

Skin and Soft Tissue Substitutes (for New Jersey Only)

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[Instructions for Use](#)

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Related Policies

- [Breast Reconstruction Post Mastectomy \(for New Jersey Only\)](#)
- [Prolotherapy and Platelet Rich Plasma Therapies \(for New Jersey Only\)](#)

Application

This Medical Policy only applies to the state of New Jersey.

Coverage Rationale

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:

- Affinity®
- AlloSkin™
- AlloWrap®
- Amnio Wound™
- AmnioArmor™
- AmnioBand®
- AMNIOEXCEL®, AMNIOEXCEL Plus, or BioDExcel™
- AmnioFix®
- AMNIOMATRIX® or BioDMatrix™
- Architect®
- Artacent® Wound or Artacent AC
- ArthroFLEX®
- bio-ConneKt®
- BioDence™ or BioDfence
- DryFlex™
- Bioskin™
- Bioskin™ Flow
- Biovance®
- Cellesta™ or Cellesta Flowable Amnion
- CLARIX®
- CLARIX FLO®
- Coll-e-Derm™
- Conexa™
- CorMatrix®
- Cygnus™
- Cymetra™
- Cytal™
- * [DermACELL](#)® (see asterisked note below when DermACELL is used during breast reconstruction)
- Derma-Gide™
- DermaPure™
- DermaSpan™
- Dermavest® or Plurivest®
- EpiCord®
- EpiFix®

- Excellagen®
- E-Z Derm®
- FlowerAmnioFlo™ or FlowerFlo™
- FlowerAmnioPatch™ or FlowerPatch™
- FlowerDerm™
- GammaGraft™
- Genesis Amniotic Membrane
- Grafix®
- GrafixPL®
- Grafix PRIME®
- GrafixPL PRIME®
- Guardian
- Helicoll™
- hMatrix®
- Hyalomatrix®
- Integra® Flowable Wound Matrix
- InteguPly®
- Interfyl™
- Keramatrix®
- Kerecis™ Omega3
- Keroxx™
- Matrion™
- MatriStem®
- Mediskin™
- MemoDerm™
- MIRODERM™
- NeoPatch™
- NEOX®
- NEOX FLO®
- Novachor™
- NuShield®
- PalinGen® Amniotic Tissue Allograft and PalinGen® Flow products
- PriMatrix®
- ProMatrX™
- PuraPly®, PuraPly AM, or PuraPly XT
- Repriza®
- Restorigin™
- Revita™
- Revitalon®
- SkinTE™
- STRATTICE™
- Stravix™ or StravixPL™
- SurgiGRAFT™
- Talymed®
- TenSIX®
- TheraSkin®
- TranZgraft®
- TruSkin™
- WoundEx®
- WoundEx™ Flow
- XCM BIOLOGIC® Tissue Matrix
- XWRAP™

*Refer to the Coverage Determination Guideline titled [Breast Reconstruction Post Mastectomy](#) 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).

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

Applicable Codes

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

HCPCS Code	Description
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 square centimeter
Q4136	Ez-derm, per square centimeter
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 square centimeter
Q4143	Repriza, per square centimeter
Q4145	EpiFix, injectable, 1 mg
Q4146	Tensix, per square centimeter
Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per 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 square centimeter
Q4155	Neox Flo or Clarix Flo 1 mg
Q4156	Neox 100 or Clarix 100, per sq cm
Q4157	Revitalon, per square centimeter
Q4158	Kerecis Omega3, per sq cm
Q4159	Affinity, per square centimeter

HCPSC Code	Description
Q4160	Nushield, per sq cm
Q4161	Bio-connekt wound matrix, per square centimeter
Q4162	WoundEx Flow, BioSkin Flow, 0.5 cc
Q4163	WoundEx, BioSkin, per sq cm
Q4164	Helicoll, per square centimeter
Q4165	Keramatrix or Kerasorb, per sq cm
Q4166	Cytal, per square centimeter
Q4167	Truskin, per square centimeter
Q4168	Amnioband, 1 mg
Q4169	Artacent wound, per square centimeter
Q4170	Cygnus, per square centimeter
Q4171	Interfyl, 1 mg
Q4173	Palingen or palingen xplus, per square centimeter
Q4174	Palingen or promatrix, 0.36 mg per 0.25 cc
Q4175	Miroderm, per square centimeter
Q4176	Neopatch, per square centimeter
Q4177	Floweramnioflo, 0.1 cc
Q4178	Floweramniopatch, per square centimeter
Q4179	Flowerderm, per square centimeter
Q4180	Revita, per square centimeter
Q4181	Amnio wound, per square centimeter
Q4182	Transcyte, per square centimeter
Q4183	Surgigraft, per 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
Q4200	SkinTE, per sq cm
Q4201	Matrion, per sq cm
Q4202	Keroxx (2.5 g/cc), 1 cc
Q4203	Derma-Gide, per sq cm

HCPCS Code	Description
Q4204	XWRAP, per sq cm
Q4251	Vim, per sq cm
Q4252	Vendaje, per sq cm
Q4253	Zenith amniotic membrane, per sq cm

Description of Services

Wounds that are not healing in response to conventional therapy (e.g., cleansing, debridement, infection control, dressing, and offloading) may require skin grafting. Autografts or autologous skin grafts use skin from different parts of the individual's body and are usually the best choice for wound coverage. However, areas of the skin that can be harvested for autologous skin grafts may be limited and the procedure can be painful and invasive. Allografts which use skin from another human (e.g., cadaver) and xenografts which use skin from another species (e.g., porcine or bovine grafts) are usually only temporary skin replacements. Skin substitutes were developed due to the problems encountered with autografts, allografts, and xenografts (Hayes, Skin Substitutes for Chronic Foot Ulcers in Adults with Diabetes Mellitus: A Review of Reviews, November 2018; Nicholas et al., 2016).

