open-label, randomized, parallel group trial was implemented at 8 clinical sites in the United States. Eligibility criteria included adults with type 1 or type 2 diabetes mellitus who have 1 or more ulcers with a Wagner classification of grade 1 or superficial 2 measuring between 1 cm2 and 25 cm2 in area, presenting for more than 1 month with no signs of infection/osteomyelitis; ABI > 0.7; HbA1c Less than 12%; and serum creatinine less than 3.0 mg/dL. Eligible subjects were randomized (1:1) to receive either SOC alone (n = 14) or DAMA+SOC (n = 15) until wound closure or 6 weeks, whichever occurred first. The endpoint was the proportion of subjects with complete wound closure (defined as complete reepithelialization without drainage or need for dressings. Thirty-five percent of subjects in the DAMA+SOC cohort achieved complete wound closure at or before week 6, compared with 0% of the SOC alone cohort. There was a more robust response noted in the per protocol population, with 45.5% of subjects in the DAMA+SOC cohort achieving complete wound closure, while 0% of SOC-alone subjects

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 and discectomy), soft tissue, tendon, and nerve applications. Other AmnioFix products include AmnioFix Injectable that is intended for 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 randomized controlled trial (RCT) and three cases series shows that micronized AmnioFix injection is safe, relieves pain and improved function up to 3 months in patients with tendinopathies and arthritis. The RCTs were related to plantar fasciitis with three case series were related to arthritis and tendinosis. While the evidence is favorable for AmnioFix, larger RCTs are needed to validate results and assess long term outcomes. There were no studies evaluating 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. Randomized controlled trials comparing AmnioFix with other skin substitutes and reporting on patient 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 (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-blind RCTs with active treatment comparators (injectables, surgery, 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 Sport FLOW, Clarix FLO, and AmnioFix (Hayes, 2019, updated 2021).

Cazzell et al. (2018) conducted a prospective, single-blind, randomized controlled trial at 14 sites in the United States to evaluate the efficacy of micronized dehydrated human amnion/chorion membrane (dHACM) injection for plantar fasciitis (PF). Subjects were randomized to receive 1 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 compared with a 45% reduction for controls, Foot Function Index-Revised (FFI-R) scores for treatment subjects had mean reduction of 60% versus baseline, whereas control subjects had mean reduction of 40% versus baseline. Of 4 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 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 versus other advanced therapies cannot be determined. The study is also limited by a short follow-up time.

Ogaya-Pinies et al. (2018; reviewed in ECRI report above) evaluated if the use of dehydrated human amnion/chorion membrane (dHACM) allograft wrapped around the neurovascular bundles (NVB) during a robotic-assisted radical prostatectomy (RARP) accelerates the return to potency. A total of 940 patients with preoperative Sexual Health Inventory for Men (SHIM) > 20 underwent RARP with some degree of bilateral nerve sparing (NS). Of these, 235 patients underwent RARP, with bilateral placement of dHACM graft around the NVBs. They were matched in a 1:3 proportion with a similar group of patients (n = 705) who did not receive the allograft (control group or group 2). Minimum follow-up was 12 months. Postoperative outcomes were analyzed between propensity-matched dHACM graft (group 1) and non-graft groups (group 2). There were no significant demographic differences between the two groups. Potency was defined as the ability to achieve and maintain satisfactory erections firm enough for sexual intercourse, with or without the use of PDE-5 inhibitors. The mean time to potency was significantly lower in group 1 (2.37 months) versus group 2 (3.94 months). The potency recovery rates were superior for group 1 at all early time points measured except at 12 months. Patients who received the dHACM wrap around the NVB after RARP accelerates the return to potency when compared to

a similar control group without the use of the allograft. We also demonstrated that this faster return to potency occurs regardless of the degree of the NS preservation. Younger patients (< 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, extra-prostatic disease nor high Gleason score. However, potency recovery rates did not differ between groups at 12-months post-RARP.

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, composite, and health-related outcomes. All outcomes were assessed (1) in the short term (up to 2 months), (2) the intermediate term (2-6 months) and (3) the medium term (more than 6 months to 2 years). Quality assessment was performed using the Cochrane risk of bias tool. Twenty-two trials comprising 1216 patients 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 the dehydrated amniotic membrane provided significant clinical relief at 0-2 months, there were no data about this treatment at 2 months and beyond.

Zelen et al. (2013a) reported the results of a randomized clinical trial examining the efficacy of micronized dehydrated human amniotic/chorionic membrane (mDHACM) injection as a treatment for chronic refractory plantar fasciitis. Forty-five patients were randomized to receive 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 patients receiving 0.5 cc or 1.25 cc mDHACM versus controls within 1 week of treatment and throughout the study period. The authors concluded that in patients 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 addressing the use of AMNIOMATRIX or BioDMatrix. Therefore, it is not possible to conclude 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 composed of morselized amniotic membrane and amniotic fluid components 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 no published studies addressing the use of Amnio-Maxx or Amnio-Maxx Lite for wound treatment. Therefore, it is not possible to conclude 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, non-healing wounds such as diabetic foot ulcers and venous leg ulcers or soft tissue defects. The Amnio-Maxx Lite version is a single layer.

AMNIOREPAIR or AltiPly

There are no published studies addressing the use of AMNIOREPAIR or AltiPly for wound treatment. Therefore, it is not possible to conclude whether AMNIOREPAIR or AltiPly have a beneficial effect on health outcomes.

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

Amniotext

There are no published studies addressing the use of Amniotext for wound treatment. Therefore, it is not possible to conclude whether Amniotext has a beneficial effect on health outcomes.

Amniotext (Regenerative 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 no published studies addressing the use of an Amniotext patch for wound treatment. Therefore, it is not possible to conclude whether Amniotext patch has a beneficial effect on health outcomes.

Amniotext patch (Regenerative Labs) is an amniotic membrane-derived, human tissue allograft. The product serves as a wound covering and is intended for chronic non-healing wounds such as diabetic foot ulcers and venous leg ulcers

Amnion Bio

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

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

AMNIPLY

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

The product information on AMNIPLY is not currently available.

Apis

There are few published studies addressing the use of Apis. Therefore, it is not possible to conclude whether Apis has a beneficial effect on health outcomes.

Apis is an absorbable, biodegradable skin substitute comprised of gelatin (porcine derived), Manuka honey, and hydroxyapatite. Skin substitutes are used to protect large or nonhealing wounds or burns.

Architect

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

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

Artacent

There are few published studies addressing the use of Artacent for wound treatment. Therefore, it is not possible to conclude whether Artacent 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 choriamniotic 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.

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 diabetic foot ulcers (DFUs) that failed to heal 50% following standard of care (SOC) after 2-4 weeks. 26 patients 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 endpoint was complete closure at 12 weeks. The results showed baseline ulcers were larger than in most DFU clinical trials (4.65 ±4.89cm2), and for the primary endpoint, 17/26 (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 DLAM may be effective in ulcers that are more resistant to standard of care and a clinical trial with a greater sample size is planned.

Artacent Cord

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

Artacent Cord (Tides Medical) is a wound healing patch that is comprised of 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®) is an acellular dermal matrix intended for supplemental support and covering for soft-tissue repair.

An ECRI report for ArthroFLEX indicated that evidence from 3 small studies is at too high a risk of bias to determine how well it repairs rotator cuff tears. Studies suggest that Arthroflex is safe, and 1 study suggests 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).

Ascent

There are few published studies addressing the use of Ascent. Therefore, it is not possible to conclude 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 non-healing wounds and burns.

AxobioMembrane

There are few published studies addressing the use of AxobioMembrane. Therefore, it is not possible to conclude whether AxobioMembrane has a beneficial effect on health outcomes.

AxobioMembrane (Axolotl Biologix, Inc.) is a dehydrated human amniotic membrane allograft that is intended to accelerate and improve soft tissue repair.

Axolotl Ambient and Axolotl Cryo

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

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

Axolotl Graft and Axolotl DualGraft

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

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

Barrera SL or Barrera DL

There are few published studies addressing the use of Barrera SL or Barrera DL. Therefore, it is not possible to conclude whether Barrera SL or Barrera DL has a beneficial effect on health outcomes.

Barrera SL and Barrera DL (RegenTx Partners) is a dehydrated amniotic allograft. It is intended to serve as a protective wound cover to offer protection from the surrounding environment in wounds, including surgically created wounds.

BellaCell HD

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

BellaCell (HansBiomed Corp.) 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 addressing the use of bio-ConneKt for wound treatment. Therefore, it is not possible to conclude 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 or BioDfence DryFlex

There are few published studies addressing the use of BioDfence or BioDfence DryFlex. Therefore, it is not possible to conclude whether BioDfence or BioDfence DryFlex has a beneficial effect on health outcomes.

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

Bioskin

There are few published studies addressing the use of Bioskin for wound treatment. Therefore, it is not possible to conclude whether Bioskin has a beneficial effect on health outcomes.

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

Bioskin Flow

There are few published studies addressing the use of Bioskin Flow for wound treatment. Therefore, it is not possible to conclude whether BioskinFlow has a beneficial effect on health outcomes.

The product information on Bioskin Flow is not currently available.

Biovance, Biovance Tri-Layer, or Biovance 3L

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

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

Biovance 3L is a triple-layer decellularized, dehydrated human amniotic membrane, sterilized using e-beam irradiation. Biovance 3L is intended to be used as a cover or to protect from the surrounding environment in wound and surgical repair and reconstruction procedures.

An ECRI report for Biovance Amniotic Membrane Allograft (Celularity, Inc.) for treating chronic wounds indicates that the evidence for Biovance is inconclusive. The studies reviewed were very low-quality single arm studies that had major limitations which resulted in a high risk of bias. Therefore, the evidence is inconclusive (ECRI Institute. Product Brief. Biovance Amniotic Membrane Allograft (Celularity, Inc.) for Treating Chronic Wounds. Plymouth Meeting (PA): ECRI Institute; July 2020).

In a 2020 ECRI clinical evidence assessment, it was concluded that based on two very low-quality single arm studies, the efficacy of Biovance for the treating chronic wounds compared to standard of care and other skin grafts cannot be determined. Both studies had a high risk of bias due to four or more limitations, including small study size, incomplete outcomes reporting, and lack of controls, randomization, and blinding. Studies did not report on some key patient-oriented outcomes (e.g., infection, quality of life, wound size reduction). The studies assessed patients with different wound etiologies and different wound types, resulting in the results not generalizable across all patients or wound types. The pilot trial does not report outcomes for wound types separately (i.e., venous leg ulcers, diabetic foot ulcers, pressure ulcers, arterial ulcers, and collagen vascular disease associated ulcers).

Smiell et al. (2015) conducted a multicenter registry study to observe outcomes with use of a 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 patients with actively infected wounds or known hypersensitivity to DDHAM. Fifteen sites with practicing wound care clinicians of various specialties participated in this review, enrolling chronic wounds including venous, diabetic, pressure, collagen vascular, and arterial ulcers-all of various severities, durations, sizes, and previous treatments. A total of 244 wounds were observed in this study, however, this review is limited to the 179 chronic wounds in 165 patients that were enrolled at 15 of the 19 participating centers. The 4 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, patients experienced factors that significantly affected wound closure. These factors included wound infections, noncompliance with prescribed treatments (e.g., compression, off-loading, and wound care), re-injury 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 cm2 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 patient conditions in real-world environments. The authors recommended that these findings be validated in a prospective randomized controlled trial in chronic wounds with stricter enrollment criteria and monitoring of a standard of good wound care.

BioWound, BioWound Plus, and BioWound Xplus

There are few published studies addressing the use of BioWound, BioWound Plus, and BioWound Xplus. Therefore, it is not possible to conclude 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 for wounds. These products are intended for use as a wound covering, surgical covering, or wrap or barrier in acute and chronic wounds.

CarePATCH

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

CarePATCH™ (Extremity Care) is a dehydrated human amniotic membrane allograft intended to be used as a wound cover or protective wound barrier. 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 no published studies addressing the use of Celera Dual Layer or Celera Dual Membrane for wound treatment. Therefore, it is not possible to conclude whether Celera Dual Layer or Celera Dual Membrane has beneficial effect on health outcomes.

Celera™ Dual Membrane and Celera™ Dual Layer (Nvision Biomedical Technologies, Inc.) is an Extracellular Matrix (ECM) 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 addressing the use of Cellesta or Cellesta Flowable Amnion. Therefore, it is not possible to conclude whether Cellesta or Cellesta Flowable Amnion has a beneficial effect on health outcomes.

Cellesta (Ventris Medical, LLC.) is a minimally manipulated amniotic membrane allograft 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, urologic and gynecological surgeries, and burn wound reconstruction.

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

Cellesta Duo

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

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

Cellesta Cord

There are few published studies addressing the use of Cellesta Cord. Therefore, it is not possible to conclude 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, and surgically created wounds.

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

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

CLARIX Regenerative Matrix (Amniox Medical, Inc.) is comprised of cryopreserved human amniotic membrane 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 addressing the use of CLARIX Flo. Therefore, it is not possible to conclude whether CLARIX FLo has a beneficial effect on health outcomes.

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

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-blind RCTs with active treatment comparators (injectables, surgery, 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 Sport FLOW, Clarix FLO, and AmnioFix (Hayes, Human Amniotic Membrane Injections for Treatment of Chronic Plantar Fasciitis, 2021)

Cocoon Membrane

There are few published studies addressing the use of Cocoon membrane. Therefore, it is not possible to conclude 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 used as a wound covering and barrier. Cocoon Membranes are intended to serve as a covering and barrier for full and partial-thickness, chronic, and acute wounds.

