

SKIN AND SOFT TISSUE SUBSTITUTES

Policy Number: SURGERY 109.3 T2

Effective Date: January 1, 2019

[Instructions for Use](#) ⓘ

Table of Contents	Page
CONDITIONS OF COVERAGE	1
COVERAGE RATIONALE	1
DEFINITIONS	2
APPLICABLE CODES	3
DESCRIPTION OF SERVICES	4
CLINICAL EVIDENCE	5
U.S. FOOD AND DRUG ADMINISTRATION	29
REFERENCES	30
POLICY HISTORY/REVISION INFORMATION	35
INSTRUCTIONS FOR USE	35

Related Policies
<ul style="list-style-type: none"> • Bone or Soft Tissue Healing and Fusion Enhancement Products • Breast Reconstruction Post Mastectomy • Platelet Derived Growth Factors for Treatment of Wounds

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package
Referral Required (Does not apply to non-gatekeeper products)	No ^{1,2}
Authorization Required (Precertification always required for inpatient admission)	Yes ^{1,2}
Precertification with Medical Director Review Required	Yes ^{1,2}
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	All ²
Special Considerations	<p>¹Review by a Medical Director or their designee is required</p> <p>²Participating Providers in the Office Setting: Precertification is required for services performed in the office of a participating provider. Non-Participating/Out-of-Network Providers in the Office Setting: Precertification is not required, but is encouraged for out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.</p>

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](#) in individuals who require such a covering before autograft placement.

TransCyte is unproven and not medically necessary for all other indications.

Additional studies are needed to evaluate the safety and effectiveness of TransCyte for other indications.

Other Skin and Soft Tissue Substitutes

The following skin and soft tissue substitutes are unproven and not medically necessary for any indication*:

- Affinity[®]
- Alloskin[®]
- Allowrap[®]
- Amnio Wound[™]
- Amnioband[®]
- Amnioexcel[™] or Biodexcel[™]
- AmnioFix[®]
- Amniomatrix[™] or Biodmatrix[™]
- Architect Extracellular Matrix[®]
- Artacent[®]
- ArthroFLEX[®]
- Bio-ConneKt[®]
- Biodfence[™] or Biodfence Dryflex[™]
- BioSkin[™]
- BioSkin[™] Flow
- Biovance[®]
- Clarix[®]
- Clarix[®] Flo
- Conexa[™] Reconstructive Matrix
- CorMatrix[®]
- Cygnus[™]
- Cymetra[™]
- Cytal[™]
- DermACELL^{®*} (see asterisked note below when DermACELL is used during breast reconstruction)
- Dermapure[™]
- DermaSpan[™]
- Dermavest[®] or Plurivest[®]
- Epicord[™]
- Epifix[®]
- Excellagen[®]
- Ez-derm[®]
- Floweramnioflo[™] or FlowerFlo[™]
- Floweramniopatch[™] or FlowerPatch[™]
- FlowerDerm[™]
- GammaGraft[™]
- Grafix[®]
- GrafixPL[®]
- Guardian
- Helicoll[™]
- Hmatrix[®]
- HYALOMATRIX[®]
- Integra[®] Flowable Wound Matrix
- InteguPly[®]
- Interfyl[™]
- Keramatrix[®]
- Kerecis[™] Omega3
- MatriStem[®]
- Mediskin[™]
- MemoDerm[™]
- Miroderm[™]
- NeoPatch[™]
- Neox[®]
- Neox Flo[®]
- Nushield[®]
- PalinGen[®] Amniotic Tissue Allograft and PalinGen[®] Flow products
- PriMatrix[®]
- ProMatrX[™]
- PuraPly[™] or PuraPly[™] Antimicrobial
- Repriza[®]
- Revita[™]
- Revitalon[®]
- Strattice[™]
- Talymed[®]
- Tensix[®]
- TheraSkin[®]
- TranZgraft[®]
- Truskin[™]
- WoundEx[™]
- WoundEx[™] Flow
- Xcm Biologic Tissue Matrix[®]

Due to limited studies, small sample sizes, and weak study designs, there is insufficient clinical evidence to conclude that these skin substitutes have an improved health outcome over standard therapies. Well-designed, randomized comparative clinical trials are needed to demonstrate the efficacy and safety of these products.

*Refer to the [Breast Reconstruction Post Mastectomy](#) policy 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 the member specific benefit plan document 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 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, 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 and GrafixPL Prime, per sq cm
Q4134	HMatrix, per sq cm
Q4135	Mediskin, per square centimeter
Q4136	Ez-derm, per square centimeter
Q4137	AmnioExcel 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

HCPCS Code	Description
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
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, per square centimeter
Q4166	Cytal, per square centimeter
Q4167	Truskin, per square centimeter
Q4168	Amnioband, 1 mg
Q4169	Artacent wound, per square centimeter
Q4170	Cygnus, per square centimeter
Q4171	Interfyl, 1 mg
Q4173	Palingen or palingen xplus, per square centimeter
Q4174	Palingen or promatrx, 0.36 mg per 0.25 cc
Q4175	Miroderm, per square centimeter
Q4176	Neopatch, per square centimeter
Q4177	Floweramnioflo, 0.1 cc
Q4178	Floweramniopatch, per square centimeter
Q4179	Flowerderm, per square centimeter
Q4180	Revita, per square centimeter
Q4181	Amnio wound, per square centimeter
Q4182	Transcyte, per square centimeter
Q4186	Epifix, per sq cm
Q4187	Epicord, per sq cm
Q4195	PuraPly, per sq cm
Q4196	PuraPly AM, 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 2017; 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 2017)

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 15, 2018)

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.