Skin and soft tissue substitutes, also known as bioengineered skin substitutes or cellular and tissue based products (CTPs), are used to treat wounds and other conditions with the goals of facilitating healing and regeneration. They are thought to work by physically covering the wound and providing extracellular matrices to encourage regeneration and immune function. Skin substitutes are used to treat several types of wounds including lower extremity diabetic ulcers, venous ulcers, burn wounds, surgical wounds (e.g., donor sites or grafts, post-laser surgery, post-podiatric procedures), and traumatic wounds. Skin and soft tissue substitutes can also be used for repair, reconstruction, and reinforcement (Hayes, Skin Substitutes for Chronic Foot Ulcers in Adults with Diabetes Mellitus: A Review of Reviews. November 2018).

Skin substitutes can be classified in a variety of ways including the following (Debels et al., 2015; Ferreira et al., 2011; Nicholas et al., 2016; Vig et al., 2017):

- Human Skin Allografts are derived from donated human skin (e.g., cadavers) that has been processed to remove the cellular components.
- Allogeneic Matrices are derived from human tissue such as neonatal fibroblasts of the foreskin.
- Composite Matrices are 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.
- Acellular Matrices are derived from sources other than human skin and include the majority of skin substitutes. Acellular Matrices are composed of allogeneic or xenogeneic derived collagen, membrane, or cellular remnants.

Skin and soft tissue substitute products may be made with or without dead cells and biomaterials made of living cells may be comprised of autologous cells (cultured and not cultured), xenogenic, or allogenic cells (minimally manipulated and cultured). 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 May 16, 2019)

Skin substitutes are manufactured under various trade names and are marketed for various purposes. See the Clinical Evidence section of this policy for the descriptions of specific skin and soft tissue substitute products.

Skin and Soft Tissue Substitutes

Affinity

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

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

AlloSkin

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 (alloblasts 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

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

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.

Amnio Wound

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.

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.

AmnioArmor

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.

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.

AmnioBand Viable Membrane and Guardian

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.

Alvaro-Afonso et al. (2019) reviewed the recent advances in dermoepidermal 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%) and with dermal acellular substitutes (Allopatch, 80% and Hyalograft, 78.8%). 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. Nonetheless, 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.

DiDomenico et al. (2018) 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) 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. (2016) 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.

DiDomenico et al. (2017) 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 cm² to 0.2 cm², 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.

AMNIOEXCEL, AMNIOEXCEL Plus, or BioDExcel

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.

Snyder et al. (2016) 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

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.

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) 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.

In a Systematic review and network meta-analysis, Tsikopoulos et al. (2016) compared the efficacy of different injection therapies for plantar fasciopathy (historically known as 'plantar fasciitis'). Randomized trials comparing various injection therapies in adults with plantar fasciopathy were included. The primary outcome was pain relief. Secondary outcomes included functional disability, 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.

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 (RCTs) 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, 2019).

A Hayes report for Injectable Amniotic Tissue-Derived Allografts for Treatment of Chronic Plantar Fasciitis indicates that there is limited evidence to determine the safety and efficacy of injectable human amniotic tissue-derived allografts for treating chronic plantar fasciitis (Hayes, 2018).

Amniomatrix or BioDMatrix

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.

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.

Architect

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

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.

Artacent

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 choriarniotic 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.

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.

ArthroFLEX

ArthroFLEX (Arthrex®) is an acellular dermal matrix intended for supplemental support and covering for soft-tissue repair.

In a case series, Cole et al. (2018) described the outcomes of 9 patients who underwent Achilles tendon repair with acellular dermal matrix augmentation (ArthroFLEX). Functional outcomes were evaluated using the Foot Function Index-Revised long form, and the clinical results were recorded. After a mean average follow-up period of 14.4 months, the mean Foot Function Index-Revised long form score was 33.0% ± 4.2%. No cases of rerupture or complications that required additional treatment occurred during the observation period. The limitations of this study included the small patient population and the lack of a comparison group.

An ECRI report for Arthroflex Decellularized Dermal Allograft indicated that there is a very small amount of evidence available, and it is not possible to determine the safety and efficacy of ArthroFLEX for repair of rotator cuff tears (ECRI, 2017).

bio-ConneKt

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.

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.

BioDfence or BioDfence DryFlex

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.

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.

Bioskin

The product information on Bioskin is not currently available. There are few published studies addressing the use of Bioskin. Therefore, it is not possible to conclude whether Bioskin has a beneficial effect on health outcomes.

Bioskin Flow

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

Biovance

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.

Smiehl 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.

Cellesta or Cellesta Flowable Amnion

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.

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.

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

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.

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 FLO

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.

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.

Coll-e-Derm

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.

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.

Conexa

Conexa Reconstructive Matrix (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.

Lederman et al. (2016) conducted a prospective, multicenter study to determine the clinical and radiographic outcome of repair of large rotator cuff tears with extracellular matrix (ECM) graft reinforcement. The study included 61 shoulders with large repairable rotator cuff tears (3 to 5 cm). The rotator cuff tears were surgically repaired and reinforced with a xenograft ECM graft (Conexa). The average patient age was 56 years (range, 40-69 years). The average tear size was 3.8 cm. Follow-up was obtained at 6, 12, and 24 months in 58, 54, and 50 of the 61 patients, respectively. Functional outcome scores, isometric muscle strength, and active range of motion were significantly improved compared with baseline. Magnetic resonance imaging at 12 months showed return rotator cuff repairs in 33.9% of shoulders, using the criteria of a tear of at least 1 cm, and tears in 14.5% of the shoulders using the criteria of retear >80% of the original tear size. Three patients underwent surgical revision. Complications included 1 deep infection. The authors concluded that repair of large rotator cuff tears structurally reinforced with the Conexa xenograft ECM resulted in improved functional outcomes scores and strength. Adverse events were uncommon, and the rate of revision surgery was low. The main limitation of this study is the lack of a control group.