Cogenex

There are no published studies addressing the use of Cogenex amniotic membrane or Cogenex flowable amnion for wound treatment. Therefore, it is not possible to conclude 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 and 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 suspended in a saline solution, intended for treatment of deep or complex wound repair.

Coll-e-Derm

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

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

Complete AA, Complete ACA, Complete SL, and Complete FT

There are few published studies addressing the use of Complete AA, Complete ACA, Complete SL and/or Complete™ FT. Therefore, it is not possible to conclude 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 to acute and chronic wounds.

Complete AA from Samaritan Biologics LLC, is a dual layer amnion derived allograft to serve as a barrier and provide protective coverage from the surrounding environment to acute and chronic wounds. Complete™ AA is a sterile, single use, dehydrated allograft derived from donated human amnion membrane.

Complete ACA, from Samaritan Biologics LLC is a three-layer amnion-chorion-amnion derived allograft to serve as a barrier and provide protective coverage from the surrounding environment to acute and chronic wounds. Complete™ ACA is a sterile, single use, dehydrated allograft derived from donated human amnion chorion membrane.

Conexa

There are few published studies addressing the use of Conexa. Therefore, it is not possible to conclude 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 repaired by sutures or suture anchors during tendon repair surgery and reinforcement for rotator cuff, patellar, Achilles, biceps, quadriceps, or 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 addressing the use of Corecyte for any other indications. Therefore, it is not possible to conclude whether Corecyte has a beneficial effect on health outcomes.

Corecyte (Predictive Biotech) is a minimally manipulated human tissue allograft derived from the Wharton's 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 addressing the use of Coretext or Protext for wound treatment. Therefore, it is not possible to conclude 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 healing of a defect. Protext is used as replacement tissue that is inserted or injected into the joint and other injured areas.

CorMatrix

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

CorMatrix porcine SIS-ECM (CorMatrix Cardiovascular, Inc.) is a non-cross-linked extracellular matrix made from porcine small intestinal submucosa (SIS), 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.

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 2-patch repair. A CorMatrix patch was used for ventricular septal defect (VSD) closure in 77% of the patients, and/or in 75% of atrial septal defect closures. There was one in-hospital mortality (1.4%) due to respiratory failure. One patient required a pacemaker. At mid-term follow-up (1.6 years), a total of 7 patients required 8 reoperations due to cardiac-related indications, including 5 for left atrioventricular valve (LAVV) repair, 1 for LAVV replacement, and 2 isolated residual VSDs. 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 (ECM). A single-site chart review was conducted on 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 ECM or autologous pericardium were included. Follow-up echocardiography was performed on all patients. Histologic specimens were available on ECM patches from a subset of patients who required reoperation. At total of 44 patients (mean age, 62.6 ±12.2 years) underwent anterior leaflet augmentation with either porcine intestinal ECM or autologous pericardium. Eight (32%) of the patients with ECM had recurrence of severe mitral regurgitation (MR) on echocardiography at an average time of 201 ±98 days. Seven (28%) patients required reoperation because of failure of the ECM 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 ECM 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 on the use of ECM materials with a goal to decrease the failure rate experienced in this study.

Mosala Nezhad et al. (2016) attempted to systematically review the 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 subjects. The authors identified only one level II study and only four studies that could reasonably be classified as level III studies, the remainder representing level IV studies that 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 a 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 driven by robust protocols that aim to quantify the pathological process of tissue repair.

Corplex

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

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

Corplex P

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

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

Cryo-Cord

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

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

Cygnus, Cygnus Dualand Cygnus Matrix

There are few published studies addressing the use of Cygnus, Cygnus Dual and Cygnus matrix. Therefore, it is not possible to conclude whether Cygnus, Cygnus Dual and Cygnus matrix have a beneficial effect on health outcomes.

Cygnus products (VIVEX Biomedical, Inc.) are available in multiple thicknesses and are dried human amnion membrane allografts composed of a single layer of epithelial cells, a basement membrane, and an 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 semi-transparent, collagenous membrane allograft obtained with consent from healthy mothers during cesarean section delivery.

Cymetra

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

Cymetra (LifeCell™) is a micronized, particulate form of AlloDerm™ which is an acellular dermal matrix. 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 (MD) in 344 patients from 2000-2010, to determine whether the material is temporary or permanent. The indications for MD were for both temporary and permanent correction of glottic insufficiency. Twenty-nine percent of all injections resulted in unwanted absorption. Over-injection was needed and 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 over the decade). In 159 patients with long-term follow-up (> 1 year), there was a 14% incidence of reinjection. 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 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 clinical usefulness of this procedure is proven, and research with randomized controlled trials is needed to validate these findings.

Cytal

There are few published studies addressing the use of Cytal. Therefore, it is not possible to conclude 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 and 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 to other skin substitutes (ECRI, 2019).

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

DermaBind CH, DermaBind DL, and DermaBind SL

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

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

DermaBind DL (Health Tec Wound Care) is designed for application directly to acute and 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, providing protection for the wound from the external environment and maintaining a moist environment.

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

DermACELL, DermACELL AWM, and DermACELL AWM Porous

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

DermACELL, DermACELL AWM, and DermACELL AWM Porou (LifeNet Health®) are decellularized human dermal allografts that that are intended for the management of chronic non-healing 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 randomized controlled trial (RCT), DermACELL AWM appears to be safe and effective and achieves complete healing in more diabetic foot ulcers than standard of care. One small RCT provides insufficient evidence to determine how well DermACELL works to treat chronic venous leg ulcers (VLUs) compared with standard care. RCTs that compare DermACELL AWM with standard of care and other ADMs used for treating chronic wounds are needed; 3 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 standard of care (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 3 H-ADM subtypes were studied. The 6 studies included in this meta-analysis investigated 3 subtypes of H-ADM: AlloPatch Pliable, DermACELL, and GRAFTJACKET. These 3 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. Inclusion criteria indicated articles be randomized controlled trials investigating the effects on neuropathic, nonischemic DFUs. Data from 312 DFUs in total were included in the meta-analysis. The results show H-ADMs are more effective in healing patients within a 12-week (3.14; range, 2.04-4.83) and 16-week period (2.35; range, 1.25-4.43) in comparison 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) in comparison with SOC. Within the subgroups, 2 H-ADMs were associated with a higher likelihood of complete healing within 12 weeks when compared with SOC. The third H-ADM had a point estimate, which suggested superiority over SOC. According to the investigators, this study shows H-ADMs are associated with a higher likelihood of complete healing and fewer days to complete healing within a 12-week and 16-week periods when 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 utilized, and frequency of H-ADM application was not consistent in the included studies. The overall heterogeneity between studies was addressed by utilizing a random effects model for analysis. Still, this calls into question the external validity of the data. The available studies are few and the total number of DFUs from the studies covered is relatively low and often industry-associated, thus, 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 lengths of 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 ECRI report above) evaluated the safety and efficacy of decellularized human acellular dermal matrices (D-ADM; DermACELL AWM) compared with conventional wound care management in patients with chronic venous leg ulcers (VLUs) of the lower extremity. Patients were randomly assigned to receive either D-ADM or standard of care (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 patient completed 24 weekly follow-up visits. Eighteen patients were included in the D-ADM arm and 10 patients in the control arm. There was a strong trend of reduction in percent wound area for D-ADM patients with an average reduction of 59.6% at 24 weeks versus 8.1% at 24 weeks for control patients. In addition, healed ulcers in the D-ADM arm remained closed at a substantially higher rate after termination than healed ulcers in the control. The authors concluded that D-ADM demonstrated increased healing rates and reduction in wound size compared to conventional care. The small patient population and unbalanced proportion between the 2 groups (2:1) was a limitation 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 ECRI report above) conducted a prospective, multicenter study to evaluate the efficacy and safety of an acellular dermal matrix allograft, DermACELL (D-ADM; LifeNet Health), in the treatment of large, complex diabetic foot ulcers (DFUs) that probed to tendon or bone. Inclusion criteria were 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. Sixty-one 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. Mean percent wound area reduction was 80.3% at 16 weeks. Those DFUs 15 cm or smaller were substantially more likely to close than DFUs larger than 29 cm over a 16-week duration. The authors concluded that the 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 from standard of care. 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 acellular dermal matrix (ADM), D-ADM (DermACELL AWM; LifeNet Health), with a conventional care arm and an active comparator human ADM arm, GJ-ADM, for the treatment of chronic diabetic foot ulcers (DFUs). The study was a prospective, randomized controlled trial that enrolled 168 diabetic foot ulcer subjects in 13 centers across 9 states. Subjects 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 subjects in the D-ADM arm, 56 in the conventional care arm, and 23 in the GJ-ADM arm. Subjects were followed through 24 weeks with major endpoints at Weeks 12, 16, and 24. Single application D-ADM subjects showed significantly greater wound closure rates than conventional care at all three endpoints while all applications D-ADM displayed 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 the conventional care arm at 4 weeks post termination (100% vs. 86.7%). There was no significant difference between GJ-ADM and conventional care for healed wounds remaining closed. Single application D-ADM demonstrated significantly greater average percent wound area reduction than conventional care for Weeks 2-24 while single application GJ-ADM showed significantly greater wound area reduction over conventional care for Weeks 4-6, 9, and 11-12. 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, the organization that manufacturers DermACELL. The authors indicated that a potential weakness of this study was 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, randomized, controlled trial to assess the healed ulcer rate of a human acellular dermal matrix, DermACELL, compared with conventional care and a second acellular dermal matrix, Graftjacket, in the treatment of full-thickness diabetic foot ulcers. 168 patients were randomized into DermACELL, conventional care, and Graftjacket treatment arms in a 2:2:1 ratio. Patients in the acellular dermal matrix groups received either 1 or 2 applications of the graft at the discretion of the investigator. Weekly follow-up visits were conducted until the ulcer healed or the endpoint was reached. The results showed at 16 weeks, the DermACELL arm had a significantly higher proportion of completely healed ulcers than the conventional care arm, and a non-significantly higher proportion than the Graftjacket arm (67.9% vs 47.8%). The DermACELL arm also exhibited 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 3 groups based on relative population size. The authors concluded that DermACELL is an appropriate clinical option in the treatment of diabetic foot ulcers, with significant increases in healing rates and rate of percentage wound closure as compared with conventional care options. This study was sponsored by LifeNet Health, the manufacturer of DermACELL.

Dermacyte

There are few published studies addressing the use of Dermacyte Amniotic Wound Care Matrix for wound treatment. Therefore, it is not possible to conclude whether the Dermacyte Amniotic Wound Care Matrix has a beneficial effect on health outcomes.

Dermacyte Amniotic Wound Care Matrix (Merakris Therapeutics, Inc.) is a cross-linked human amniotic membrane 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 addressing the use of Derma-Gide. Therefore, it is not possible to conclude whether Derma-Gide has a beneficial effect on health outcomes.

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

Armstrong et al. (2020) in an observational pilot study evaluated the safety and preliminary efficacy of a Derma-Gide, a novel decellularized purified reconstituted bilayer matrix (PRBM) in treating diabetic foot ulcers (DFUs). Ten consecutive diabetic wounds that failed four weeks of standard wound care were treated weekly with the PRBM for up to 12 weeks. At each weekly visit, the wound was evaluated, photographed, and cleaned, followed by application of new graft if not completely epithelialized. 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, percent area reduction, and the cost of product(s) used. Nine of 10 patients achieved complete wound closure within 4 weeks, and 1 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 nor wound complications were observed. The author notes that this is the first published data using PBRM to treat a non-healing DFU. These early clinical findings suggest that the PRBM may be an effective tool in the treatment of diabetic foot ulcers. Large, randomized studies are needed to validate the finding in this small observational study.

DermaPure

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

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

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 which was followed until complete closure. A statistical analysis was performed with the end point being complete healing. All wounds on average had a duration of 56 weeks and healed in an average time of 10 weeks. Individual wound categories included diabetic foot ulcers, 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 addressing the use of DermaSpan. Therefore, it is not possible to conclude whether this product has a beneficial effect on health outcomes.

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

Dermavest and Plurivest

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

Dermavest and Plurivest (AediCell) are human amnion/chorion, umbilical cord and placental disk tissue matrixes intended to replace or supplement damaged or inadequate skin tissue and re-stabilize a debrided wound.

Derm-Maxx

There are few published studies addressing the use of Derm-Maxx for wound treatment. Therefore, it is not possible to conclude 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 serve as a covering for wounds and skin defects.

Dual Layer Impax Membrane

There are few published studies addressing the use of Dual layer impax membrane . Therefore, it is not possible to conclude 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 human amniotic membrane allograft 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.

Emerge Matrix

Studies are lacking regarding the use of Emerge Matrix for wound treatment. Therefore, it is not possible to conclude 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 derived from placental tissue that retain the structural and functional characteristics of the tissue. Emerge™ Matrix consist primarily of extracellular matrix proteins and serves as a natural, biologic barrier or wound cover. The typical patient population includes those with full thickness acute and chronic wounds where a biologic barrier or wound cover is required.

Enverse

There are no published studies addressing the use of Enverse for wound treatment. Therefore, it is not possible to conclude whether Enverse has a beneficial effect on health outcomes.

Enverse™ is comprised of dehydrated human amniotic membrane obtained from donated placental tissue. Enverse™ contains non-viable cells and is to be used as a wound covering or barrier membrane, over chronic and acute wounds, including dermal ulcers or defects.

EpiCord

There are several published studies addressing the use of EpiCord, all with study limitations. Therefore, it is not possible to conclude whether EpiCord has a beneficial effect on health outcomes.