CLINICAL EVIDENCE

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.

Amnioband Viable Membrane and Guardian

Amnioband and Guardian (MTF Wound Care[®], a division of the Musculoskeletal Transplant Foundation) are human tissue allografts made of donated placental membrane. Although marketed under two different brand names, the products are identical.

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.

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.

Regulski (2017) conducted a small case series with the aim of evaluating a viable human amnion membrane allograft (vHAMA) for the treatment of chronic nonhealing wounds in elderly patients (aged > 65 years) with multiple comorbidities. Four patients (age range, 69-85 years) with 5 chronic wounds of varying etiologies and sizes (2 traumatic wounds, 2 diabetic foot ulcers, and 1 venous leg ulcer) that persisted for at least 4 weeks and failed previous treatment with standard of care were included in this study. Comorbidities included diabetes mellitus, obesity, polymyalgia rheumatica, lymphedema, peripheral vascular disease, steroid use, and neuropathy. All patients received vHAMA (AmnioBand Viable Membrane) once weekly or as deemed appropriate. All patients reached complete wound closure with no complications or adverse events. Mean time to closure was 4.8 weeks (range, 2-8 weeks) with an average of 4.2 grafts (range, 1-8). There was no wound recurrence. The authors concluded that the successful closure of wounds indicates the use of vHAMA may be beneficial for treatment of chronic wounds in elderly patients with comorbidities. This study is limited by a very small number of participants and the absence of a control group limits the ability to draw conclusions about the efficacy of vHAMA treatment for chronic wounds.

Amnioexcel 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.

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.

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.

Patel et al. (2015) conducted an observational study with retrospective data collection and propensity-matched analysis of patients undergoing placement of dehydrated human amnion/chorion membrane (dHACM) around the neurovascular bundle (NVB) during nerve-sparing (NS) robot-assisted laparoscopic prostatectomy (RARP). AmnioFix was placed over each neurovascular bundles (NVBs) as a nerve wrap in 58 patients. A similar group of 58 patients

was computer-matched with the AmnioFix group. dHACM use did not increase operative time, blood loss, or oncologic outcomes. Minimum 8-week follow-up was completed for all patients in both groups, with an average follow-up of 4 months. Continence at 8 weeks returned in 81.0% of dHACM patients and 74.1% of control patients (not significant). The mean time to continence was significantly shorter in dHACM patients (1.21 months) than in control patients (1.83 months). Potency at 8 weeks returned in 65.5% of dHACM patients and 51.7% of control patients. The mean time to potency was significantly shorter in dHACM patients (1.34 months) than in control patients (3.39 months). According to the authors, dHACM accelerated the return of continence and potency in patients following NS RARP, with no adverse effects. The authors indicated this study has several limitations; it is an observational study with retrospective data collection and is subject to patient recall bias. An adequately powered, prospective randomized trial of dHACM around the prostatic NVB needs to be conducted to further understand the treatment effect of this new approach.

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 Extracellular Matrix

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 (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.

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.

Carpenter et al. (2017) conducted a study of a small case series to report the clinical results of interpositional arthroplasty using acellular dermal matrix in 4 patients (age 32 to 42 years) for the treatment of advanced ankle osteoarthritis. The primary findings included relief of pain, with improvement in tibiotalar joint range of motion from a mean of 16.5° preoperatively to a mean of 31° postoperatively. All 4 patients underwent open arthrotomy of the anterior and posterior tibiotalar capsule with plafond exostectomy and debridement of all deleterious tissue within the ankle capsule, and ArthroFlex acellular dermal matrix applied. The follow-up period ranged from 12 to 18 months. The mean pre- and 12-month postoperative Association of Orthopaedic Foot and Ankle Society hindfoot-ankle scale scores were 35 and 88.5, respectively. The authors concluded that these outcomes suggest that interpositional tibiotalar arthroplasty using an acellular dermal matrix is successful in improving function and range of motion and decreasing pain. This study is limited by a small number of participants and lack of a control arm. Larger randomized controlled trials are needed and should include longer follow-up periods, histologic testing, and arthroscopic evaluations to further assess the durability of this procedure.

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 BioSkinFlow has a beneficial effect on health outcomes.

Biovance

Biovance (Alliqua Biomedical, Inc.) 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.