CorMatrix

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.

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.

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. A 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.

Cygnus

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.

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

Cymetra

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

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.

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

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).

DermACELL

DermACELL (LifeNet Health®) is a technologically advanced human acellular dermal matrix intended for the treatment of chronic wounds.

Cazzell et al. (2017) 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 posttermination (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 manufactures 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) 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 nonsignificantly 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.

Derma-Gide

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

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.

DermaPure

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 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

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).

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.

Dermavest and Plurivest

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.

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.

EpiCord

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.

Tettelbach et al. (2019b) 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 cm² 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 hydropolymer secondary dressing, and gauze bandage roll (n=54). Study visits were conducted for 12 weeks. At each weekly visit, the DFU was cleaned and debrided as necessary, 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.

EpiFix

EpiFix (MiMedx Group, Inc.) is a dehydrated amniotic membrane extracellular collagen allograft comprised of an epithelial layer and two fibrous connective tissue layers that is proposed for acute and chronic wound care.

Diabetic Foot Ulcers

Alvaro-Afonso et al. (2019) reviewed the recent advances in dermoepidermal 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%) and with dermal acellular substitutes (Allopatch, 80% and Hyalograft, 78.8%). 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. Nonetheless, 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.

Tettelbach et al. (2019a) conducted a manufactured sponsored randomized, controlled multicentre clinical trial 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. 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 dHACM 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. The findings of this study need confirmation through an independently conducted randomized controlled trial.

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.

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. 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.

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. 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.

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). The mean number of grafts used and the graft cost per patient were lower in the EpiFix group compared to the Apligraf group. 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. The authors indicated patients were followed for only 1 week after healing, and they were allowed to withdraw from the study after 6 weeks if their wound had not reduced in size by at least 50%. Therefore, the authors were unable to compare the rates of healing at 12 weeks, or the rates of wound recidivism in this study. In addition, this study includes a variety of lower extremity diabetic ulcers, both plantar and dorsal. The sample size was not sufficient to stratify by location, nor was it possible to perform any meaningful sub-group analysis to determine factors influencing outcomes or speed of healing. This study was funded by the manufacturer, MiMedx Group, Inc, which has the potential for introducing bias in the reporting of outcomes. Three of the authors had financial affiliations with MiMedx.

Zelen et al. (2016) continued the above 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.

In a Cochrane database systematic review, Santema et al. (2016) evaluated the benefits and harms of skin grafting and tissue replacement for treating foot ulcers in people with diabetes. The review included seventeen randomized clinical trials (RCTs) studies with a total of 1655 participants. Risk of bias was variable among studies. Blinding of participants, personnel and

outcome assessment was not possible in most trials because of obvious differences between the treatments. The lack of a blinded outcome assessor may have caused detection bias when ulcer healing was assessed. However, possible detection bias is hard to prevent due to the nature of the skin replacement products that were assessed, and the fact that they are easily recognizable. Strikingly, nearly all studies (15/17) reported industry involvement; at least one of the authors was connected to a commercial organization or the study was funded by a commercial organization. In addition, the funnel plot for assessing risk of bias appeared to be asymmetrical; suggesting that small studies with 'negative' results are less likely to be published. Thirteen of the studies included in this review compared a skin graft or tissue replacement with standard care. Four studies compared two grafts or tissue replacements with each other. When the results were pooled for the individual studies, the skin grafts and tissue replacement products that were used in the trials increased the healing rate of foot ulcers in patients with diabetes compared to standard care (risk ratio (RR) 1.55, 95% confidence interval (CI) 1.30 to 1.85, low quality of evidence). However, the strength of effect was variable depending on the specific product that was used (e.g., EpiFix® RR 11.08, 95% CI 1.69 to 72.82 and OrCel® RR 1.75, 95% CI 0.61 to 5.05). Based on the four included studies that directly compared two products, no specific type of skin graft or tissue replacement showed a superior effect on ulcer healing over another type of skin graft or tissue replacement. Sixteen of the included studies reported on adverse events in various ways. No study reported a statistically significant difference in the occurrence of adverse events between the intervention and the control group. Only two of the included studies reported on total incidence of lower limb amputations. The authors found fewer amputations in the experimental group compared with the standard care group when we pooled the results of these two studies, although the absolute risk reduction for amputation was small (RR 0.43, 95% CI 0.23 to 0.81; risk difference (RD) -0.06, 95% CI -0.10 to -0.01, very low quality of evidence). The authors concluded that based on the studies included in this review, the overall therapeutic effect of skin grafts and tissue replacements used in conjunction with standard care shows an increase in the healing rate of foot ulcers and slightly fewer amputations in people with diabetes compared with standard care alone. However, the data available was insufficient to draw conclusions on the effectiveness of different types of skin grafts or tissue replacement therapies. In addition, evidence of long term effectiveness is lacking.