EpiCord (MiMedx Group, Inc.) is a minimally manipulated, dehydrated, non-viable cellular umbilical cord allograft. EpiCord is intended to be used in the treatment and management of chronic and acute wounds and burns to replace or supplement damaged or 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 Diabetic Foot Ulcers reviewed one small randomized controlled trial (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 ECRI report above) evaluated the safety and effectiveness of dehydrated human umbilical cord allograft (EpiCord) compared with alginate wound dressings for the treatment of chronic, non-healing diabetic foot ulcers (DFU). A multicenter, randomized, controlled, clinical trial was conducted at 11 centers in the United States. Individuals with a confirmed diagnosis of Type 1 or Type 2 diabetes presenting with a 1 to 15 cm^2 ulcer located below the ankle that had been persisting 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 off-loading, 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 alginate wound dressing, non-adherent silicone dressing, absorbent non-adhesive hydro polymer 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, with the wound photographed pre- 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 Silhouette camera. Data for randomized subjects meeting study inclusion criteria were included in an intent-to-treat (ITT) analysis. Additional analysis was conducted on a group of subjects (n = 134) who completed the study per protocol (PP) (EpiCord, n = 86, alginate, n = 48) and for those subjects receiving adequate debridement (EpiCord, n = 67, alginate, n = 40). 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%) for EpiCord and alginate dressings, respectively. Healing rates at 12 weeks for subjects

treated PP were 70 of 86 (81%) for EpiCord-treated and 26 of 48 (54%) for alginate-treated DFUs. For those 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. There were no adverse events related to either EpiCord or alginate dressings. According to the authors, these results demonstrate the safety and efficacy of EpiCord as a treatment for non-healing DFUs. MiMedx Group Inc. sponsored the study and provided study oversight and data compilation.

EPIEFFECT

There are few published studies addressing the use of EPIEFFECT. Therefore, it is not possible to conclude 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 in acute and chronic wounds.

EpiFix Injectable

There are few published studies addressing the use of EpiFix Injectable. Therefore, it is not possible to conclude whether EpiFix Injectable has a beneficial effect on health outcomes.

EpiFix Injectable (MiMedx Group, Inc.) is a micronized powder form of EpiFix amniotic membrane.

EpiFix Amnion/Chorion Membrane (Non-Injectable)

EpiFix (MiMedx Group, Inc.) is a dehydrated amnion/chorion membrane extracellular collagen allograft comprised of an epithelial layer and two fibrous connective tissue layers that is proposed for acute and 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 5 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 (NHS) care for any indication. Two of the 5 studies included in the report were written by the same group of authors and 4 studies were funded by the manufacturer of EpiFix (NICE 2018).

Diabetic Foot Ulcers

Mohammed et al. (2022) conducted a systematic review and meta-analysis comparing the use of dehydrated human amnion and chorion allograft (DHACA) plus SOC versus standard of wound care (SOC) alone in the treatment of diabetic foot ulcers. The results included ten published RCTs and one unpublished RCT. The pooled effect estimate from 11 RCTs showed that DHACA was superior to SOC regarding the complete wound healing in both 6th and 12th week [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]. Also, the analysis favored the DHACA regarding the mean time to heal in the 12th-week [MD = -12.07, 95%CI: (-19.23, -4.91), p = 0.001]. The wound size reduction was better with DHACA [MD = 1.18, 95%CI: (-0,10, 2.26), p = 0.03]. Authors note there were some limitations yet the strength of RCTs indicated that DHACA with SOC has better efficacy than SOC alone in enhancing wound healing, reducing the mean time to wound healing, and diminishing the risk of adverse events. (Tettlebach 2019, Zelen 2016 and Zelen 2015 included below)

Lakmal et al. (2021) conduced a systematic review to assess the impact of amniotic membrane in diabetic foot ulcers. The potential of human amniotic membrane to act as an allograft has been studied in diabetic foot wounds. The intent of this study is to evaluate the current scientific evidence on its effectiveness in healing diabetic foot ulcers. Research included studies from January 2000 to 30th March 2020. When searched with Mesh terms, 12 citations in PubMed, 22 citations in Cochrane library and 30 in other data bases were found After screening the studies and their reference lists, 12 studies met the inclusion criteria, and the others were excluded. There were 8 randomized control trials (RCTs), 2 prospective studies and 2 retrospective studies employing different preparation methods of the amniotic membranes. A wide variation in study end points were noted. Majority of the RCTs (n = 7) were concluded with significantly higher wound closure rate compared to 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 using amniotic membrane allografts give reliable evidence of reduction in healing time over

conventional methods. Further prospective randomized controlled studies with larger populations with 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 human amniotic membrane (HAM) allograft in treating chronic diabetic foot ulcers (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 mean time to complete healing and adverse events. The proportion of complete wound healing in HAM plus standard of care (SOC) group was 3.88 times as high as that in 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, -22.72)]. 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 6weeks and 12 weeks. According to the investigators, this review had several limitations. First, there are some potential biases, especially from the implementation of blinding patients that are due to the special feature of surgical trials [8 studies (88.9%) were unable to blind patients]. Second, change in the quality of life is important for patients with DFUs, but the meta-analysis failed to pool them together, because no original study investigated it.

Alvaro-Afonso et al. (2020) reviewed the recent advances in dermo epidermal skin substitutes (DSS) for the treatment of DFUs. 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 to standard of care, 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 DSS. Healing rates after 12 weeks and time to complete closure in DFUs were heterogeneous among the 28 RCT. The best healing rates at 12 weeks were accomplished with dermal cellular substitutes (Epifix, 100% and Amnioband, 85%). The authors concluded that based on these studies, DSS used in conjunction with standard care appear to improve the healing rates of DFUs, as 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 DSS. According to the authors, future RCTs should include patients with severe comorbidities, in order to be more representative of clinical reality.

An ECRI report for Epifix for treating chronic wounds including diabetic foot ulcers (DFUs) indicated that evidence from 4 small randomized controlled trials (RCTs) on DFUs indicates that Epifix promotes healing better than standard of care. Weekly Epifix healed 70% of wounds in 12 weeks, biweekly Epifix healed 92% of wounds in 6 weeks and one RCT showed 97% at 12 weeks with biweekly Epifix. One RCT reported that weekly EpiFix treatment healed more wounds in 4 weeks than biweekly EpiFix (90% versus 50%; $p = 0.014$). Weekly treatment also lowered the mean time to complete healing (2.4 versus 4.1 weeks; $p = 0.039$). 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)

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 conclusively 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 manufactured sponsored randomized, controlled multicenter clinical trial (NCT01693133) at 14 wound care centers in the United States to confirm the efficacy of dehydrated human amnion/chorion membrane allograft (dHACM; EpiFix) for the treatment of chronic lower extremity ulcers in persons with diabetes. Inclusion criteria for the study included the following: ulcer size $\geq 1\ cm^2$ and $< 25\ cm^2$; Type I or 2 Diabetes; Ulcer duration of ≥ 4 weeks; unresponsive to standard wound care; no clinical signs of infection; serum creatinine < 3.0 mg/dL (within the last 6 months); glycated hemoglobin test (HgA1c) < 12% (within the last 60 days); and adequate circulation to the affected extremity as demonstrated by dorsum transcutaneous oxygen test (TcPO2) ≥ 30 mm Hg, ankle -brachial index (ABI) between 0.7 and 1.2, or triphasic or biphasic Doppler arterial

waveforms at the ankle of affected leg. The exclusion criteria included current participation in another trial; Charcot foot; index wound duration of > 52 weeks without intermittent healing index; ulcer probing to tendon, muscle, capsule, or bone; currently receiving radiation or chemotherapy, known or suspected malignancy of current ulcer; a diagnosis of autoimmune connective tissue disease; the use of biomedical/topical growth factor within previous 30 days; pregnant or breast feeding; taking medications considered to be immune system modulator; allergy or known sensitivity to gentamicin or streptomycin; wounds improving greater than 25% over the 2-week run-in period of the trial using standard of care dressing and Camboot offloading; patient taking Cox-2 inhibitors; and planned use of Dakin's solution, Mafenide acetate, scarlet red dressing, Tincoban, zinc sulfate, povidone-iodine solution, Mafenide acetate, Polymyxin/nystatin, or chlorhexidine during trial. Patients 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 less than or equal to 25% wound closure after run-in were randomly assigned to receive weekly epiFix application in addition to offloading or standard of care with alginate wound dressings, for 12 weeks. A total of 110 patients were included in the intent-to-treat (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 percentage of study ulcers completely healed in 12 weeks, with both ITT and per-protocol participants receiving weekly dHACM significantly more likely to completely heal than those not receiving dHACM. A Kaplan-Meier analysis was performed to compare the time-to-healing performance with/without dHACM, showing a significantly improved time to healing with the use of allograft. Cox regression analysis showed that dHACM-treated subjects were more than twice as likely to heal completely within 12 weeks than subjects 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 patient population.

Zelen et al. (2016; reviewed in the Su, Alvaro Alfonso, Luck, and ECRI systematic reviews above) continued the below study (Zelen et al. 2015) in order to achieve at least 100 patients and to assess rates and time to closure. With the larger cohort, clinical outcomes were compared at 12 weeks in 100 patients with chronic lower extremity diabetic ulcers 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 within 12 weeks, adjusting for all significant covariates. A Kaplan-Meier analysis was conducted to compare time-to-heal within 12 weeks for the three treatment groups. Clinical characteristics were well matched across study groups. The proportion of wounds achieving complete closure within the 12-week study period were 73% (24/33), 97% (31/32), and 51% (18/35) for Apligraf, EpiFix and SWC, respectively. Subjects treated with EpiFix had a very significant higher probability of their wounds healing compared to SWC alone. No difference in probability of healing was observed for the Apligraf and SWC groups. Patients 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. Mean time-to-heal within 12 weeks was 47·9 days with Apligraf, 23·6 days with EpiFix group and 57·4 days with the SWC alone group. Median number of grafts used per healed wound were six (range 1-13) and 2·5 (range 1-12) for 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 to Apligraf for the treatment of lower extremity diabetic wounds. The authors indicated that the following limitation for this study: patients were followed 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, multi-center clinical trial at three sites to compare the healing effectiveness of treatment of chronic lower extremity diabetic ulcers with either weekly applications of Apligraf (Organogenesis, Inc.), EpiFix (MiMedx Group, Inc.), or standard wound care 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 percent change in wound area per week and velocity of wound closure. A total of 65 subjects entered the 2-week run-in period and 60 were randomized (20 per group). The proportion of patients in the EpiFix group achieving complete wound closure within 4 and 6 weeks was 85% and 95%, significantly higher than for patients 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. Median time to healing was significantly faster with EpiFix (13 days) compared to 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 to Apligraf or standard of care, 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 dehydrated human amnion/chorion membrane allograft (dHACM) (EpiFix) for the treatment of diabetic foot ulcers (DFUs). Using a wound care-specific electronic medical record database, the authors assessed real-world outcomes in 218 patients with 226 DFUs receiving treatment in 2014 at 99 wound care centers. The analysis included DFUs ≥ 1 and < 25 cm2 with duration ≤ 1 year and area reduction ≤ 20% in 14 days prior to treatment (n = 163, BLCC; n = 63, dHACM). The average baseline areas and durations were 6.0 cm2 and 4.4 months for BLCC and 5.2 cm2 and 4.6 months for

dHACM, respectively. Patients treated with dHACM had more applications compared to those treated with BLCC (median 3.0 vs. 2.0). A Cox model adjusted for key covariates including area and duration found the median time to closure for BLCC was 13.3 weeks compared to 26 weeks for dHACM, and the proportion of wounds healed were significantly higher for 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, and as such, there may be missing data or data entry errors.

In 2014, Zelen (2014a) published follow-up data from the Zelen et al., 2013 trial described above. Eighteen of 22 eligible patients returned for follow-up examination. At the 9–12-month follow-up visit, 17 of 18 (94.4%) wounds treated with dehydrated human amnion/chorion membrane (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 dehydrated human amnion/chorion membrane allograft reduces time to heal more effectively than biweekly application for treatment of diabetic foot ulcers. The study was an institutional review board-approved, registered, prospective, randomized, comparative, non-blinded, single-center clinical trial. Patients with non-infected ulcers of ≥ 4 weeks duration were included and randomized to receive weekly or biweekly application of allograft in addition to a non-adherent, moist dressing with compressive wrapping. The primary study outcome was mean time to healing. Overall, during the 12-week study period, 92·5% (37/40) ulcers completely healed. Mean time to complete healing was 4·1 ±2·9 versus 2·4 ±1·8 weeks in the biweekly versus weekly groups, respectively. According to the authors, these results validate previous studies showing that the allograft is an effective treatment for diabetic ulcers and show that wounds treated with weekly application heal more rapidly than with biweekly application. Limitations of this study include a small sample size. The lack of a standard care group not receiving dehydrated human amnion/chorion membrane (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 frequency of application and not compare with other treatment modalities. The authors state 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, Alvaro Alfonso, Luck, and ECRI systematic reviews above) compared healing characteristics of diabetic foot ulcers treated with dehydrated human amniotic membrane allografts (EpiFix®, MiMedx) versus standard of care. The study included criteria for the following: ulcer size ≥ 1 cm2 and < 25 cm2 , Type I or 2 Diabetes, Ulcer duration of ≥ 4 weeks, unresponsive to standard wound care, no clinical signs of infection, serum creatinine < 3.0 mg/dL(within the last 6 months, HgA1c < 12% (within the last 60 days), adequate circulation to the affected extremity as demonstrated by dorsum transcutaneous oxygen test (TcPO2) ≥ 30 mm Hg, ABI between 0.7 and 1.2, or triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg. The exclusion criteria included current participation in another trial, Charcot foot, index wound duration of > 52 weeks without intermittent healing index ulcer probing to bone; currently receiving radiation or chemotherapy, known or suspected malignancy of current ulcer, a diagnosis of autoimmune connective tissue disorder, the use of biomedical/topical growth factor within previous 30 days, pregnant or breast feeding, taking medications considered to be immune system modulators and an allergy or known sensitivity to gentamicin or streptomycin. Patients 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 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% versus 97.1% ±7.0% after 4 weeks, whereas at 6 weeks wounds were reduced by -1.8% ±70.3% versus 98.4% ±5.8%, standard care versus 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, respectively. The authors concluded that patients treated with EpiFix achieved superior healing rates over 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 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 possible conflict of interest and lack of masking to the intervention.