In a 2009 open-label pilot trial, Letendre et al. sought to determine the healing rates using Biovance for partial and full-thickness in 14 patients with chronic non healing diabetic foot ulcers, with a secondary objective of determining the time to complete wound closure and a safety profile. The results showed 60.1% of total participants received a benefit from using Biovance wound covering, and there were no adverse reactions to the tissue. The authors concluded that Biovance helps decrease healing time for patients with chronic nonhealing diabetic partial or full-thickness foot ulcers, and randomized, controlled studies may be warranted. This pilot trial is limited by a very small number of participants.

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

CLARIX Regenerative Matrix (Amnio 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 (Amnio 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.

Conexa Reconstructive Matrix

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.

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.

Rosario-Quinones et al. (2015) reviewed a series of congenital cardiac patients who had a reoperation after the implantation of CorMatrix patches. Of 25 patients who had received CorMatrix patches during cardiac operations, 6 patients had undergone reoperations. All patients had hemodynamically significant lesions at the site of the CorMatrix implantation. Explanted specimens were associated with an intense inflammatory reaction consisting of numerous eosinophils, histiocytes, and plasma cells, with accompanying granulation tissue and fibrosis. The authors concluded that reaction to implanted CorMatrix patches may cause hemodynamic dysfunction and produce an intense, predominantly eosinophilic inflammatory response with developing fibrosis. The authors indicated that although this study is limited to a small sample of congenital cardiac patients, precautions should be taken in its use in pediatric cardiac patients, and long-term follow-up is warranted.

Padalino et al. (2015) conducted a multicentric study to outline surgical indications and evaluate mid-term outcomes of porcine extracellular matrix (ECM) in surgery for congenital heart disease (CHD). The use of ECM was categorized into four major groups: A, valve repair; B, septal reconstruction; C, arterial plasty; D, other use. Primary endpoints of analysis were reintervention (either surgical or interventional) when related to ECM, and functional ECM failure. Secondary endpoints were evidence of calcification and of persistent inflammation at follow-up. One hundred and three patients (M/F = 61/42, median age 19.7 months, 1 day-62 years) underwent surgical repair for CHD. Among ECM use categories, 38 patients were in Group A, 16 in Group B, 71 in Group C and 7 in Group D. There were neither complications nor deaths related to ECM. At a median follow-up of 23.3 months, 19 patients underwent reoperation (ECM-related in 6); 11 patients underwent interventional cardiology procedures (ECM-related in 8). Re-interventions were significantly more frequent on the aortic valve and pulmonary arteries. In addition, interventional procedures on pulmonary arteries were significantly more frequent in infants <12 months. The authors concluded that surgical use of ECM in CHD repair is characterized by a suboptimal functional late performance on reconstruction of valve leaflet or pulmonary artery wall. According to the authors, longer follow-up and larger clinical experience may support these preliminary results on mid-term outcomes, so as to assess the optimal indication for an ECM graft.

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.

Milstein et al. (2005) conducted a retrospective review to reassess possible long-term results of patients with unilateral vocal fold paralysis who received Cymetra injection laryngoplasty between March 2001 and March 2004. Twenty patients were identified in the study population. Cymetra injection was performed an average of 45.1 months after onset of vocal fold paralysis, and average follow-up postinjection was 11.2 months. Preoperative voice samples and videostroboscopic findings were compared with the most recently available postoperative data to assess efficacy of the procedure. A panel of voice experts analyzed both vocal and vibratory function in these samples. In addition, pre- and postoperative voice-related quality of life measures and patients' self-ratings of voice outcomes were compared. The results showed when comparing pre- and postoperative measures, voice quality, glottal closure, and degree of vocal fold bowing were all improved by injection. Quality of life measures and patients' self-perceptions of vocal quality were also improved. Fifteen (75%) patients showed long-lasting results. Eight patients showed improvement for more than 12 months after injection. The authors concluded that Cymetra injection laryngoplasty offers improved vocal and vibratory function to patients with unilateral true vocal fold paralysis. This study was limited by a small sample size and lack of a control group.

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 and Cytal Burn 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 and/or burns. Evidence gaps remain on how well Cytal performs compared to other skin substitutes. (ECRI, 2017)

DermACELL

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

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 that 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.

A Hayes report for DermACELL Human Acellular Matrix concluded that the evidence is insufficient regarding the long term safety and efficacy of DermACELL for chronic wounds. (Hayes, 2018)

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 a duration of 56 weeks and healed in an average time of 10 weeks. Individual wound categories included diabetic foot ulcers, which healed in 8 weeks; venous leg ulcers, which healed in 11 weeks; and surgical/traumatic wounds, which healed in 11 weeks. This study was limited by a small sample size and lack of a control group.

DermaSpan

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.

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

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

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

Bianchi et al. (2017) 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 this 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.

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.

Ez-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.

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.

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 insufficient published evidence to evaluate this technology on patient outcomes for treatment of wounds. (Hayes, 2017)

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.

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 (Anika Therapeutics) 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.

In a 2018 prospective, noncomparative 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. (2011) 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.