In a prospective, randomized, single-center clinical trial, Zelen et al. (2013b) compared healing characteristics of diabetic foot ulcers treated with dehydrated human amniotic membrane allografts (EpiFix®, MiMedx) versus standard of care. The study included patients with a diabetic foot ulcer of at least 4-week duration without infection having adequate arterial perfusion. Patients were randomized to receive standard care alone or standard care with the addition of EpiFix. 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. It is also unknown how the EpiFix product performs in other patient populations and for other medical or surgical indications since the study was limited to patients with chronic diabetic foot ulcers.

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.

Zelan 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.

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 $\leq 20\%$ 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.

Venous Leg Ulcers

The earlier study reported by Bianchi et al. (2018) (see 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) 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) conducted a randomized, controlled, multicentre 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 centres 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.

Serena et al. (2014) 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.

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 $\geq 40\%$ and 24 (55%) had $< 40\%$ reduction during the initial study. Complete healing occurred in 16/20 (80%) of the $\geq 40\%$ 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.

Lower Extremity Free Flap Ulcers in Individuals with Venous Insufficiency and/or Lymphedema

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.

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).

An ECRI report for EpiFix Amnion/Chorion Membrane Allograft states that the evidence is “somewhat favorable” for EpiFix. The evidence suggests that EpiFix promotes diabetic foot ulcer (DFU) healing better than standard of care with alginate dressings and off-loading. The ECRI report also states that the evidence suggests that EpiFix promotes venous leg ulcer (VLU) healing. The ECRI report indicates that these results should be confirmed in independent randomized controlled trials since the EpiFix manufacturer MiMedx funded these studies (ECRI, 2018).

Excellagen

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

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.

E-Z-Derm

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.

Burkey et al. (2016) retrospectively reviewed the medical records of patients with superficial partial-thickness burns treated with Porcine xenograft (PX) (Ex Derm) admitted to a paediatric burn center. A total of 164 patients met the inclusion criteria. Burn total body surface area (TBSA) ranged from 0.5% to 28%. After the placement of PX, significant decreases were seen in the need for narcotic analgesics and burn dressing changes. Only four of 164 patients (2.4%) developed infections, although only one of these infections was at the site of the xenograft. The authors concluded that PX appears to reduce pain and eliminate the need for procedural intravenous sedation in many patients. According to the authors, this can make burn wound care more child-friendly and shorten hospital length of stay. This study is an uncontrolled retrospective review.

In a retrospective review of medical records, Troy et al. (2013) evaluated the use of EZ Derm on partial-thickness burns in 157 patients. The average length of follow-up was 94.2 days. A total of 15.3% of patients (24/157) were lost to follow up. Eighteen complications were reported from 16 patients. Complications were attributed to positioning, infection, incomplete epithelialization at time of separation, need for additional excision and grafting, hypertrophic scarring, and cryptogenic. Clinically significant infections were seen in 22% (4/18) of complications and 3% of patients overall. The authors concluded that EZ Derm has proven to be a robust wound dressing that provides consistent durable wound coverage with minimal complications that resolve without long-term adverse sequelae. This study is limited by the retrospective nature of the data collection.

FlowerAmnioFlo

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.

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.

FlowerAmnioPatch

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.

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.

FlowerDerm

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.

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.

GammaGraft

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

Sivak et al. (2016) conducted a retrospective review of patients undergoing scalp reconstruction utilizing GammaGraft and subsequent skin grafting with GammaGraft. Five patients treated with GammaGraft and subsequent skin grafting had both immediate and long-term follow-up available. Indications for scalp reconstruction included erosions of prior skin grafts and direct excision of full-thickness scalp and pericranium. The results showed an average time to definitive skin grafting was 3 weeks; repeat application of GammaGraft was required in some patients with reapplication to subsequent smaller wounds as

healing occurred. Complications were minor and consisted of ongoing wound drainage. Alternative flap reconstruction was not required in any patient due to treatment failures. No major complications, wound infections, or early reoperations occurred in any of the patients; 1 patient required repeat reconstruction due to recurrent disease. The authors concluded that coverage of bare skull defects with GammaGraft and subsequent skin grafting provides an alternative method in surgical care of complex scalp defects with exposed bone. This study is limited by a small number of patients. Further research with randomized controlled trials is needed to validate these findings.

Genesis Amniotic Membrane

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.

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.

Grafix

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.

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 cm². 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 authors, 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 cm² and an average wound duration of 102 days prior to vCPM treatment. For evaluation of clinical outcomes, 350 DFUs larger than 0.25 cm² 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) 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 $\leq 5 \text{ cm}^2$: 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 (amnio) 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.

In a randomized controlled study, Lavery et al. (2014) 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). 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.

Frykberg et al. (2017) reported the results of a prospective, multicentre, open-label, single-arm clinical trial to establish clinical outcomes when viable cryopreserved human placental membrane (Grafix) is applied weekly to complex diabetic foot ulcers (DFUs) with exposed deep structures. Patients with type 1 or type 2 diabetes and a complex DFU extending through the dermis with evidence of exposed muscle, tendon, fascia, bone and/or joint capsule were eligible for inclusion. Of the 31 patients enrolled, 27 completed the study. The mean wound area was 14.6 cm², and mean duration was 7.5 months. For patients completing the protocol, the primary endpoint, 100% wound granulation by week 16, was met by 96.3% of patients in a mean of 6.8 weeks. Complete wound closure occurred in 59.3% (mean 9.1 weeks). The 4-week percent area reduction was 54.3%. There were no product-related adverse events. Four patients (13%) withdrew, two (6.5%) for non-compliance and two (6.5%) for surgical intervention. This study was limited by a small sample size and lack of a control group.

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.

A Hayes Report for Grafix Cryopreserved Placental Membrane concluded that there is sufficient published evidence to evaluate this technology. However, the study abstracts indicate conflicting findings regarding Grafix (Hayes, 2018).