Venous Leg Ulcers

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

An ECRI report for Epifix for treating chronic wounds including venous leg ulcers (VLUs) reported evidence from two small randomized controlled trials (RCTs) regarding VLUs. One RCT reported weekly EpiFix plus compression treatment healed more wounds than moist wound dressing plus compression in 12 weeks (60% versus 35%; p = 0.0128). The other RCT

reported that 62% of wounds treated with EpiFix plus compression therapy achieved > 40% closure at 4 weeks compared with 32% 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 (PP) study results (n = 109, 52 EpiFix and 57 standard care patients), although there were 128 patients 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 ECRI report above) is to report intention-to-treat (ITT) results on all 128 randomized subjects and assess if both ITT and PP data analyses arrive at the same conclusion of the efficacy of EpiFix as a treatment for venous leg ulcers (VLUs). Rates of healing for the ITT and PP populations were, respectively, 50% and 60% for those receiving EpiFix and 31% and 35% for those in the standard care cohort. Within both ITT and PP analyses, these differences were statistically significant. The authors concluded that the results of this study show that, in both ITT and PP analyses, VLUs 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 ECRI report above) conducted a randomized, controlled, multicenter clinical trial to evaluate the efficacy of Epifix, a dehydrated human amnion/chorion membrane allograft as an adjunct to multilayer compression therapy for the treatment of non-healing full-thickness venous leg ulcers. A total of 109 subjects were randomly assigned to receive EpiFix and multilayer compression (n = 52) or dressings and multilayer compression therapy alone (n = 57). Patients were recruited from 15 centers around the USA and were followed up for 16 weeks. The primary end point of the study was defined as 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 standard wound care and compression (60% versus 35% at 12 weeks and 71% versus 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 using the allograft. Cox regression analysis showed that subjects treated with EpiFix had a significantly higher probability of complete healing within 12 weeks versus without EpiFix. According to the authors, these results confirm the advantage of EpiFix allograft as an adjunct to multilayer compression therapy for the treatment of non-healing, full-thickness venous leg ulcers. These findings require confirmation in larger randomized controlled trials. 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 8 lower extremity free flaps with ulcerations in the context of venous insufficiency and/or lymphedema. The first 4 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 dehydrated human amnion/chorion membrane (EpiFix) grafts. The primary endpoint was time to healing. Comparison of Kaplan-Meier survival curves revealed a significant difference between the conservatively and dehydrated human amnion/chorion membrane-treated flap ulcers, favoring graft treatment. In those ulcers that healed, the average time to healing was 87 days for the conservative treatment group and 33 days for the dehydrated human amnion/chorion membrane treatment group (with an average of 1.7 grafts per ulcer). The authors concluded that dehydrated human amnion/chorion membrane may accelerate healing of ulcers on lower extremity free flaps in patient 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. There is also no true randomized control or comparison group available, so it cannot be firmly concluded that dHACM accelerates healing of ulcers on free flaps with lymphedematous or venous-insufficient limbs.

Serena et al. (2015) evaluated correct correlation between an intermediate rate of wound reduction (40% wound area reduction after 4-weeks treatment) and complete healing at 24 weeks in patients with a venous leg ulcer (VLU) in a retrospective follow-up of the study by Serena et al. (2014) described above. Outcomes assessed were rates of complete healing within 24 weeks of enrolment and days to healing. Data were divided into two groups based on status at RCT completion (healed at least 40% yes or no). 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 4-week and 24-week status. Fifty-five patients at 5 study sites were included. Some 47 without complete healing during the initial study were eligible. As three patients were lost to follow-up, a total of 44 records were evaluated. Of these, 20 (45.4%) had reduced wound size of ≥ 40% and 24 (55%) had < 40% reduction during the initial study. Complete healing occurred in 16/20 (80%) of the ≥ 40% group at a mean of 46 days and 8/24 (33.3%) of the < 40% group at a mean of 103.6 days. Overall, correct correlation of status at 4 weeks and ultimate healing status of VLU occurred in 32/44 patients (73%). The authors indicated that these results confirm that the intermediate outcome used in our initial study is a viable predictor of ultimate VLU healing. According to the authors there are limitations of 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 ECRI report above) conducted a multicenter, randomized, controlled study to evaluate the safety and efficacy of one or two applications of dehydrated human amnion/chorion membrane allograft and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers (VLU). Patient inclusion criteria included presence of a VLU extending through the full thickness of the skin but not down to muscle, tendon, or bone, VLU present for at least 1 month, and VLU has been treated with compression therapy for at least 14 days. The primary study outcome was the proportion of patients achieving 40% wound closure at 4 weeks. Of the 84 participants enrolled, 53 were randomized to receive 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 showed a greater than 40% wound closure, thus showing a significant difference between the allograft-treated groups and the multilayer compression therapy alone group at the 4-week surrogate endpoint. After 4 weeks, wounds treated with allograft had reduced in size a mean of 48.1% compared with 19.0% for controls. The authors concluded that venous leg ulcers treated with allograft had a significant improvement in healing at 4 weeks compared with multilayer compression therapy alone. According to the authors, lack of long-term follow-up data did not allow for the validation of duration of healed wounds.

Esano A, Esano AAA, Esano AC, or Esano ACA

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

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

Esano AAA (Evolution Biologyx, LLC) is a tri-layered, decellularized, dehydrated human amniotic membrane (DDHAM) with a preserved natural epithelial basement membrane and an intact extracellular matrix structure with is biochemical components to provide a protective cover and aid in wound care and surgical sites.

Esano AC (Evolution Biologyx, LLC) is a dual-layer, decellularized, dehydrated human amniotic membrane allograft that is intended for use as a cover or barrier for acute and chronic wounds and to provide protective coverage from the surrounding environment for acute and chronic wounds

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

Excellagen

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

Excellagen is a pharmaceutically formulated fibrillar Type I bovine collagen gel for wound care management.

E-Z-Derm

There are limited studies related to E-Z-Derm for use on partial-thickness skin loss, donor sites, skin ulcerations and abrasions. Therefore, it is not possible to conclude 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 intended for use on partial-thickness skin loss, donor sites, skin ulcerations and abrasions.

FlowerAmnioFlo

There are few published studies addressing the use of FlowerAmnioFlo for wound treatment. Therefore, it is not possible to conclude 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 non-healing 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 addressing the use of FlowerAmnioPatch for wound treatment. Therefore, it is not possible to conclude 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 non-healing 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 addressing the use of FlowerDerm. Therefore, it is not possible to conclude whether FlowerDerm has a beneficial effect on health outcomes.

FlowerDerm (Flower Orthopedics Corporation) hydrated acellular (human) dermal allograft matrix used for the treatment of non-healing wounds and burn injuries. According to the manufacturer, FlowerDerm contains extracellular matrix (ECM) 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 addressing the use of Fluid Flow and Fluid GF. Therefore, it is not possible to conclude 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 and chronic wounds and soft tissue injury, degenerative tissue disorders, and inflammatory conditions such as tendonitis and fasciitis.

GammaGraft

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

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

Genesis Amniotic Membrane

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

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

Grafix, GrafixPRIME, and GrafixPL PRIME

Grafix (Osiris Therapeutics, Inc.) is a cryopreserved placental membrane comprised of an extracellular matrix (ECM) containing collagen, growth factors, fibroblasts, mesenchymal stem cells (MSCs), and epithelial cells 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.

An ECRI Clinical Evidence Assessment for Grafix Cellular Repair Matrix for Treating Chronic Wounds indicates that evidence from 2 RCTs (Ananian et al., 2018; Lavery et al., 2014) and 3 retrospective studies and 7 prospective studies suggest Grafix is safe and may be more effective than EpiFix dressing and noninferior to Dermagraft® at promoting chronic wound healing. Evidence from 12 studies of varied designs and quality indicates Grafix is safe and may aid 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 RCT's would be useful to understand Grafix wound closure rate, healing time and likelihood of wound reoccurrence, plus other studies comparing Grafix with other active dressings and autologous skin grafts. (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 suggesting that adjunctive treatment with Grafix Cryopreserved Placental Membrane may improve healing of chronic diabetes-related foot ulcers. There is insufficient evidence comparing Grafix

with other skin substitutes. 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 standard wound care alone. Studies addressing appropriate patient selection criteria are also needed to establish which patients and wound types would most benefit from Grafix (Hayes, Grafix Cryopreserved Placental Membrane (Osiris Technologies Inc.) for Treatment of Chronic Foot Ulcers in Patients with Diabetes Mellitus 2019, updated October 2022).

In a prospective single-center open-label single-arm study, Farivar et al. (2019) enrolled patients with active venous leg ulcers (VLUs) 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 patients 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 standard therapy, with each patient serving as his own control. There were 30 VLUs in 21 consecutive eligible patients who were enrolled in the study. All patients 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 VLUs 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. Eighty percent of VLUs 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 to achieve complete wound closure in a significant proportion of chronic VLUs refractory to standard therapy and that adjunctive therapy with hVWM provides superior healing rates in refractory VLUs. According to the author's, large, randomized trials are needed to confirm these preliminary results.

Raspovic et al. (2018) conducted a real world setting retrospective analysis to evaluate the effectiveness of viable cryopreserved placental membrane (vCPM; Grafix) for diabetic foot ulcers (DFUs) management using electronic health records. The primary endpoint was the proportion of DFUs that achieved complete closure. De-identified EHR data for 360 patients with 441 wounds treated with vCPM were extracted from the database. 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 4 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 9 (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 the 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, randomized, controlled clinical trial for chronic diabetic foot ulcers (DFUs) that was previously reported by Lavery and colleagues in 2014. In the extension phase, 26 patients in the standard wound care (SWC) arm whose DFUs did not close in the blinded phase chose to receive weekly applications of Grafix in an open-label extension phase. Seventeen (65.4%) patients closed their wounds in a median of 34 days and 3 visits. There were fewer total adverse events (AEs) (24 CPM vs. 52 SWC) and index wound-related infections (5 CPM vs. 12 SWC) during Grafix application compared with the number of AEs for the same patients during the SWC treatment in the blinded phase of the trial. According to the authors, these results corroborate the benefits of this cryopreserved placental membrane combined with SWC over SWC alone for chronic DFUs 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 ECRI report above) analyzed clinical outcomes between a viable cryopreserved placental membrane (vCPM; Grafix) and a human fibroblast-derived dermal substitute (hFDS; Dermagraft) for the treatment of chronic diabetic foot ulcers in a prospective, multicenter, randomized, single-blind study. The outcomes of 62 patients were analyzed: 31 patients in the vCPM treatment group and 31 patients in the hFDS treatment group. Utilizing a non-inferiority trial design and the established treatment regimen of 8 applications for hFDS, the authors demonstrated that vCPM was not inferior to hFDS for the proportion of patients achieving complete wound closure. However, preliminary findings show that vCPM may have better outcomes for wounds ≤ 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-blind design of the study, the lack of stratification by wound location and size for analyses, the lack of a follow-up period after the treatment phase of the trial, and the 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 diabetic foot ulcers (DFU) healing. Following the inclusion and exclusion criteria,

randomized controlled trials (RCT) 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 patients. 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 occurs 2.32 times more often and is 32 days faster in comparison with the group that used conventional dressings. The authors concluded that there is no statistical evidence to support the effectiveness of amniotic membrane in comparison with other conventional dressings. However, there is a clear tendency for the use of 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 the definitive evidence for the use of amniotic membrane on DFUs.

Haugh et al. (2017) performed a meta-analysis examining randomized controlled trials comparing amniotic tissue products with standard of care in nonhealing diabetic foot ulcers. A search of 3 databases identified 596 potentially relevant articles. Application of selection criteria led to the selection of 5 randomized controlled trials. The 5 selected randomized controlled trials represented a total of 311 patients. Three of the trials included compared EpiFix, a dehydrated amniotic membrane product, to 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 to SOC alone (Snyder et al., 2016). One trial compared Grafix, a cryopreserved amniotic product to 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 diabetic foot ulcers with amniotic membrane improves healing rates in diabetic foot ulcers. The authors state that further studies are necessary to confirm the findings identified in these 5 trials and to determine whether amniotic products have the same impact on all diabetic patients seen in clinical practice. The authors also state that although this analysis indicates that amniotic membrane has great potential for use in diabetic foot ulcers (DFUs) in clinical practice, patients in all 5 of the included trials had to demonstrate adequate tissue perfusion and a lack of any signs of infection to enroll. As many patients who develop DFUs do not demonstrate adequate tissue perfusion and are often plagued by chronic infections, it is unclear how these products would translate into every day clinical care of diabetic patients. According to the authors, the lack of follow-up of patients 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 patients with chronic diabetic foot ulcers (DFUs). All randomized controlled trials (RCTs) comparing human amnion/chorion membrane plus standard therapy and standard therapy alone in patients with DFUs were included in the analysis. Eligible studies were reviewed, and data extracted into 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 patients receiving amniotic membrane plus standard therapy had far fewer incomplete healing wounds than those receiving standard of care 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 standard of care treatment heals DFUs significantly faster than standard of care alone. When using the amnion in patients 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 randomized controlled trials (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, however statistically equal and homogenous patient cohorts receiving either a viable intact cryopreserved human placental membrane (vCPM) or a dehydrated human amnion/chorion membrane (dHACM), for the management of wounds at a single center. A total of 79 patients with 101 wounds were analyzed: 40 patients with 46 wounds received vCPM (Grafix) and 39 patients with 55 wounds received dHACM (EpiFix). The proportion of wounds achieving complete wound closure was 63.0% (29/46) for vCPM and 18.2% (10/55) for dHACM for all treated wounds combined. According to the authors, the retrospective and nonrandomized nature of this single-center study present significant limitations.