A Hayes report for Hyalomatrix concluded that there is insufficient published evidence to assess the safety and/or health outcomes in the use of HYALOMATRIX for burns. (Hayes, 2017)

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 (Alliqua Biomedical, Inc.) is a decellularized and dehydrated placental disc (chorionic plate) derived extracellular matrix. Interfyl is intended for treating deep dermal wounds, irregularly-shaped and tunneling wounds, 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.

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.

Baldursson et al. (2015) compared the effect of fish skin acellular dermal matrix (ADM) against porcine small-intestine submucosa extracellular matrix in the healing of 162 full-thickness 4-mm wounds on the forearm of 81 volunteers. The fish skin product was noninferior at the primary end point, healing at 28 days. The wounds treated with fish skin acellular matrix healed significantly faster. These results might give the fish skin ADM an advantage because of its environmental neutrality when compared with livestock-derived products. The study results on these acute full-thickness wounds might apply for diabetic foot ulcers and other chronic full-thickness wounds, and the shorter healing time for the fish skin-treated group could influence treatment decisions. To test the autoimmune reactivity of the fish skin, the participants were tested with the following ELISA (enzyme-linked immunosorbent assay) tests: RF, ANA, ENA, anti-ds DNA, ANCA, anti-CCP, and anticollagen I and II. These showed no reactivity. The authors concluded that the study results demonstrate the claims of safety and efficacy of fish skin ADM for wound care. Further research with randomized controlled trials is needed to validate these findings.

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)

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, randomised, 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 randomised 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 a significantly lower cost per subject and 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.

A Hayes report for MatriStem Urinary Bladder Matrix Products concluded that the evidence from small studies suggest a potential benefit in wound management, but longer follow-ups and larger studies are needed to confirm these benefits. (Hayes, 2017)

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 (Amnio[®] 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 (Amnio[®] 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.

A Hayes report for Neox Wound Allograft concluded that there are very few published studies regarding Neox Wound Allograft and it is not possible to determine the efficacy of this product for the treatment of wounds. (Hayes, 2017)

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.

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 or PuraPly Antimicrobial (formerly called FortaDerm)

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.

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

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

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.

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.

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. 11 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 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.

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.

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.

A Hayes report for TheraSkin concluded that there is insufficient published evidence to assess the safety and/or impact on patient management of TheraSkin for treating non-healing wounds. (Hayes, 2017)

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 multicenter study, Purdue et al. (1997) compared the use of a biosynthetic human skin substitute [Dermagraft-TC (now known as TransCyte)] with frozen human cadaver allograft for the temporary closure of excised burn wounds. Burn wounds in 66 patients with a mean age of 36 years and a mean burn size of 44% total body surface area (28% total body surface area full-thickness) were surgically excised. Two comparable sites, each approximately

1% total body surface area in size, were randomized to receive either Dermagraft-TC or allograft. Both sites were then treated in the same manner. When clinically indicated (more than 5 days after application) both skin replacements were removed and the wound beds were evaluated and prepared for grafting. Dermagraft-TC was equivalent or superior to allograft with regard to autograft take at post-autograft day 14. Dermagraft-TC was also easier to remove, had no epidermal slough, and resulted in less bleeding than did allograft while maintaining an adequate wound bed. According to the authors, overall satisfaction was better with Dermagraft-TC.

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.

Kumar et al. (2004) compared the effectiveness of three burns dressings (TransCyte, a bio-engineered skin substitute; Biobrane; and Silvazine cream in treating children with partial-thickness burns. The primary objective was to determine the days until > or =90% re-epithelialization. The secondary objectives were to evaluate the number of wounds requiring autografting and the number of dressing changes/local wound care required. Study wounds were identified on each patient and the patients were randomized to receive TransCyte or Biobrane or Silvazine. Assessment of study wound closure began at 2 days after treatment and continued at least every other day until the wounds re-epithelialized or were autografted. A laser Doppler imaging system was used as an adjunct to assessing the depth of the burn. Thirty-three patients with 58 wound sites were enrolled in the study (TransCyte, n = 20, Biobrane, n = 17; Silvazine, n = 21). Mean time to re-epithelialization was 7.5 days for TransCyte, 9.5 days for Biobrane, and 11.2 days for Silvazine. The number of wounds requiring autografting were 5/21 (24%) for Silvazine, 3/17 (17%) for Biobrane, and 1/20 (5%) for TransCyte. The authors concluded that when used in partial-thickness burns in children, TransCyte promotes fastest re-epithelialization and required less overall dressings than Biobrane or Silvazine. Patients who received Silvazine or Biobrane require more autografting than those treated with TransCyte.

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 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.

George et al. (2014) reported the first series of using XCM Biologic Tissue Matrix for chest wall reconstruction. It was used either alone or in conjunction with the Synthes titanium system to provide additional support. Since April 2010, 21 (12 females) patients received the device. Average age at operation was 47 ± 17 years. Eleven (52%) patients had the patch inserted alone, while the remaining 10 received it in combination with another implantable medical device. The biological tissue matrix was used to reconstruct chest wall defects in cancer involving chest wall (n=9), chest wall deformity (n=6), chest wall hernia (n=5) and chest wall repair following empyema drainage (n=1). Complications occurred in 3 patients receiving the combined XCM and Synthes bar mechanisms; infection (n=2) and bar displacement and infection (n=1). The authors concluded that the XCM patch can be safely used to provide the

strength required for chest wall reconstruction and to replace previously infected reconstructions. This is an uncontrolled study with a small sample size.