GrafixPL

The product information on GrafixPL is not currently available. There are few published studies addressing the use of GrafixPL. Therefore, it is not possible to conclude whether GrafixPL has a beneficial effect on health outcomes.

Grafix PRIME and GrafixPL PRIME

Grafix PRIME (Osiris Therapeutics, Inc.) is a cryopreserved amnion matrix that is intended to repair acute and chronic wounds. GrafixPL Prime (Osiris Therapeutics, Inc.) is a placental tissue allograft that is intended for use as a cover for wounds, including diabetic foot ulcers, venous leg ulcers, pressure ulcers, surgical wounds, burns, dehisced wounds, and wounds with exposed tendon, bone, and/or muscle.

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

Helicoll

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.

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

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.

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.

Hyalomatrix

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.

Marcasciano et al. (2018) describe the use of dermal substitute in a 2-stage surgery protocol for selected patients to remove non-melanoma skin cancers (NMSC) of the head region. The first stage consisted of traditional surgical excision and immediate coverage with Hyalomatrix. After histology confirmed diagnosis and clearance of the margins, full-thickness skin autografts were performed. All of the patients reached complete tumour excision and wound healing. No local recurrences were registered during 24 months follow up. The authors indicated that when patients cannot tolerate invasive and long surgical procedures, general anaesthesia, and long hospitalization, skin grafting following temporary skin substitute coverage can

achieve oncological clearance and provide good functional results. This study is limited by a small sample size and lack of a control group.

In a 2018 prospective, non-comparative clinical case series, Simman et al. 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 randomization and small number of participants.

In a 2011 multicenter, prospective, observational study (The FAST study), Caravaggi et al. evaluated the performance and safety of Hyalomatrix PA (a dermal substitute) in the treatment of chronic wounds of different etiology. This study included 70 Italian centers and 262 elderly patients. Patients were observed from the start of treatment with Hyalomatrix PA until healthy dermal tissue suitable for a thin autograft was visible or until the growth of new epithelium from the wound edge was reported. Tracking the wound edge advancement was used to assess the dermal substitute's performance. The main endpoint was the reduction in threshold area ($\geq 10\%$) of the ulcer. Treated ulcers were characterized as follows: 46% vascular, 25% diabetic foot, 12% traumatic wounds, 2% pressure ulcers and 15% other. Re-epithelization ($\geq 10\%$) was achieved in 83% of ulcers in a median time of 16 days. Twenty-six percent (26%) of wounds achieved 75% re-epithelization within the 60-day follow-up period using only HPA treatment. A follow-up showed that 84% of ulcers achieved complete re-epithelialization by secondary intention. The authors concluded that these findings indicate that Hyalomatrix is a safe and effective dermal substitute. This study is limited by a lack of randomization.

The ECRI report for Hyalomatrix Tissue Reconstruction Matrix for treating burns and chronic wounds indicated that the evidence for these products are inconclusive because there is limited evidence (ECRI Hyalomatrix Tissue Reconstruction Matrix for treating burns, 2018; ECRI Hyalomatrix Tissue Reconstruction Matrix for treating chronic wounds, 2018).

Integra Flowable Wound Matrix

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.

An ECRI report for Integra Flowable Wound Matrix concluded that available evidence is insufficient to determine whether Integra Flowable Wound Matrix is effective and safe for treating deep soft-tissue or tunneling wounds or how it compares with other wound care options (ECRI, 2017).

InteguPly

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.

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.

Interfyl

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.

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.

Keramatrix

Keramatrix (Molecular Biologicals, LLC) is an open-cell wound dressing used for chronic wounds and ulcers. 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.

Kerecis Omega3 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.

Dorweiler et al. (2018) reported the cumulative experience of three centers for vascular surgery regarding use of the Kerecis Omega3 Wound matrix in selected patients with complicated wounds. In this study, 23 patients with 25 vascular and/or diabetes mellitus-associated complicated wounds and partially exposed bony segments were treated with the Omega3 Wound matrix. In several patients, conventional wound treatment with vacuum therapy had previously been carried out sometimes over several weeks without durable success. Following initial debridement in the operating room, the matrix was applied and covered with a silicone mesh. In the further course, wound treatment was conducted on an outpatient setting if possible. In total, 25 wounds were treated. The time to heal varied between 9 and 41 weeks and between 3 and 26 wound matrices were applied per wound. The authors concluded that the Omega3 Wound matrix was an effective treatment option in 25 complicated wounds. This study is limited by low numbers and lack of a control group. Further studies are necessary to evaluate the impact of the wound matrix on stimulation of granulation tissue and re-epithelialization.

Yang et al. (2016) evaluated the use of piscine acellular fish-skin graft product (Kerecis) to treat hard-to-heal ulcers. The primary objective was to assess the percentage of wound closure area from baseline after 5 weekly fish-skin graft applications in 18 patients with at least 1 "hard-to-heal" criterion. Patients underwent application of the fish skin for 5 sequential weeks, followed

by 3 weeks of standard care. Wound area, skin assessments, and pain were assessed weekly. A 40% decrease in wound surface area and a 48% decrease in wound depth was seen with 5 weekly applications of the fish-skin graft and secondary dressing. Complete closure was seen in 3 of 18 patients by the end of the study phase. The authors concluded that the fish-skin product appears to provide promise as an effective wound closing adjunctive extracellular matrix (ECM). According to the authors, the limitations of this pilot study include a small sample size and lack of a control arm.