In a randomized controlled study, 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, a human viable wound matrix (hVWM) (n = 50), to standard wound care (n = 47) to heal diabetic foot ulcers (DFUs). Standard care included off-loading and nonadherent dressings (Adaptic) and either saline-moistened gauze or Allevyn for moderately draining wounds. The primary endpoint was the proportion of patients with complete wound closure by 12 weeks. Secondary endpoints included the time to wound closure, adverse events, and wound closure in the crossover phase. The proportion of patients who achieved complete wound closure was significantly higher in patients who received Grafix (62%) compared with controls (21%). The median time to healing was 42 days in Grafix patients compared with 69.5 days in controls. There were fewer Grafix patients with adverse events (44% versus 66%) and fewer Grafix patients with wound-related infections (18% versus 36%). Among the study subjects that healed, ulcers remained closed in 82% of patients (23 of 28 patients) in the Grafix group versus 70% (7 of 10 patients) 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 showed that Grafix is a safe and more effective therapy for treating DFUs than standard wound therapy. These findings require confirmation in a larger study.

Grafix Core

There are few published studies addressing the use of Grafix Core. Therefore, it is not possible to conclude whether GrafixCore has a beneficial effect on health outcomes.

Grafix Core is a cryopreserved chorion matrix with limited product information.

GRAFIX PLUS

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

GRAFIX PLUS (Smith and 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 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 conclude whether Helicoll has a beneficial effect on health outcomes.

Helicoll (MCT Medical Solutions LLC) is a semi occlusive, self-adhering collagen sheet 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 in pediatric wound management and new treatments published in the literature to date. Databases were searched for relevant sources including Pubmed, Embase, Web of Science and DynaMed. Findings noted that amniotic membrane living skin equivalent is a cellular matrix that has been reportedly successful in treating pediatrics 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 involving larger sample sizes are necessary, in order to determine the specific role these advanced products play in pediatric wounds and to identify their safety and efficacy.

Dhanraj (2015) conducted a prospective randomized controlled study to compare Helicoll, a type I pure collagen dressing, to OpSite dressing and to Scarlet Red dressing in the treatment of standardized split-thickness skin grafts (STSG) donor sites. Thirty patients, 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, healing time of the donor site, initial absorption of the applied dressing and rate of infection with the three different dressings. Patients in the Helicoll group reported significantly less pain, less infection rate and required no dressing change when compared with the OpSite or the Scarlet Red groups. Healing time of the donor site in the Helicoll group was shorter than that in the Scarlet Red group; however, it was comparable to 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 only one wound type (STSG donor site) was evaluated.

hMatrix

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

hMatrix PR ADM (Bacterin International, Inc) is an acellular dermal matrix allograft 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 (HHF10-P)

There are no published studies addressing the use of Human Health Factor 10 Amniotic Patch (HHF10-P*)* for wound treatment. Therefore, it is not possible to conclude whether HHF10-P has a beneficial effect on health outcomes.

HHF10P is a single-layer amniotic allograft derived from donated and screened, full-term human birth tissue, specifically the immunoprivileged amnion layer. It is a semi-transparent, minimally manipulated, terminally sterilized membrane allograft. HHF10-P TM is intended for homologous use to act as a covering or barrier to offer protection from the surrounding environment in clinical applications.

Hyalomatrix

There are several non-comparative published studies addressing the use of Hyalomatrix, all with study limitations. Therefore, it is not possible to conclude whether Hyalomatrix has a beneficial effect on health outcomes.

Hyalomatrix (Medline Industries, Inc.) is a non-woven pad comprised of a wound contact layer made of a derivative of hyaluronic acid (HA) in fibrous form with an outer layer comprised of 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 are inconclusive because there is limited evidence. No data are available to determine how Hyalomatrix compares to 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 ECRI report above) sought to analyze the efficacy of a hyaluronic acid-based matrix (HYALOMATRIX) in the treatment of lesions where the extracellular matrix was lost. Twelve patients 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. There was no graft failure. 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 and shows a strong trend for Hyalomatrix to play an important role in supporting wound healing in complex, surgical wounds. Limitations include lack of a control group and small number of participants.

InnovaMatrix AC or Innovamatrix FS

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

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

InnovaMatrix FS is a decellularized extracellular matrix (ECM) topical wound covering derived from porcine placental tissue.

Integra Flowable Wound Matrix

There are several published studies addressing the use of Integra Flowable Wound Matrix, all with study limitations. Therefore, it is not possible to conclude whether Integra Flowable Wound Matrix has a beneficial effect on health outcomes.

Integra flowable wound matrix (Integra Life Sciences, Inc.) is an advanced wound care product comprised of granulated cross-linked bovine tendon collagen and glycosaminoglycan. It is intended for the management of deep or 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 versus a wet dressing in patients

with diabetic foot ulcers. The study was conducted in the General Surgery Unit and Geriatric of the Second University of Naples, Italy, for 12 months. Forty-six cases of diabetic foot ulcers (Grades 3 Wagner) were equally and randomly divided into control and test groups. The first group treated with Integra Flowable Wound Matrix, while the control group with a wet dressing. Both groups were evaluated once a 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 compared to the treatment group; therefore, the difference was statistically significant. The Integra Flowable Wound Matrix was significantly superior, compared to the wet dressing, by promoting the complete healing of diabetic foot ulcers. The authors concluded that this product is appropriate in the management of diabetic foot ulcers, but additional research is needed, and will shed more light on the promising advantages of this material in healing diabetic foot ulcers. This study was excluded from the AHRQ report (Snyder et al., 2020) because it did not meet the criteria for using adequate standard of care.

An ECRI report for Integra Flowable Wound Matrix concluded that 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 diabetic foot ulcers. Only one randomized controlled trial comparing treatment with Integra Flowable Wound Dressing to treatment with a wet dressing was identified. This RCT has several limitations including a small sample size, no blinding, and being conducted in a single medical center in a single country, the need for longer follow up resulting in a risk of bias. (ECRI, 2019).

IntéguPly

There are few published studies addressing the use of InteguPly. Therefore, it is not possible to conclude whether this product has a beneficial effect on health outcomes.

InteguPly (AZIYO® Biologics) is a human acellular dermal matrix intended for the treatment of chronic diabetic foot ulcers, venous leg ulcers and pressure wounds. It is also intended for the Support, protection, reinforcement or covering of tendon, ligament, and rotator cuff.

Interfyl

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

Interfyl (Celularity) 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, augmentation of deficient/inadequate soft tissue, and the repair of small surgical defects.

Keramatrix

There are several studies related to Keramatrix, all with study limitations. Therefore, it is not possible to conclude whether Keramatrix has a beneficial effect on health outcomes.

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

Loan et al. (2016) conducted a controlled study that included 40 patients with superficial or partial thickness burn injuries treated with Keramatrix, compared to 40 historical controls who received standard of care 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 is a small, nonrandomized trial.

Davidson et al. (2013) conducted a randomized controlled trial using a standard care alginate (Algisite) dressing side by side with an experimental dressing (Keramatrix) on 26 patients with partial-thickness donor site wounds. The proximal/distal placement of the control and treatment was randomized. Percentage epithelialization after approximately 7 days was estimated from which time to fully epithelialize can be inferred. Patients were grouped into "young" (≤ 50 y/o) and "old" (> 50 y/o). For the "old" patients (n = 15), the median epithelialization percentage at 7 days is 5% and was significantly greater for the experimental dressing. For the "young" patients (n = 11), the median epithelialization percentage at 7 days was 80% and there is no significant difference between the experimental and Standard Care control dressings. The authors concluded that Keramatrix dressing significantly increases the rate of epithelialization of acute, traumatic partial-thickness wounds in older patients. This study was limited by a small sample size and short follow-up time.

Kerasorb

There are few published studies addressing the use of Kerasorb. Therefore, it is not possible to conclude 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 Products

There are several studies related to Kerecis® Omega3 Products all with study limitations. Although the evidence for this product is somewhat favorable, there is limited evidence related to the safety and long-term outcomes of these products.

Kerecis® (formally known as Marigen®) produces skin and tissue-based products for use in surgery and for treating wounds. Kerecis® products include Omega3 Wound, Omega3 Burn, and Omega3 Surgical. These products are made from fish (piscine) dermis designed for treating chronic wounds.

A Hayes evolving evidence review for Kerecis® Omega3 Wound (Kerecis® Limited) for the management of chronic lower extremity wounds includes 3 poor quality and one fair quality study describing the clinical benefits of wound healing. One randomized controlled trial (RCT) found better healing outcomes with Kerecis® than a collagen-alginate dressing. Additional RCTs are needed to determine if Kerecis® Omega 3 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 was identified with major limitations and a high risk of bias (ECRI April 2020).

An ECRI report for Omega3 Wound Matrix (Kerecis®) for Treating Chronic Wounds indicated that the evidence is inconclusive due to too few data on outcomes and comparisons of interest. One RCT and three case series were assessed and the case series all have a high risk of bias, and the RCT only comparisons with collagen/alginate dressings. All three studies examined the effects on DFUs, with just one including some vascular leg ulcers. Two recently completed RCTs and two ongoing will help address evidence gaps for DFUs. Future studies should include larger populations and different types of chronic wounds, as well as quality of life outcomes. (ECRI Updated 2023).

In 2023, Lantis et al. (included in the ECRI report on chronic wounds above) reported the final results of a prospective multicenter randomized controlled trial evaluating the efficacy of an omega-3 rich acellular fish skin graft (FSG), Kerecis Omega3 MariGen compared to collagen alginate therapy (CAT) Fibracol Plus Collagen Wound Dressing with Alginate in the management of chronic DFUs. Previous results were reported in 2021 (Lullove et al., 2021). One hundred and two patients were recruited and randomized 1:1 to the study arm and control arm. The primary end point was the absolute percentage of patients who achieved wound closure at 12 weeks. Secondary outcomes included the effect of FSG, healing rate, and percentage wound area reduction (PAR). Of the 102 participants, 77 comprised the per protocol (PP) cohort, 25 intention to treat participants were excluded from the PP analysis due to protocol deviations or were not on track to achieve healing. All 102 Although all 102 patients were included in the ITT analysis these patients were excluded from time to healing and wound area reduction (WAR calculations). The primary endpoint 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 endpoints were assessed at 6 and 12 weeks in the ITT and PP groups and showed the same healing time for both with the mean time to healing 7.31 weeks in the CAT arm and 7.17 weeks in the FSG arm. The mean PAR at 6 weeks was 51.6% for 32 patients in the CAT group and 71.6% for 36 patients in the FSG group, in both the ITT and PP analyses the mean PAR at 12 weeks was 64% for 27 patients in the CAT group and 86.3% for 38 patients in the FSG group. At 6-12 month follow up, one ulcer recurrence was reported in the CAT arm and 3 ulcer recurrences were recorded in the FSG arm, which may be related to 3 of the 4 patients not having appropriate offloading footwear. The authors concluded that the use of FSG resulted in significantly more healed DFUs within 12 weeks compared to CAT. This RCT is limited by a small group of participants as well as only assessing DFUs. This RCT was also impacted by the COVID-19 pandemic which resulted in a 24.5% drop out rate. Further high quality research with larger patient populations and different types of wounds are necessary to validate these findings.

Luze et al. (2022) conducted a systematic review summarizing the current published evidence on the use of acellular fish skin (AFS) 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 investigating the effects of acellular fish skin in burn wounds or split-thickness donor sites were determined eligible and included in the present review. Nile Tilapia were evaluated in seven of the trials and Kerecis® Omega 3 (North Atlantic cod) was evaluated in five trials. Present evidence on the use of acellular fish skin shows an acceleration of wound healing, reduction in pain and necessary dressing changes as well as improved aesthetic and functional outcomes compared to conventional treatment options. Study limitations includes a small size of study cohorts, and the results cannot be pooled; studies are geographically limited based on availability of xenografts and comparison studies are needed between products. Acellular fish skin xenografts may be an effective treatment of superficial- and partial-thickness burns. Larger cohort studies are needed to clarify the full potential of this promising approach.