Many of the skin and tissue substitutes listed 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).

Professional Societies

Infectious Diseases Society of America (IDSA)

In an evidence-based guideline on the diagnosis and treatment of diabetic foot infections (Lipsky et al., 2012), the IDSA states that no adjunctive therapy has been proven to improve resolution of infection, but for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents (strength of recommendation weak, quality of evidence moderate).

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 of 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, allogeneic 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)

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>. (Accessed May 15, 2018)
- **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>. (Accessed May 15, 2018)
- **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>. (Accessed May 15, 2018)
- **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>. (Accessed May 15, 2018)

REFERENCES

- The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2018T0592B]
- Agency for HealthCare Research and Quality (AHRQ). Chronic venous ulcers: a comparative effectiveness review of treatment modalities. Dec 2013.
- Agency for Healthcare Research and Quality (AHRQ). Skin substitutes for treating chronic wounds. Technology Assessment Report. December 18, 2012.
- Atieh MA, Alsabeeha N, Tawse-Smith A, et al. Xenogeneic collagen matrix for periodontal plastic surgery procedures: a systematic review and meta-analysis. *J Periodontol Res*. 2016 Aug;51(4):438-52.
- Baldursson BT, Kjartansson H, Konrádssdóttir F, et al. Healing rate and autoimmune safety of full-thickness wounds treated with fish skin acellular dermal matrix versus porcine small-intestine submucosa: A Noninferiority Study. *Int J Low Extrem Wounds*. 2015 Mar 9.
- Bassetti RG, Stähli A, Bassetti MA, et al. Soft tissue augmentation procedures at second-stage surgery: a systematic review. *Clin Oral Investig*. 2016 Sep;20(7):1369-87.
- Bianchi C, Cazzell S, Vayser D, et al.; EpiFix VLU Study Group. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix®) allograft for the treatment of venous leg ulcers. *Int Wound J*. 2017 Oct 11.
- Burkey B, Davis W 3rd, Glat PM. Porcine xenograft treatment of superficial partial-thickness burns in paediatric patients. *J Wound Care*. 2016 Feb;25(2):S10-5.
- Campitiello F, Mancone M, Della Corte A, et al. To evaluate the efficacy of an acellular flowable matrix in comparison with a wet dressing for the treatment of patients with diabetic foot ulcers: a randomized clinical trial. *Updates Surg*. 2017 Dec;69(4):523-529.
- Caravaggi C, Grigoletto F, Scuderi N. Wound bed preparation with a dermal substitute (Hyalomatrix® PA) facilitates re-epithelialization and healing: results of a multicenter, prospective, observational study on complex chronic ulcers (The FAST Study). *Wounds*. 2011 Aug; 23(8):228-35.
- Carpenter B, Duncan K, Ernst J, et al. Interposition ankle arthroplasty using Acellular Dermal Matrix: A small series. *J Foot Ankle Surg*. 2017 Jul - Aug;56(4):894-897.
- Davidson A, Jina NH, Marsh C, et al. Do functional keratin dressings accelerate epithelialization in human partial thickness wounds? A randomized controlled trial on skin graft donor sites. *Eplasty*. 2013 Aug 29;13:e45.
- Debels H, Hamdi M, Abberton K, et al. Dermal matrices and bioengineered skin substitutes: a critical review of current options. *Plast Reconstr Surg Glob Open*. 2015 Feb 6;3(1):e284.
- Demling RH, DeSanti L. Management of partial thickness facial burns (comparison of topical antibiotics and bio-engineered skin substitutes). *Burns*. 1999 May;25(3):256-61.
- Dhanraj P. A Clinical Study Comparing Helicoll with Scarlet Red and OpSite in the treatment of split thickness skin graft donor sites-a randomized controlled trial. *Indian J Surg*. 2015 Dec;77(Suppl 2):385-92.
- DiDomenico LA, Orgill DP, Galiano RD, et al. A retrospective crossover study of the use of aseptically processed placental membrane in the treatment of chronic diabetic foot ulcers. *Wounds*. 2017 Jul 26.
- DiDomenico LA, Orgill DP, Galiano RD, et al. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. *Plast Reconstr Surg Glob Open*. 2016 Oct 12;4(10):e1095.
- ECRI Institute. Hotline Response. Amniotic Membrane Transplantation for Ophthalmic Surgery, Wound Care, and Orthopedic Procedures. August 2014. Archived.
- ECRI Institute. Hotline Response. Amniotic Tissue Products for Wound Healing. August 2016. Archived.
- ECRI Institute. Hotline Response. Bioengineered Skin and Dermal Cell Replacement for Managing Chronic Diabetic and Venous Ulcers. March 2014. Archived.
- ECRI Institute. Product Brief. Affinity Human Amniotic Allograft (Nutech Medical) for Use in Chronic and Surgical Wounds. September 2015. Archived.
- ECRI Institute. Product Brief. AmnioBand Allograft Placental Matrix (MTF Wound Care) for Treating Surgical and Chronic Wounds. June 2016.
- ECRI Institute. Product Brief. AmnioFix Amnion/Chorion Membrane Allograft (MiMedx) for Surgical Wounds. July 2016.
- ECRI Institute. Product Brief. Arthroflex Decellularized Dermal Allograft (Arthrex, Inc.) for Repairing Rotator Cuff Tears. October 2017.