An ECRI report for Omega3 Wound Matrix (Kerecis) for Treating Chronic Wounds indicated that the evidence for this product is inconclusive due to too few data on outcomes and no data on comparisons of interest (e.g., porcine or bovine extracellular matrices, human amnion/chorion membranes, alternative acellular dermal matrices) (ECRI, 2019).

A Hayes report for Kerecis Omega3 Skin Substitute concluded that there is insufficient evidence to support the use of Kerecis Omega3 fish skin graft for the treatment of wounds (Hayes, 2018).

Keroxx

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.

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.

Matrion

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.

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.

MatriStem

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.

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.

An ECRI report for MatriStem MicroMatrix for treating surgical and chronic wounds indicated that the evidence for this product is inconclusive because there is not enough data (ECRI, 2018).

Mediskin

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. Aquacel was shown to be significantly easier for the caregiver to use than Allevyn and Mediskin I. The authors stated that their results support the use of Aquacel in the treatment of split-thickness skin graft donor sites.

MemoDerm

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.

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.

MIRODERM

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.

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.

NeoPatch

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

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.

NEOX

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.

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 FLO

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.

There are few 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.

Novachor

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.

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.

NuShield

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.

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.

PalinGen

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.

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 Orthopaedic 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.

In a study conducted by Werber (2015), 44 patients experiencing heel pain caused by chronic plantar fasciosis and Achilles tendinosis, who did not respond to standard therapies for a minimum of 6 months were treated with one implantation of

PalinGen SportFLOW. The patients were given a standard protocol for postimplant active rehabilitation. Preoperative pain was self-reported as severe in all patients, and changes in self-reported pain were monitored every 2 weeks for 12 weeks after procedure. Changes in pain over time were statistically determined using the Friedman nonparametric repeated measures ANOVA with Dunn's post hoc test for multiple comparisons. By the fourth week after treatment, all patients had significantly reduced self-reported pain. Twelve weeks following the procedure the average pain level had reduced to only 2. No adverse reactions were reported in any of the patients. The authors concluded that granulated amniotic membrane and amniotic fluid can be successfully used to treat both chronic plantar fasciosis and Achilles tendinosis. This study is limited by a small number of participants and lack of randomization and control. Further high quality studies in larger patient populations are needed to validate these results.

PriMatrix

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

Sabolinski and Gibbons (2018) compared the effectiveness of bilayered 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.

Kavros et al. (2014) conducted a multicenter study to prospectively evaluate the healing outcomes of chronic diabetic foot ulcers (DFUs) treated with PriMatrix, a fetal bovine acellular dermal matrix. For inclusion, the subjects were required to have a chronic DFU that ranged in area from 1 to 20 cm² and failed to heal more than 30% during a 2-week screening period when treated with moist wound therapy. A total of 55 subjects were enrolled at 9 US centers with 46 subjects progressing to study completion. Ulcers had been in existence for an average of 286 days, and initial mean ulcer area was 4.34 cm². PriMatrix was secured into a clean, sharply debrided wound; dressings were applied to maintain a moist wound environment, and the DFU was pressure off-loaded. Wound area measurements were taken weekly for up to 12 weeks, and PriMatrix was reapplied at the discretion of the treating physician. The results showed 76% of ulcers were healed by 12 weeks with a mean time to healing of 53.1 ± 21.9 days. The mean number of applications for these healed wounds was 2.0 ± 1.4, with 59.1% healing with a single application of PriMatrix and 22.9% healing with 2 applications. For subjects not healed by 12 weeks, the average wound area reduction was 71.4%. The authors concluded that these results demonstrate that the use of PriMatrix integrated with standard-of-care therapy is a successful treatment regimen to heal DFUs. This study is limited by a small number of participants and lack of randomization and control.

Lullove (2012) retrospectively compiled and analyzed the clinical application and effectiveness of an extracellular matrix biomaterial derived from fetal bovine dermis (PriMatrix) in patients treated by a single physician and monitored postsurgically in an outpatient wound care center. A retrospective medical record review was conducted of consecutive patients treated from January 2007 through January 2009 with meshed PriMatrix after sharp/surgical debridement and coverage with standard moist wound therapy dressings. Twenty-nine patients with 34 wounds were analyzed. All of the wounds were unresponsive to conservative treatment owing to complications, including infection, exposed bone or tendon, and other comorbidities known to delay healing. There were 11 diabetic ulcers, 8 venous stasis ulcers, 10 nonhealing traumatic wounds, and 5 other chronic wounds. The results showed that thirty of 34 wounds healed, with four patients lost to follow-up. Mean time to healing for diabetic foot ulcers was 105 days with an average of 2.6 PriMatrix applications. Mean time to healing for venous, traumatic, and other chronic wounds was 74 to 82 days with an average of 1.2 to 1.4 PriMatrix applications. The author concluded that in patients with comorbidities known to delay healing, the implantation of PriMatrix promoted the healing and, ultimately, full reepithelialization of otherwise unresponsive wounds of varied etiology, including those with complications of infection or exposed bone or tendon. This study is limited by a small number of participants and lack of randomization and control.

ProMatrX

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.

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.

PuraPly, PuraPly AM (formerly called FortaDerm), or PuraPly XT

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.

An ECRI report for PuraPly Wound Matrices for treating acute and chronic wounds indicated that the evidence for this product is inconclusive because no evidence is available (ECRI, 2018).

A Hayes report for PuraPly Antimicrobial Wound Matrix indicated that there is limited evidence to determine the safety and efficacy of PuraPly for wound care (Hayes, 2018).

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

Repriza

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

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.

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.

Revita

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.

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.

Revitalon

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

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.

SkinTE

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

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.