Lullove et al. (2021, included in the ECRI report above) conducted a randomized controlled trial to evaluate the fish skin graft with standard of care (SOC) using collagen alginate dressing in the management of treatment-resistant diabetic foot ulcers (DFUs) not involving tendon capsule or bone. Patients 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 receiving SOC or SOC plus fish skin graft applied weekly for up to 12 weeks. The main endpoint was the percentage of wounds closed at 12 weeks. Forty-nine patients were included in the final study. At 12 weeks, 16 of 24 patients' DFUs (67%) in the fish skin arm were completely closed, compared with 8 of 25 patients' DFUs (32%) in the SOC arm [p value = .0152 (n = 49); significant at p < .047]. At 6 weeks, the percentage area reduction was 41.2% in the SOC arm and 72.8% in the fish skin arm. The application of fish skin graft to previously nonresponsive DFUs resulted in significantly more fully healed wounds at 12 weeks than SOC alone. Study limitations included small study population and intrinsic blinding where the patient and member applying the product was aware of knowing the fish skin graft was being applied. The study findings show favorable results for the use of fish skin graft for chronic DFUs that do not heal with SOC treatment. These findings need confirmed in a larger study population.

Kirsner et al. (2020) in a prospective randomized controlled trial compared fish skin grafts to human amnion/chorion membrane allografts in acute would healing. Grafts can come from the patient'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, 4 mm in diameter, on healthy volunteers to compare two materials frequently used to treat chronic wounds: fish skin and dHACM. The purpose is 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-blind study. All volunteers were given two identical punch biopsy wounds, one of which was treated with a fish skin graft and the other with dehydrated human amnion/chorion membrane allograft (dHACM). In the study, 170 wounds were treated (85 wounds per group). The primary endpoint was defined as time to heal (full epithelialization) by blinded assessment at days 14, 18, 21, 25, and 28. The superiority hypothesis was that the fish skin grafts would heal the wounds faster than the dHACM. To evaluate the superiority hypothesis, a mixed Cox proportional hazard model was used. Wounds treated with fish skin healed significantly faster (hazard ratio 2.37; 95% confidence interval: (1.75–3.22; p = 0.0014) compared with wounds treated with dHACM. The results show that acute biopsy wounds treated with fish skin grafts heal faster than wounds treated with dHACM. Limitations of this study included acute wounds from a punch biopsy rather than chronic non-healing wounds. Larger studies are needed to include participants with chronic unhealing wounds.

Keroxx

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

Keroxx Flowable Wound Matrix (Molecular Biologicals, Inc.) is wound matrix comprised of keratin enriched proteins that 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 conclude whether Lamellas and/or Lamellas XT has a beneficial effect on health outcomes.

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

Matrion

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

Matrion (LifeNet Health) is a regenerative human placental allograft 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 the surgical sites, enhance healing, and act as a barrier.

MatriStem MicroMatrix

There are several studies related to MariStem, all with study limitations. Therefore, it is not possible to conclude whether MatriStem has a beneficial effect on health outcomes.

MatriStem (ACell Inc.) products consist of collagens, carbohydrates, and proteins 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 of at thirteen centers throughout the United States to assess the application of MatriStem MicroMatrix (MSMM) and MatriStem Wound Matrix (MSWM) (porcine urinary bladder derived extracellular matrix) compared with Dermagraft (DG) (human fibroblast-derived dermal substitute) for the management of non-healing diabetic foot ulcers (DFUs).There were 95 subjects that entered into the standard of care (SOC) four-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 MS were non-inferior to those of DG after eight weeks. The authors present the planned interim results of this study after one half of the projected enrolment was completed. At the planned interim analysis, there was significant improvement in patient quality of life for the subjects treated with MS compared with those managed with DG. 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 subjects with complete wound closure. This study reports only interim results.

Mediskin

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

Mediskin is a porcine derived decellularized fetal skin product.

In a prospective randomized, 3-arm, clinical study, Karlsson et al. (2014) compared Aquacel, Allevyn, and Mediskin I in the treatment of split-thickness skin graft donor sites in 67 adults. Patients 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 re-epithelialization for patients treated with Aquacel or Mediskin I compared with Allevyn. Regarding infections, there were no significant differences between the groups. Patients wearing Aquacel experienced significantly less pain changing the dressing and less impact on everyday life than the patients 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, or Membrane Wrap-Hydro

There are few published studies addressing the use of Membrane Graft, Membrane Wrap, and Membrane Wrap-Hydro. Therefore, it is not possible to conclude 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 post-surgical wounds.

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

MemoDerm

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

MemoDerm (Stryker®) is an acellular dermal matrix 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 diabetic foot ulcers.

Microlyte Matrix

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

Microlyte® Matrix comprises a polyelectrolyte multilayer (PEM) 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.

MIRODERM

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

MIRODERM (Miromatrix Medical) 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.

Mirragen

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

Mirragen Advanced Wound Matrix is a synthetic, resorbable skin substitute 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.

Armstrong et al. (2022a) in a randomized controlled trial investigated the healing potential of Mirragen Advanced Wound Matrix (BBGFM) in subjects with chronic DFUs comparing the healing rate to treatment with SOC (SOC, collagen alginate dressing) alone at 12 weeks. Both groups received standard diabetic foot care including glucose monitoring, weekly debridements when needed and an offloading device. The primary endpoint was percentage of full-thickness, non-infected, non-ischemic wounds healed at 12 weeks, with secondary endpoints including percent area reduction (PAR) and changes in Semmes-Weinstein monofilament testing. The result illustrated in the intent-to-treat 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 = .006). Mean PAR at 12 weeks was 79% in the BBGFM group compared with 37% in the SOC group (adjusted p = .027). 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 = .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, there were study weaknesses. The main weakness being lack of investigator binding and not withdrawing subjects that were not responding and providing them with a different treatment. In conclusion, this trial has established that the addition of a bioactive glass microfiber matrix containing 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 no published studies addressing the use of MLG-Complete for wound treatment. Therefore, it is not possible to conclude whether MLG-Complete has a beneficial effect on health outcomes.

MLG Complete™ is a full thickness amnion-chorion derived allograft for management of wounds and burn injuries. MLG Complete™ is a sterile, single use, dehydrated allograft 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.

MyOwn Skin

There are few published studies addressing the use of MyOwn Skin. Therefore, it is not possible to conclude 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.

NeoMatriX

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

NeoPatch (Cryolife, Inc.) is a wound covering derived from terminally sterilized, dehydrated human placental membrane tissue comprised of both amnion and chorion.

NEOX

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

NEOX Wound Allografts (Amniox® Medical, Inc.) are comprised of 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 human amniotic membrane indicated for minor and superficial dermal wounds. Both are indicated as wound covering for dermal ulcers and defects.

NEOX FLO

There are no published studies addressing the use of NEOX FLO for wound treatment. Therefore, it is not possible to conclude whether this product has a beneficial effect on health outcomes.

NEOX FLO (Amniox® Medical, Inc.) is a particulate form of NEOX and comprised of amniotic membrane and umbilical cord products 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, NeoStim TL

There are no published studies addressing the use of NeoStim products. Therefore, it is not possible to conclude 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 human amniotic membrane; NeoStim products serve as a barrier or provides 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 addressing the use of Novachor. Therefore, it is not possible to conclude whether Novachor has a beneficial effect on health outcomes.

Novachor (Organogenesis, Inc.) is comprised of 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, post-traumatic wounds and post-surgical wounds.

Novafix

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

Novafix (Triad Life Sciences, Inc.) is a dehydrated human amniotic membrane allograft indicated for use in the management of wounds.

Novafix DL

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

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

NovoSorb SynPath

There are few published studies addressing the use of NovaSorb SynPath. Therefore, it is not possible to conclude whether NovaSorb SynPath has a beneficial effect on health outcomes.

NovoSorb® SynPath is a synthetic dermal matrix comprised of a porous network of nontoxic, biodegradable synthetic polymers that acts as a scaffold to support the proliferation of cells involved in cellular repair. NovoSorb BTM (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 addressing the use of NuDYN for wound treatment. Therefore, it is not possible to conclude whether NuDYN has a beneficial effect on health outcomes.

NuDYN (Fida Pharma) is an injectable, flowable amniotic membrane derived allograft packaged in sterile vials intended for topical application to the wound surface and supports wound healing and soft tissue repair. It is a non-surgical alternative for healthcare providers to offer their patients and compliments products such as Hyalgen. Its properties include hyaluronic acid, collagen, and growth factors which protect, lubricate, and support the tissue.

NuShield

There are few published studies addressing the use of NuShield. Therefore, it is not possible to conclude whether NuShield has a beneficial effect on health outcomes.

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

Omeza Collagen Matrix

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

Omeza® Collagen Matrix is a wound care matrix comprised of hydrolyzed fish collagen 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 patient'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-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, superficial partial thickness burns, skin tears) and draining wounds.

ORION

There are few published studies addressing the use of ORION. Therefore, it is not possible to conclude whether ORION has a beneficial effect on health outcomes.

ORION (Legacy Medical Consultants, LLC) is a sterile dehydrated dual layered human amniotic membrane 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.

PalinGen

There are several studies related to PalinGen, all with study limitations. Therefore, it is not possible to conclude whether PalinGen has a beneficial effect on health outcomes.

PalinGen Membrane (Amnio Technology, LLC) is a human allograft comprised of 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 LLC) are human allografts comprised of 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-blind RCTs with active treatment comparators (injectables, surgery, 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 Sport FLOW, 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), to a traditional treatment, corticosteroid. The hypothesis was that c-hAM would be safe and comparable to corticosteroids for plantar fasciitis (PF) in regard to patient outcomes. A randomized, controlled, double-blind, single-center pilot study was completed. Patients were randomized into one of 2 treatment groups: c-hAM or corticosteroid. Patients 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 Visual Analog Scale (VAS) and verbally reported percentage improvement. Data were analyzed between groups for the 2 different cohorts (1 injection versus 2 injections). Twenty-three patients had complete follow-up. Fourteen were randomized to receive corticosteroid and 9 were randomized to receive c-hAM. Three patients in each group received second injections. With the numbers available, the majority of outcome measurements showed no statistical difference between groups. The corticosteroid did, however, have 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. Cryopreserved hAM had greater FHSQ foot pain improvement at 18 weeks in the 2-injection cohort. The authors concluded that cryopreserved hAM injection may be safe and comparable to corticosteroid injection for treatment of plantar fasciitis. According to the authors, this is a pilot study and 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 patients with chronic PF. Study limitations include small sample size, no comparison of baseline characteristics, limited follow-up, and lack of power analysis.

Zelen et al. (2013) reported the results of a randomized clinical trial examining the efficacy of micronized dehydrated human amniotic/chorionic membrane (mDHACM) injection as a treatment for chronic refractory plantar fasciitis. An institutional review board-approved, prospective, randomized, single-center clinical trial was performed. Forty-five patients 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 patients receiving 0.5 cc or 1.25 cc mDHACM versus controls within 1 week of treatment and throughout the study period. At 1-week, American Orthopedic Foot and Ankle Society (AOFAS) Hindfoot scores increased by a mean of 2.2 ±17.4 points for controls versus 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 AOFAS Hindfoot scores increased by a mean of 12.9 ±16.9 points for controls versus 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 patients receiving 0.5 cc versus 1.25 cc mDHACM. The authors concluded that in patients with refractory plantar fasciitis, mDHACM is a viable treatment option. Study limitations include lack of a power analysis, small sample size, limited follow-up, lack of an active comparator, and lack of blinding of outcome assessors.

PermeaDerm B, PermeaDerm Glove, or PermeaDerm C

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

PermeaDerm B, PermeaDerm C and PermeaDerm Glove (Stedical Scientific) are identical in chemical composition and 3D structure. They are all composed of a monofilament nylon knitted fabric 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 versus PermeaDerm C and PermeaDerm Glove) are in the number and orientations of slits per unit area.

- PermaDerm 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-Moh’s, post-laser surgery, podiatric, 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 addressing the use of Phoenix Wound Matrix for any other indications. Therefore, it is not possible to conclude whether Phoenix Wound Matrix has a beneficial effect on health outcomes.

The Phoenix Wound Matrix (Nanofiber Solutions) is a sterile, single use device intended for the management of wounds. The Phoenix Wound Matrix is a conformable, non-woven, fibrous, three-dimensional matrix. The Phoenix Wound Matrix is made from two types of polymer fibers: Poly(lactide-co-caprolactone) and Polyglycolic acid, which are bio absorbed 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-Moh's surgery, post laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second degree burns, skin tears) and draining wounds.

Polycyte

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

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

PriMatrix

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

PriMatrix (Integra Life Sciences, Inc.) is a bovine derived acellular dermal matrix indicated for the treatment of a variety of wounds.

An ECRI report for PriMatrix Dermal Repair Scaffold for treating a variety of wounds (i.e., partial and full-thickness wounds; pressure, diabetic, and venous ulcers; second-degree burns; surgical, trauma, and draining wounds; 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 Apilgraf, but there is limited data and too high 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 a randomized controlled trial was to evaluate the safety and efficacy of a fetal bovine acellular dermal matrix (FBADM) plus standard of care (SOC) for treating hard-to-heal diabetic foot ulcers (DFUs). A prospective, multi-center randomized controlled trial was carried out. The study included a 2-week run-in period, a 12-week treatment phase and a 4-week follow-up phase. The primary endpoint was complete wound closure at 12 weeks. Twenty-one US sites enrolled and randomized 226 patients with hard-to-heal DFUs. The study was terminated early due to the COVID-19 pandemic, which led to a modified intent-to-treat (mITT) population of 207 patients, with 103 in the FBADM group and 104 in the SOC group. Of these participants, 161 completed the study per protocol (mPP population), with 79 receiving FBADM, and 82 without. At the first analysis point, patients treated with FBADM were found to be significantly more likely to achieve complete wound closure compared with SOC alone (mITT: 45.6% versus 27.9% p = 0.008; mPP: 59.5% versus 35.6% p = 0.002). The difference in outcome yielded an odds ratio of 2.2 (95% confidence interval (CI): 1.2, 3.9; p = 0.008). Median time to closure within 12 weeks was 43 days for the FBADM group compared to 57 days for 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 included the following: early termination of the study, lack of blinding for both the investigator and the subject, subjects were only studied for four weeks post wound closure and selection bias since the subjects 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 bi layered living cellular construct (BLCC; Apligra) and an acellular fetal bovine collagen dressing (FBCD; Primatrix) for the treatment of venous leg ulcers. Data an electronic medical record (EMR) database was used to analyze 1021 refractory venous leg ulcers treated at 177 facilities. Kaplan-Meier analyses showed that BLCC (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 BLCC versus FBCD showed significant differences in both time 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 patient assessments and standardization of general wound care practices.