ECRI Institute. Product Brief. Biovance Amniotic Membrane Allograft (Alliqua Biomedical, Inc.) for Treating Wounds. January 2017.

ECRI Institute. Product Brief. Cytal Wound Matrix and Cytal Burn Matrix (ACell, Inc.) for Managing Wound Healing. October 2017.

ECRI Institute. Product Brief. Dermacell Advanced Decellularized Dermis (LifeNet Health Bio-Implants Division) for Breast Reconstruction. March 2018.

ECRI Institute. Product Brief. Dermacell Advanced Decellularized Dermis (LifeNet Health Bio-Implants Division) for Chronic Wound Care. March 2018.

ECRI Institute. Product Brief. Grafix Cellular Repair Matrix (Osiris Therapeutics, Inc.) for Treating Chronic Wounds. November 2012. Updated October 2015. Archived.

ECRI Institute. Product Brief. Helicoll (EnColl, Corp.) Type-I Collagen-based Sterile Dressing for Treating Burns and Wounds. August 2014. Archived.

ECRI Institute. Product Brief. NEOX Wound Allografts (AmnioX Medical, Inc.) for Treating Chronic and Surgical Wounds. December 2015. Archived.

ECRI Institute. Product Brief. NuShield Placental Allograft (Nutech Medical) for Use in Chronic and Surgical Wounds. September 2015. Archived.

ECRI Institute. Product Brief. XCM Biologic Tissue Matrix (Ethicon US, LLC) for Reconstructive Surgery. November 2015. Updated July 2016.

Ferreira M.C., Paggiaro A.O., Isaac C., et al., dos Santos G.B. Skin substitutes: current concepts and a new classification system. *Rev. Bras. Cir. Plást.* 2011;26:696–702.

Frykberg RG, Cazzell SM, Arroyo-Rivera J, et al. Evaluation of tissue engineering products for the management of neuropathic diabetic foot ulcers: an interim analysis. *J Wound Care.* 2016 Jul; 25 Suppl 7:S18-25.

Frykberg RG, Gibbons GW, Walters JL, et al. A prospective, multicentre, open-label, single-arm clinical trial for treatment of chronic complex diabetic foot wounds with exposed tendon and/or bone: positive clinical outcomes of viable cryopreserved human placental membrane. *Int Wound J.* 2017 Jun;14(3):569-577.

Game FL, Apelqvist J, Attinger C, et al. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. *Diabetes Metab Res Rev.* 2016;32(Suppl 1):154-168.

George RS, Kostopanagiotou K, Papagiannopoulos K. The expanded role of extracellular matrix patch in malignant and non-malignant chest wall reconstruction in thoracic surgery. *Interact Cardiovasc Thorac Surg.* 2014 Mar;18(3):335-9.

Gómez R, Cancio LC. Management of burn wounds in the emergency department. *Emerg Med Clin North Am.* 2007 Feb;25(1):135-46.

Hanselman AE, Tidwell JE, Santrock RD. Cryopreserved human amniotic membrane injection for plantar fasciitis: a randomized, controlled, double-blind pilot study. *Foot Ankle Int.* 2015 Feb;36(2):151-8.

Haugh AM, Witt JG, Hauch A, et al. Amnion membrane in diabetic foot wounds: a meta-analysis. *Plast Reconstr Surg Glob Open.* 2017 Apr 25;5(4):e1302.

Hayes, Inc. Health Technology Brief. EpiFix (MiMedx Group) for Treatment of Nonhealing Wounds. Lansdale, PA: Hayes, Inc.; August 2015. Updated June 2016. Archived November 2017.

Hayes Inc. Health Technology Brief. Injectable amniotic tissue-derived allografts for treatment of chronic plantar fasciitis. Lansdale, PA: Hayes. September 2016. Updated August 28, 2017.

Hayes, Inc. Clinical Research Response. Amniotic allografts for orthopedic indications. product comparison. Lansdale, PA: Hayes, Inc.; January 2017.

Hayes, Inc. Clinical Research Response. AmnioFix (MiMedx) for prostatectomy. Lansdale, PA: Hayes, Inc.; January 2016. Archived October 11, 2017.

Hayes, Inc. Clinical Research Response. BioDFence (BioDlogics LLC) Human Amniotic Allograft Lansdale, PA: Hayes, Inc.; March 9, 2018.