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 for 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 end-points 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 end-points did not reach statistical significance. These findings are in line with those of a recent consensus review from a European working group (Köckerling et al., 2018) that does not recommend the routine use of biologic meshes for abdominal wall reconstruction.

Huntington et al. (2016) conducted a study to examine long-term outcomes of biologic mesh for ventral hernia repair in a tertiary care institution. Prospective operative outcomes data was queried for open ventral hernia repair with biologic mesh. Univariate and multivariate analysis were used to compare mesh outcomes. 223 patients underwent open ventral hernia repair with biologic mesh, including 40 with Alloderm, 23 AlloMax, 70 FlexHD, 68 Strattice, and 22 Xenmatrix. Biologic mesh was used as a fascial bridge in 19.6%, component separation was performed in 47.5%, and 82% had concomitant procedure. Inpatient

mortality was 1.4%. Hernia recurrence varied significantly by mesh type: 35% Alloderm, 34.5% AlloMax, 37.1% FlexHD, 14.7% Strattice, and 59.1% Xenmatrix. The mean follow-up was 18.2 months. After multivariate analysis comparing to Strattice, AlloMax had a 3.4 higher odds ratio for recurrence, FlexHD a 2.9 odds ratio, and Xenmatrix a 7.8 odds ratio. The rate of mesh infections requiring explantation was <1%. The authors concluded that these results showed that Strattice, a porcine acellular dermal mesh, had significantly lower odds of hernia recurrence compared with AlloMax, FlexHD, and Xenmatrix, and that the choice of biologic mesh affects long-term postoperative outcomes in ventral hernia repair. This study is limited by a small number of participants and lack of randomization and control.

Stravix and StravixPL

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.

Sundblad and Tassis (2018) conducted a pilot study to assess the use of a viable cryopreserved umbilical tissue (vCUT) (Stravix) as a complementary surgical wrap in 5 primary tendon repair cases, with particular focus on the peroneus brevis. All patients were followed for an average of 24.15 months after surgery. For primary safety measures, erythema, tenderness, drainage, heat, and swelling was absent in all 5 surgical sites. None of the patients required post-op use of narcotics past day 7. The potential for long-term rehabilitative improvement with adjunct use of vCUT was also demonstrated through reduced pain and reduced transition times to functional and non-assisted ambulation in normal shoe wear as compared to historical controls managed without vCUT. The authors concluded that these preliminary findings demonstrate favorable clinical and rehabilitative outcomes over historically observed controls. A prospective randomized study, comparing vCUT utilization in surgical tendon repair to non-augmented controls is necessary.

SurgiGRAFT

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.

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.

Talymed

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.

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

The product information on TenSIX is not currently available. 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.

TheraSkin

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

In a pilot prospective, head-to-head, single-site, randomized clinical trial, Towler et al. (2018) 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) 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 cm² that closed $\leq 40\%$ 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) 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 Apligraf, 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) 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.

An ECRI report for TheraSkin Human Skin Allograft indicated that the evidence for this product is inconclusive because there is not enough data (ECRI, 2019).

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

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

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.

TruSkin

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.

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.

WoundEx

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.

In a retrospective cohort study, Lullove (2017) evaluated a dehydrated, human amniotic membrane (WoundEx Membrane, Skye Biologics, Inc.) to treat 20 patients with wounds. The patients underwent a run-in period of 2 weeks, where standard of care was

used to clear the wound of bioburden. WoundEx was applied at weeks 1 (2 weeks post run-in), 3, and 5, if necessary. Wound measurements and photographs were performed weekly. Data were collected through a standard form in each patient's medical record to improve reliability and reproducibility. Reduction of bias was performed by selecting patients whose wounds already were established and in temporal sequence. In this review of 20 patients treated with WoundEx, the author was able to effectively close all wounds in approximately 9.9 weeks (69.3 days). A linear relationship was discovered between wound size in cm² and days to closure. Diabetic foot ulcers closed on average in 11.8 weeks (82.6 days) and venous leg ulcers in 9.2 weeks (64.4 days). No adverse events were noted secondary to WoundEx application, which shows this is a safe and effective treatment option. The authors concluded that the use of WoundEx allograft effectively closed diabetic foot ulcerations in 82.6 days and median wound closure in 69.3 days. The lack of a control group limits the validity of the results of this study.

WoundEx Flow

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.

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.

XCM BIOLOGIC

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.

Bassetti et al. (2016) conducted a systematic review was to evaluate the efficacy of XCM Biologic Tissue Matrix and other soft-tissue augmentation/correction methods in terms of increasing the peri-implant width of keratinized mucosa (KM) and/or gain of soft tissue volume during second-stage surgery. Overall, eight prospective studies (risk of bias: high) and two case series (risk of bias: high) were included. Depending on the surgical technique and graft material used, the enlargement of keratinized tissue (KT) ranged between -0.20 and 9.35 mm. An apically positioned partial-thickness flap/ vestibuloplasty (APPTF/VP) in combination with a free gingival graft (FGG) or a xenogeneic graft material (XCM) was most effective. Applying a roll envelope flap (REF) or an APPTF in combination with a subepithelial connective tissue graft (SCTG), mean increases in soft tissue volumes of 2.41 and 3.10 mm, respectively, were achieved. Due to the heterogeneity of study designs, no meta-analysis could be performed. According to the authors, within the limitations of this review, regarding the enlargement of peri-implant KT, the APPTF in the maxilla and the APPTF/VP in combination with FGG or XCM in the lower and upper jaw seem to provide acceptable outcomes.