Procenta

There are few published studies addressing the use of Procenta for wound treatment. Therefore, it is not possible to conclude 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 non-healing wounds, such as venous stasis and diabetic foot ulcers to assist in the wound healing process.

ProgenaMatrix

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

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

ProMatrX

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

ProMatrX ACF™ (Amnio Technology, LLC) is a human allograft comprised of 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 related to PuraPly, PuraPly AM (formerly called FortaDerm), or PuraPly XT, all with study limitations. Therefore, it is not possible to conclude whether PuraPly, PuraPly AM (formerly called FortaDerm), or PuraPly XThas 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 (PHMB) 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) on cutaneous wounds by conducting a prospective cohort study of 307 patients (67 venous leg ulcers, 62 diabetic foot ulcers, 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 were 81, 71 and 85%, respectively. The authors concluded that PCMP demonstrated clinically meaningful benefits to patients with various types of cutaneous wounds. This study is limited because there was no comparator treatment group.

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 along with standard wound care achieved complete wound closure in about 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 size, single center, lack of controls, binding, and randomization. The studies were lacking in long-term outcomes and patient-oriented outcomes. Large multicenter randomized controlled trials are needed that address long-term and cosmetic outcomes as well as complications.

Rebound Matrix

Studies are lacking regarding the use of Rebound Matrix for wound treatment. Therefore, it is not possible to conclude 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 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 patient population includes those with chronic full thickness ulcers and other skin defects where a biological barrier or cover is required.

REGUaRD

There are no published studies addressing the use of REGUaRD. Therefore, it is not possible to conclude whether REGUard has a beneficial effect on health outcomes.

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

Relese

There are no published studies addressing the use of Relese for wound treatment. Therefore, it is not possible to conclude whether Relese has a beneficial effect on health outcomes.

Relese™ is a sheet skin substitute product that contains non-viable cells and is intended for use as a selective barrier and to protect wounds from the surrounding environment for chronic and acute wounds including dermal ulcers and other defects.

Repriza

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

Repriza (Promethean Life Sciences, Inc) is an acellular dermal matrix prepared from human skin allograft. Repriza is intended for implantation for reconstructive surgery wherever an acellular dermal matrix may be used, for example in abdominal wall reconstruction, and augmentation of soft tissue irregularities.

Cockcroft and Markelov (2018) followed 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 acellular dermal matrix 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 admitting to complete pain resolution. All

patients had an overall subjective improvement in symptoms. Ninety-one percentage of patients achieved postoperative opposition of the thumb and fifth digit. Comparison with preoperative x-rays showed mean thumb metacarpal subsidence of 27%. Zigzag deformity and extra-articular acellular dermal matrix migration, due to lack of patient compliance with splint, were observed complications. The authors concluded that this technique is safe and effective for Eaton grades III and IV thumb carpometacarpal arthritis. Long-term study with a larger sample size are needed to investigate this technique further.

Restorigin

There are few published studies addressing the use of Restorigin. Therefore, it is not possible to conclude 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 for individuals with chronic, non-healing wounds and burns.

Restrata

There are few published studies addressing the use of Restrata. Therefore, it is not possible to conclude whether Restrata has a beneficial effect on health outcomes.

Restrata is a synthetic, resorbable fiber matrix that resembles human extracellular matrix (ECM) and acts as a scaffold material 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.

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 diabetic foot ulcers, 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 included the following: this was an initial review of the implantable nanomedical scaffold and lack of a control group and randomization, which limit the ability to draw conclusions about the effectiveness of the scaffold. Additional research is needed along with large, randomized control studies to further predict efficacy and safety.

Revita

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

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

RevoShield+ Amniotic Barrier

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

RevoShield+ Amniotic Barrier (4Front Strategic Partners, Surgenex, LLC) is a minimally manipulated dual layer tissue-based product derived from the amniotic membrane of the human placenta. Following preparation of the wound (e.g., 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 or to provide protective coverage from the surrounding environment for acute and chronic wounds.

Signature APatch

There are no published studies addressing the use of Signature APatch for wound treatment. Therefore, it is not possible to conclude whether Signature APatch has a beneficial effect on health outcomes.

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

SkinTE

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

SkinTE (PolarityTE, Inc.) is a fully autologous, homologous skin product 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 the patient'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 treatment of acute burns requiring excision, 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, all with study limitations. Therefore, it is not possible to conclude whether Strattice has a beneficial effect on health outcomes.

STRATTICE (Allergan) is a porcine derived acellular dermal biological mesh 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 which require the use of reinforcing or bridging material to obtain the desired surgical outcome.

Jakob et al. (2020) conducted a two-arm randomized study to compare the outcome after prophylactic, intraperitoneal implantation of a biologic Strattice mesh with standard abdominal closure in patients undergoing emergency abdominal surgery. Patients 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, patient enrollment had to be closed prematurely. Eligibility for inclusion was assessed in 61 patients. A total of 48 patients were randomized (21 in the mesh group, 28 in the no-mesh group). No differences in baseline characteristics were found. Abdominal wall complications requiring re-operations were more frequent in the mesh group compared to the no mesh group [5 of 13 (83.3%) vs 1 of 13 (14.3%) patients, p = 0.026]. Mesh-associated abdominal wall complications included non-integration of the mesh into the abdominal wall, dissolution of the mesh, and mesh-related infections. The investigators concluded that in patients undergoing emergency abdominal surgery, intraperitoneal biologic Strattice mesh implantation is associated with significantly more frequent abdominal wall complications requiring re-operation. 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 the clinical efficacy and patient satisfaction following Strattice placement in complex abdominal wall hernia repair (CAWHR). The aim of this study was to evaluate clinical efficacy and patient satisfaction following Strattice™ placement in patients treated for CAWHR in three academic and peripheral hospitals in Germany. Patients underwent abdominal examination, an ultrasound was performed, and patients completed quality-of-life questionnaires. Twenty-seven patients 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 patients. Four patients had passed away. During outpatient clinic visit, six out of 23 patients (26.1%) had a recurrence of hernia, one patient had undergone reoperation. Five patients (21.7%) had bulging of the abdominal wall. Quality-of-life questionnaires revealed that patients 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 is 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 acellular dermal matrices (ADMs) in abdominal wall reconstruction (AWR). Hernia recurrence and surgical site occurrence (SSO) were the primary and secondary endpoints. Kaplan-Meier survival curves and logistic regression models were used to evaluate risks for hernia recurrence and SSO. A total of 229 patients underwent AWR with 1 of 3 ADMs. 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 Fortiva, Strattice, and Alloderm groups. Surgical site occurrence for each mesh was 56.9%, 49.0%, and 49.2%, respectively. Seroma was significantly lower in the Fortiva group (1.4%). Independent risk factors hernia recurrence included body mass index of 30 kg/m or higher and hypertension. Adjusted risk factors included oncologic resection for hernia recurrence and a wound class of contaminated or dirty/infected for SSO. The authors concluded that acellular dermal matrices provide a durable repair with 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 abdominal wall reconstruction.

Trippoli et al. (2018) conducted a meta-analysis to evaluate the treatment of primary and incisional ventral hernia using biologic meshes. The study consisted of the following phases: a) Identification of the biologic meshes available on the market; b) Literature search focused on efficacy and safety of these meshes; c) Analysis of the findings derived from the literature search. The information was reviewed and presented according to standard meta-analysis. The main endpoints of the analysis included infection of surgical wound at 1 month and recurrence at 12 months. Eleven trials that evaluated 5 biological meshes were identified: Permacol (706 patients), Strattice (324 patients), Surgisis (44 patients), Tutomesh (38 patients) and Xenmatrix (22 patients). These studies generally showed a poor methodological quality, and surgical wound infection showed wide range between studies variability. A significantly lower rate of recurrence at 12 months was found for 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 endpoints 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 biologic meshes for abdominal wall reconstruction. 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.

Stravix and StravixPL

There are several studies related to Stravix and StravixPL, all with study limitations. Therefore, it is not possible to conclude whether Stravix and/or StravixPL has a beneficial effect on health outcomes.

Stravix and Stravix PL (Osiris Therapeutics, Inc.) are thicker versions of Grafix PRIME and GrafixPL PRIME. These products use umbilical amnion and Wharton's Jelly to support wound repair. Stravix and Stravix PL are intended for treating ulcers, burns, Pyoderma Gangrenosum, Epidermolysis Bulosa, and other types of wounds.

An ECRI report for Stravix Cryopreserved Placental Tissue (Osiris Therapeutics, Inc.) is a ready-to-use, cryopreserved amniotic membrane graft 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 patient.

Supra SDRM

There are no published studies addressing the use of Supra SDRM for wound treatment. Therefore, it is not possible to conclude whether Supra SDRM has a beneficial effect on health outcomes.

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

SUPRATHEL

There are several studies related to SUPRATHEL, all with study limitations. Therefore, it is not possible to conclude whether SUPRATHEL has a beneficial effect on health outcomes.

SUPRATHEL® is indicated in superficial (2a°) and deep dermal/partial thickness (2b°) skin loss diseases, such as burn wounds, split-thickness skin graft (STSG) donor sites, as well as trauma and surgical wounds.
An ECRI 2023 clinical evidence assessment for Suprathel for Treating Burns suggest that Suprathel is safe, yet the studies are at high risk for bias and there are too few patients per comparison to make the findings conclusive about the comparative effectiveness.

An ECRI 2021 clinical evidence assessment for Suprathel Skin Substitute (PolyMedics Innovations GmbH) for Treating Donor Site Wounds suggest that Suprathel is safe, but whether it improves patient outcomes compared with other dressings cannot be determined because available studies are at high risk of bias and assess too few patients per comparison. There was one randomized controlled trial (RCT) and 2 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. Schwarz 2007 and Markl 2010 included in this report).

Blome-Eberwein et al. (2021) in a retrospective chart review from **a** single center burn center reviewed Suprathel, a new bio-degradable synthetic membrane that was recently introduced to treat second degree burns in adults and pediatric patients. There were 229 burn patients (141 male, 88 females, (138 pediatric)) with a mean age of 18 years (9 weeks to 73 years) were included in the study. 474 sheets of the synthetic membrane were applied to second degree burns (superficial and deep). The average burn size was 8.9% (range 1 to 60% TBSA. 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, absorptive gauze followed by an ACE® wrap. The outer dressing was removed every one to four days, depending on exudate, in order 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, patient pain level, hypertrophic scarring, and rate of infection. All wounds in this study that were treated with Suprathel® healed without grafting. The average TBSA (Total Body Surface Area) was 8.9% (1%-60%). Average time to healing was 13.7 days for ≥ 90% epithelialization with 11.9 days for pediatric patients versus 14.7 days for adults. Throughout the treatment period, the average pain level was 1.9 on a 10-point scale. 27 patients developed hypertrophic scarring in some areas (11.7%). Average Length of stay (LOS) 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 were that of any retrospective study in addition to no control group. Author's note that Suprathel is a good treatment option when treating second degree burns. It's a basic treatment that provides a physiologic healing environment with good outcomes and less pain than previously used options used by the providers at the same institution. Authors indicate that a prospective long- term outcome study with control group is in preparation to confirm these preliminary findings.

Hundeshagen et al. (2018) in a prospective single center randomized controlled trial compared Mepilex Ag (M), a silver-impregnated foam dressing, and Suprathel (S), a DL-lactid acid polymer, in the outpatient treatment of partial-thickness burns in pediatric and adult patients. Re-epithelialization, 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 $p < 0.05$. Sixty-two patients (S n = 32; M 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 burn in the Suprathel group in all patients ($p = 0.03$) 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. Patients treated with Suprathel reported better overall scar quality (S: 2; M: 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 included results that were assessed by clinical judgement rather than objective assessment tools such as doppler, there were a number of participants that 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.

Markl et al. (2010) in an open label single-center randomized controlled trial evaluated 3 different synthetic wound dressings for treating split-thickness skin graft donor sites. Seventy-seven participants were randomly assigned to 3 study groups: Suprathel, Biatain-Ibu, 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 5th 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 re-epithelization period of the 3 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 split-thickness skin grafts. Suprathel represents an absorbable, synthetic wound dressing with properties of natural epithelium. Twenty-two burn patients who were treated with split-thickness skin grafts, and 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. First gauze change was carried out the fifth day postoperatively followed by regular wound inspection until complete re-epithelization. The study focused on patient 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 for patients 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 included a small sample size, lack of blinding, participants were their own control group (both dressings applied to different areas of the same wound) and subjective reporting outcomes. While these results are promising, larger robust studies are needed.

Surederm

There are few published studies addressing the use of Surederm. Therefore, it is not possible to conclude whether Surederm has a beneficial effect on health outcomes.

Surederm (HansBiomed Corp.) is a human acellular dermal matrix. 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 addressing the use of SurFactor for wound treatment. Therefore, it is not possible to conclude whether SurFactor has a beneficial effect on health outcomes.