Hayes, Inc. Clinical Research Response. Clarix Regenerative Matrix. Lansdale, PA: Hayes, Inc.; January 2015. Archived July 6, 2017.

Hayes, Inc. Clinical Research Response. CorMatrix CanGaroo Envelope (CorMatrix Cardiovascular Inc.). Lansdale, PA: Hayes, Inc.; November 2016. Archived January 2, 2018.

Hayes Inc. Clinical Research Response. Cryopreserved Versus Dehydrated Placental/Amniotic Allografts. Lansdale, PA: Hayes, Inc.; October 2017.

Hayes Inc. Clinical Research Response. DermACELL Human Acellular Matrix (Novodaq) for Nonhealing Wounds. Lansdale, PA: Hayes, Inc.; March 2018.

Hayes Inc. Clinical Research Response. PalinGen Amniotic Tissue Allografts (Amnio ReGen Solutions LLC) for Orthopedic Indications. Lansdale, PA: Hayes. December 2015. Archived October 11, 2017.

Hayes Inc. Comparative Effectiveness Review. Skin Substitutes for Chronic Foot Ulcers in Adults with Diabetes Mellitus: A Review of Reviews. Lansdale, PA: Hayes. November 2017.

Hayes Inc. Comparative Effectiveness Review. Skin Substitutes for Chronic Venous Leg Ulcers in Adults: A Review of Reviews. Lansdale, PA: Hayes. November 2017.

Hayes, Inc. Product Comparison. Flowable amniotic tissue allografts for neurosurgical use. Lansdale, PA: Hayes, Inc.; January 2015. Archived July 6, 2017.

Hayes, Inc. Search and Summary. Grafix Cryopreserved Placental Membrane (Osiris Technologies Inc.) for Treatment of Diabetic Foot Ulcer. Lansdale, PA: Hayes, Inc.; June 2016. Archived July 3, 2017.

Hayes, Inc. Search and Summary. Grafix Cryopreserved Placental Membrane (Osiris Technologies Inc.) for Treatment of Chronic Nonhealing Wounds. Lansdale, PA: Hayes, Inc.; August 25, 2017.

Hayes, Inc. Search and Summary. Hyalomatrix (Anika Therapeutics) for treatment of partial and full thickness wounds. Lansdale, PA: Hayes, Inc.; September 2015. Archived March 2017.

Hayes, Inc. Search and Summary. Kerecis Omega3 Skin Substitute (Kerecis Limited) for Treatment of Wounds. Lansdale, PA: Hayes, Inc.; June 2018.

Hayes, Inc. Search and Summary. Neox Wound Allograft (Amnio Medical) for treatment of wounds. Lansdale, PA: Hayes, Inc.; February 2017.

Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg.* 2016;63(2 Suppl):3S-21S.

Huntington CR, Cox TC, Blair LJ, et al. Biologic mesh in ventral hernia repair: Outcomes, recurrence, and charge analysis. *Surgery.* 2016 Dec; 160(6):1517-1527.

Johnson EL, Marshall JT, Michael GM. A comparative outcomes analysis evaluating clinical effectiveness in two different human placental membrane products for wound management. *Wound Repair Regen.* 2017 Jan;25(1):145-149.

Karlsson M, Lindgren M, Jarnhed-Andersson I, et al. Dressing the split-thickness skin graft donor site: a randomized clinical trial. *Adv Skin Wound Care.* 2014 Jan;27(1):20-5.

Kavros SJ, Dutra T, Gonzalez-Cruz R, et al. The use of PriMatrix, a fetal bovine acellular dermal matrix, in healing chronic diabetic foot ulcers: a prospective multicenter study. *Adv Skin Wound Care.* 2014 Aug; 27(8):356-62.

Kelechi TJ, Mueller M, Hankin CS, et al. A randomized, investigator-blinded, controlled pilot study to evaluate the safety and efficacy of a poly-N-acetyl glucosamine-derived membrane material in patients with venous leg ulcers. *J Am Acad Dermatol.* 2012 Jun;66(6):e209-15.

Kelley TM Jr, Kashem M, Wang H, et al. Anterior leaflet augmentation with cormatrix porcine extracellular matrix in twenty-five patients: unexpected patch failures and histologic analysis. *Ann Thorac Surg.* 2017 Jan;103(1):114-120.

Kimmel H, Gittleman H. Retrospective observational analysis of the use of an architecturally unique dermal regeneration template (Derma Pure®) for the treatment of hard-to-heal wounds. *Int Wound J.* 2017 Aug;14(4):666-672.

Kirsner RS, Sabolinski ML, Parsons NB, et al. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. *Wound Repair Regen.* 2015 Sep;23(5):737-44.

Kumar RJ, Kimble RM, Boots R, et al. Treatment of partial-thickness burns: a prospective, randomized trial using Transcyte. *ANZ J Surg.* 2004 Aug;74(8):622-6.

Landsman AS, Cook J, Cook E, et al. A retrospective clinical study of 188 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin) on the treatment of diabetic foot ulcers and venous leg ulcers. *Foot Ankle Spec.* 2011 Feb;4(1):29-41.