Atieh et al. (2016) conducted a systematic review and meta-analysis to evaluate the clinical and patient-centered outcomes of xenogeneic collagen matrix (XCM) compared to other mucogingival procedures. Applying guidelines of the Preferred Reporting Items for Systematic Reviews and Meta analyses statement, randomized controlled trials were searched for in electronic databases and complemented by hand searching. The risk of bias was assessed using the Cochrane Collaboration's Risk of Bias tool and data were analyzed using statistical software. A total of 645 studies were identified, of which, six trials were included with 487 mucogingival defects in 170 participants. Overall meta-analysis showed that connective tissue graft (CTG) in conjunction with the coronally advanced flap (CAF) had a significantly higher percentage of complete/mean root coverage and mean recession reduction than XCM. Insufficient evidence was found to determine any significant differences in width of keratinized tissue (KT) between XCM and CTG. The XCM had a significantly higher mean root coverage, recession reduction and gain in KT compared to CAF alone. No significant differences in patient's aesthetic satisfaction were found between XCM and CTG, except for postoperative morbidity in favor of XCM. Operating time was significantly reduced with the use of XCM compared with CTG but not with CAF alone. According to the authors, there is no evidence to demonstrate the effectiveness of XCM in achieving greater root coverage, recession reduction and gain in KT compared to CTG plus CAF. Superior short-term results in treating root coverage compared with CAF alone are possible. There is limited evidence that XCM may improve aesthetic satisfaction, reduce postoperative morbidity and shorten the operating time. The authors stated that further long-term randomized controlled trials are required to endorse the supposed advantages of XCM.

XWRAP

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.

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.

Many skin and tissue substitutes are included in research studies that are registered with ClinicalTrials.gov which is a registry and results database of publicly and privately supported research studies conducted in the United States and around the world. See the following for more information: www.clinicaltrials.gov and search by specific product name.

Other Organizations and Technology Assessments

The National Institute for Health and Care Excellence (NICE) 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 2016).

The Agency for Healthcare Research and Quality (AHRQ) Technology Assessment Report on Skin Substitutes for Treating Chronic Wounds states that applicability of the evidence base to address important questions about the effectiveness of skin substitutes in typical populations is limited. The overall applicability of the evidence base is limited to a small number of skin substitute products examining diabetic foot ulcers and venous and/or arterial leg ulcers and to patients in generally good health. According to the authors, the studies that are available are not generalizable to broader patient populations that are not as healthy as the patients in the reviewed studies. According to the AHRQ report, additional studies in this area of wound care would be helpful to provide treatment data for many of the other skin substitute products, to allow better comparisons between wound care products, and to provide better information on wound recurrence when using skin substitute products (AHRQ 2012).

AHRQ (2013) completed a comparative effectiveness review of treatment modalities for chronic venous ulcers. Due to the insufficient evidence, AHRQ was unable to draw conclusions regarding the effectiveness of acellular human skin equivalent dressings vs. compression, or cellular (cryo-preserved human fibroblast-derived dermal substitute) vs. compression.

In 2015, the International Working Group on the Diabetic Foot (IWGDF) released a clinical guideline for guidance 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 (Game et al., 2016). For use of topically applied treatments, the IWGDF recommended that clinicians not select agents reported to improve wound healing by altering the biology of the wound, including growth factors, bioengineered skin products, and gases, in preference to accepted standards of good quality care. The IWGDF considered the available evidence to be of low quality, and their recommendation was strong (i.e., based on the quality of evidence, balance between benefits and harms, patient values and preferences, and costs or resource utilization).

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:

- 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).

Society for Vascular Surgery and the American Venous Forum (SVS/AVF)

The SVS/AVF published guidelines for the management of venous leg ulcers for all aspects of diagnosing and treating venous ulcers (O'Donnell et al., 2014). They suggest the use of split-thickness skin grafting, allogenic bilayer skin replacements, or porcine small intestinal submucosal tissue adjunctive to wound care and compression therapy in patients whose wounds have not healed within 4 to 6 weeks of standard care. The strength of the recommendation is based on the grading of recommendation assessment, development, and evaluation (GRADE) system, in which GRADE 1 is strong (recommend), GRADE 2 is weak (suggest), and the quality of evidence is rated A, B, or C by standard evidence-based methodologic criteria. The guidelines state the following:

- Guideline 4.20: Cellular Therapy. Suggest the use of cultured allogeneic bilayer skin replacements (with both epidermal and dermal layers) to increase the chances for healing in patients with difficult to heal venous leg ulcers in addition to compression therapy in patients who have failed to show signs of healing after standard therapy for 4 to 6 weeks (GRADE 2A).
- Guideline 4.22: Frequency of Cellular Therapy Application. Suggest reapplication of cellular therapy as long as the venous leg ulcer continues to respond on the basis of wound documentation (GRADE 2C).
- Guideline 4.23: Tissue Matrices, Human Tissues, or Other Skin Substitutes. Suggest the use of a porcine small intestinal submucosal tissue construct in addition to compression therapy for the treatment of venous leg ulcers that have failed to show signs of healing after standard therapy for 4 to 6 weeks (GRADE 2B).

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. See 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. See 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. See the following website for more information: <http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/RegulationofTissues/ucm150485.htm>.

- Humanitarian Device Exemption (HDE): The regulatory pathway for products intended for diseases or conditions that affect small populations, or are rare. See the following website for more information:
<https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/humanitariandeviceexemption/default.htm>.

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Policy History/Revision Information

Date	Summary of Changes
10/01/2021	<p>Applicable Codes</p> <ul style="list-style-type: none"> Updated list of applicable HCPCS codes to reflect quarterly edits; added Q4251, Q4252, and Q4253 <p>Supporting Information</p> <ul style="list-style-type: none"> Archived previous policy version CS153NJ.G

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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