SurFactor (Surgenex, LLC) is an injectable amniotic membrane allograft that is packaged in sterile vials intended injection to the wound surface and supports wound healing and soft tissue repair.

SurgiCORD

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

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

SurgiGRAFT-DUAL

There are few published studies addressing the use of SurgiGRAFT-DUAL. Therefore, it is not possible to conclude whether SurgiGRAFT-DUAL has a beneficial effect on health outcomes.

SurgiGRAFT-DUAL (Synergy Biologics, LLC) is a bilayer human amniotic tissue allograft that is intended to be used to treat chronic, non-healing wounds including neuropathic ulcers, post-traumatic and pressure ulcers.

SurgiGRAFT

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

SurgiGRAFT (Synergy Biologics, LLC) is a minimally manipulated human amnion-only regenerative extracellular tissue matrix derived from human placental tissue. It is intended for use in the following conditions: neuropathic ulcers, venous stasis ulcers, post-traumatic wounds, pre- and post- surgical 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 Products

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

SurGraft (Surgenex, LLC) is a human amniotic membrane scaffold which is used as a wound covering and is intended for treating non-healing foot ulcers including diabetic, pressure and venous ulcers. The SurGraft family products include SurGraft, SurGraft ACA, SurGraft® FT, SurGraft® TL and SurGraft® XT.

Symphony

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

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

TAG

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

TAG (Conventus Flower Orthopedics, Inc.) 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 addressing the use of Talymed. Therefore, it is not possible to conclude whether Talymed has a beneficial effect on health outcomes.

Talymed is a wound care management product composed of shortened fibers of poly-N-acetyl glucosamine (pGlcNAc) 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, poly-N-acetyl glucosamine (pGlcNAc), nanofiber-derived, wound-healing technology (Talymed) among patients with venous leg ulcers (VLUs) compared to treatment with standard care plus pGlcNAc (applied only once, every other week, or every 3 weeks) or to standard care alone. The results showed among the 82 randomized patients, 71 completed the study with 7 lost to follow-up and 4 discontinued because of systemic infection. There were no significant group differences with regard to baseline demographic, illness, and VLU characteristics. At 20 weeks, the proportion of patients with completely healed VLUs 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, versus 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 patients unblinded to treatment allocation. Further research with randomized controlled trials is needed to validate these findings.

TenSIX

There are few published studies addressing the use of TenSIX. Therefore, it is not possible to conclude whether TenSIX has a beneficial effect on health outcomes.

The product information on TenSIX is not currently available.

TheraGenesis

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

TheraGenesis is a bilayered wound matrix comprised of a biodegradable porcine tendon-derived atelocollagen layer and a silicone film layer. The collagen matrix acts as a scaffold material the body uses for revascularization and soft tissue regeneration. The silicone layer contains a non adhesive 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 heterogenous in the etiology of the wound. Larger studies are needed. (ECRI, 2023).

TheraSkin

There are several studies related to TheraSkin, all with study 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 randomized controlled trial, Armstrong et al. (2022b) is study compared the healing potential of Theraskin (BSA) in subjects with chronic diabetic foot ulcers (DFUs), compared to treatment with SOC alone. There were 100 subjects with non-healing DFUs of which 50 were treated with a cryopreserved bioactive split thickness skin allograft (BSA) and 50 subjects were treated with standard of care (SOC, collagen alginate dressing) at 12 weeks. Both groups received standardized care that included glucose monitoring, weekly debridement's as appropriate, and an offloading device. The primary endpoint was proportion of full-thickness wounds healed at 12 weeks, with secondary endpoints including differences in percent area reduction (PAR) at 12 weeks, changes in Semmes-Weinstein monofilament score, VAS pain, and w-QoL. The result illustrated in the intent-to-treat analysis at 12 weeks showed that 76% (38/50) of the BSA-treated DFUs healed compared with 36% (18/50) treated with SOC alone (adjusted p = .00056). Mean PAR at 12 weeks was 77.8% in the BSA group compared with 49.6% in the SOC group (adjusted p = .0019). While the design was robust, there were study weaknesses. The main weakness being lack of investigator blinding and 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 as well as 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 standard of care when compared to standard of care alone. Data was extracted from a patient 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 bioactive split-thickness skin allograft (BSA) that were matched to 778 standard of care cohorts. Both cohorts received standard of care. 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 reoccurrences 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 to the control cohort ($p = 0.0045$). The healing rate with the graft was better than standard of care across multiple subclasses, but the most significant improvement was noted in the worst wounds that had a duration of 90-179 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 of the control cohort at 20 weeks (0.9% vs. 1.5%, respectively). This study demonstrated that diabetic ulcers treated with a cryopreserved bioactive split-thickness skin allograft were more likely to heal and remain closed compared to ulcers treated with standard of care alone. There were study limitations as a result of the data being obtained retrospectively from electronic medical records. This has the potential for inaccuracies, lack of information regarding treatment, wound description, limb vascularity and HbA1C. 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 is not enough data. Evidence from three very small comparative studies and two case series needs validation in larger multicenter randomized controlled trials (RCTs) that report patient-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 ECRI report above) evaluated the effectiveness of 2 biologically active grafts, TheraSkin and Apligraf, in conjunction with compression therapy to treat venous leg ulcers (VLUs). The study, not industry-sponsored, was designed to assess differences in healing rates, and adverse outcomes. A total of 31 subjects were enrolled and randomized into 1 of the 2 cohorts. There were 4 subjects 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 2 treatment options.

Treadwell et al. (2018; reviewed in ECRI report above) conducted a real-world setting analysis to compare the effectiveness of a bioengineered living cellular construct (BLCC; Apligraf) to a cryopreserved cadaveric skin allograft (CCSA; TheraSkin) for the treatment of venous leg ulcers (VLUs). Treatment records were collected from a large wound care-specific electronic medical record database on 717 patients (799 VLUs) receiving treatment at 177 wound care centers. Ulcers ≥ 28 day's duration, between ≥ 1 and < 40 cm^2 that closed ≤ 40% within the 28 days before treatment were included. Patient 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 for 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 VLUs. The authors concluded that treatment with a bioengineered cellular technology significantly improved the incidence and speed of wound closure compared with a 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 patient assessments and standardization of general wound care practices.

DiDomenico et al. (2011; reviewed in ECRI report above) evaluated whether the rate of wound closure and the number of grafts required would be the same when treating diabetic foot ulcers with TheraSkin, a cryopreserved split-thickness skin allograft (SSA), as compared to Apligraft, a bioengineered skin substitute (BSS). A prospective study using sequentially enrolled patients seen in a large podiatric practice encompassing multiple locations was conducted. Patients were sequentially enrolled and treated with either BSS or SSA. All other factors of treatment were standardized across the patient population. Data analysis included an analysis of co-factors in each group in order to determine if anything else may have influenced the outcomes. Data from 17 wounds (16 patients) treated with BSS and 12 wounds treated with SSA were analyzed. The average wound sizes were comparable, as was the average number of applications utilized. 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 ECRI report above) conducted a retrospective study of 188 subjects, with 134 venous leg ulcers (VLUs) and 54 diabetic foot ulcers (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 12th week, DFUs closed 60.38% of the time and VLUs closed 60.77% of the time. After 20 weeks, the number of closed DFUs increased to 74.1% and the number of VLUs increased to 74.6%. The mean wound size in the DFU group was 6.2 cm in the VLU 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 VLUs and DFUs with an acceptable safety profile. Further research with randomized controlled trials is needed to validate these findings.

Therion

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

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

TransCyte

TransCyte (Organogenesis, Inc.), formally 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 within 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 randomized controlled trials 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

randomized controlled trials with sufficient long-term follow up are necessary to strengthen the overall evidence regarding the efficacy of tissue-engineered skin substitutes.

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 on 14 patients. Wounds treated with TransCyte healed more quickly (mean 11.14 days to 90% epithelialization vs 18.14 days). A non-comparison evaluation was then done for an additional 18 patients, 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 postburn) 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 versus a biological skin substitute wound closure (TransCyte) for mid-partial thickness burns of the face. Twenty-one adult patients 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 2-3 times daily (n = 11). The authors found a significant decrease in wound care time (0.35 ±0.1 versus 1.9 ±0.5 h), decrease in pain of 2 ±1 versus 4 ±2 and re-epithelialization time (7 ±2 versus 13 ±4 days) in the skin substitute group compared to topical antibiotics group. The authors concluded that a bioengineered skin substitute significantly improves the management and healing rate of partial thickness facial burns compared to the standard open topical ointment technique.

TranZgraft

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

TranZgraft (AZIYO® Biologics) is an acellular collagen matrix intended for repair of sports related injuries, including tendons and ligaments.

TruSkin

There are few published studies addressing the use of TruSkin for wound treatment. Therefore, it is not possible to conclude 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, rich supply of endogenous growth factors, and living skin cells.

Vim

There are no published studies addressing the use of Vim. Therefore, it is not possible to conclude whether this product has a beneficial effect on health outcomes.

VIM™ is a dehydrated, decellularized, human amniotic membrane. 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.

Vendaje

There are no published studies addressing the use of Vendaje. Therefore, it is not possible to conclude whether this product has a beneficial effect on health outcomes.

Vendaje (BioStem Technologies, Inc.) 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 A

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

Vendaje A (BioStem Technologies, Inc.) is a decellularized human amniotic and chorionic allograft product derived from placental tissues and is intended for use as a protective covering for soft tissue wounds.

WoundEx

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

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

WoundEx Flow

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

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

WoundFix, WoundFix Plus, and WoundFix XPlus

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

WoundFix, WoundFix Plus and WoundFix XPlus (Human Regenerative Technologies, LLC) are single-layer, human tissue allografts 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 or E-Graft

There are few published studies addressing the use of WoundPlus membrane or E-Graft for wound treatment. Therefore, it is not possible to conclude whether WoundPlus membrane or E-Graft has a beneficial effect on health outcomes.

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

Xcell Amnio Matrix

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

Xcell Amnio Matrix® (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 provide 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 addressing the use of XCellerate for wound treatment. Therefore, it is not possible to conclude whether XCellerate has a beneficial effect on health outcomes.

XCellerate (Precise Bioscience) is a lyophilized amniotic membrane allograft intended for use in the treatment of non-healing 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 addressing the use of XCelliStem for wound treatment. Therefore, it is not possible to conclude whether XCelliStem has a beneficial effect on health outcomes.
XCelliStem Wound Powder is a proprietary blend of multiple extracellular matrix materials derived from the multi-tissue platform (MTP) that maintains and supports a healing environment for wound management.

XCM BIOLOGIC

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

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

XWRAP

There are few published studies addressing the use of XWRAP. Therefore, it is not possible to conclude 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.

Zenith

There are no published studies addressing the use of Zenith. Therefore, it is not possible to conclude whether this product has a beneficial effect on health outcomes.

Zenith™ Amniotic Membrane 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 patients 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 diabetic foot ulcers 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, 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. Re-evaluation of vascular status, infection control, and offloading is recommended to ensure optimization before initiation of adjunctive wound therapy (Grade 1B)
- Consideration of living cellular therapy using a bilayered keratinocyte/fibroblast construct or a fibroblast-seeded matrix for treatment of diabetic foot ulcers when the individual is recalcitrant to standard therapy (Grade 2B)
- Consideration of the use of extracellular matrix products employing acellular human dermis or porcine small intestinal submucosal tissue as an adjunctive therapy for diabetic foot ulcers 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 WSH concluded that level I evidence suggests that cellular and acellular skin equivalents improve the healing of diabetes-related foot ulcers. The underlying principle is that healthy living skin cells assist in the healing foot ulcers by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed (Lavery et al., 2016).

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 diabetic foot ulcers 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 2020, the updated clinical guideline on the use of interventions to enhance the healing of chronic ulcers of the foot in diabetes, based upon their systemic review of the evidence (Rayman et al., 2020). The following IWGDF recommendations apply to the use of skin substitutes:

- The IWGDF recommends the consideration of placental-derived products as an adjunctive treatment to the best standard of care when standard care alone has failed to reduce the size of the wound
- For use of topically applied treatments, the IWGDF recommends against the use of bioengineered skin products, among others, in preference to the best standard of care

For both of these recommendations, the IWGDF considered the available evidence to be of low quality, and their recommendation was weak (i.e., based on the quality of evidence, balance between benefits and harms, patient values and preferences, and cost or resource utilization).

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
- 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 require 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 (HDE): 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
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Policy History/Revision Information

Date	Summary of Changes
06/01/2024	**Coverage Rationale** • Revised list of skin and soft tissue substitutes that are unproven and not medically necessary for any indication: ○ Added:

Date	Summary of Changes
	▪ Acesso DL ▪ Acesso TL ▪ Activate Matrix ▪ AmniCore Pro ▪ AmniCore Pro+ ▪ Amnio Quad-Core ▪ Amnio Tri-Core Amniotic ▪ Complete AA ▪ Complete ACA ▪ DermaBind CH ▪ DermaBind DL ▪ DermaBind TL ▪ Emerge Matrix ▪ Grafix Plus ▪ Lamellas ▪ Lamellas XT ▪ Membrane Wrap-Hydro ▪ Rebound Matrix ▪ RevoShield+ Amniotic Barrier ▪ Vendaje A ○ Removed "Surgraft TL™" **Applicable Codes** • Added HCPCS codes Q4279, Q4287, Q4288, Q4289, Q4290, Q4291, Q4292, Q4293, Q4294, Q4295, Q4296, Q4297, Q4298, Q4299, Q4300, Q4301, Q4302, Q4303, and Q4304 • Revised description for HCPCS code A2004, Q4130, Q4176, and Q4225 **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS153NE.N

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