Laurent I, Astère M, Wang KR, et al. Efficacy and time sensitivity of amniotic membrane treatment in patients with diabetic foot ulcers: a systematic review and meta-analysis. *Diabetes Ther.* 2017 Oct;8(5):967-979.

Lavery LA, Davis KE, Berriman SJ, et al. WHS guidelines update: Diabetic foot ulcer treatment guidelines. *Wound Repair Regen.* 2016 Jan-Feb;24(1):112-26.

Lavery LA, Fulmer J, Shebetka KA, et al. Grafix Diabetic Foot Ulcer Study Group. The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J*. 2014 Oct;11(5):554-60.

Lederman ES, Toth AP, Nicholson GP, et al. A prospective, multicenter study to evaluate clinical and radiographic outcomes in primary rotator cuff repair reinforced with a xenograft dermal matrix. *J Shoulder Elbow Surg*. 2016 Dec;25(12):1961-1970.

Letendre S, LaPorta G, O'Donnell E, et al. Pilot trial of biovance collagen-based wound covering for diabetic ulcers. *Adv Skin Wound Care*. 2009 Apr; 22(4):161-6.

Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012; 54(12):e132-e173.

Loan F, Cassidy S, Marsh C, et al. Keratin-based products for effective wound care management in superficial and partial thickness burns injuries. *Burns*. 2016; 42(3):541-547.

Lullove E. Acellular fetal bovine dermal matrix in the treatment of nonhealing wounds in patients with complex comorbidities. *J Am Podiatr Med Assoc*. 2012 May-Jun;102(3):233-9.

Lullove EJ. Use of a dehydrated amniotic membrane allograft in the treatment of lower extremity wounds: a retrospective cohort study. *Wounds*. 2017 Nov;29(11):346-351.

Marston W, Tang J, Kirsner RS, et al. Wound Healing Society 2015 update on guidelines for venous ulcers. *Wound Repair Regen*. 2016 Jan-Feb;24(1):136-44.

Milstein CF, Akst LM, Hicks MD, et al. Long-term effects of micronized Alloderm injection for unilateral vocal fold paralysis. *Laryngoscope*. 2005 Sep;115(9):1691-6.

Miranda EP, Friedman A. Dehydrated human amnion/chorion grafts may accelerate the healing of ulcers on free flaps in patients with venous insufficiency and/or lymphedema. *Eplasty*. 2016 Sep 7;16:e26.

Moravvej H, Hormozi AK, Hosseini SN, et al. Comparison of the application of allogeneic fibroblast and autologous mesh grafting with the conventional method in the treatment of third-degree burns. *J Burn Care Res*. 2016 Jan-Feb;37(1):e90-5.

Mosala Nezhad Z, Poncelet A, de Kerchove L, et al. Small intestinal submucosa extracellular matrix (CorMatrix®) in cardiovascular surgery: a systematic review. *Interact Cardiovasc Thorac Surg*. 2016 Jun;22(6):839-50.

National Institute for Health and Care Excellence (NICE). NICE Clinical Guideline 19. Diabetic foot problems: prevention and management. London (UK): Published August 2015. Last updated January 2016.

Nicholas MN, Jeschke MG, Amini-Nik S. Methodologies in creating skin substitutes. *Cell Mol Life Sci*. 2016 Sep;73(18):3453-72.

Noordenbos J, Doré C, Hansbrough JF. Safety and efficacy of TransCyte for the treatment of partial-thickness burns. *J Burn Care Rehabil*. 1999 Jul-Aug;20(4):275-81.

O'Donnell TF Jr, Passman MA, Marston WA, et al.; Society for Vascular Surgery; American Venous Forum. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2014;60(2 Suppl):3S-59S.

Padalino MA, Quarti A, Angeli E, et al. Early and mid-term clinical experience with extracellular matrix scaffold for congenital cardiac and vascular reconstructive surgery: a multicentric Italian study. *Interact CardioVasc Thorac Surg* 2015;21:40-9.

Paggiaro AO, Menezes AG, Ferrassi AD, et al. Biological effects of amniotic membrane on diabetic foot wounds: a systematic review. *J Wound Care*. 2018 Feb 1;27(Sup2):S19-S25.

Patel VR, Samavedi S, Bates AS, et al. Dehydrated human amnion/chorion membrane allograft nerve wrap around the prostatic neurovascular bundle accelerates early return to continence and potency following robot-assisted radical prostatectomy: propensity score-matched analysis. *Eur Urol*. 2015 Jun;67(6):977-80.

Pham C, Greenwood J, Cleland H, et al. Bioengineered skin substitutes for the management of burns: a systematic review. *Burns*. 2007 Dec;33(8):946-57.

Purdue GF, Hunt JL, Still JM Jr, et al. A multicenter clinical trial of a biosynthetic skin replacement, Dermagraft-TC, compared with cryopreserved human cadaver skin for temporary coverage of excised burn wounds. *J Burn Care Rehabil*. 1997;18(1):52-57.

Regulski M. Utilization of a viable human amnion membrane allograft in elderly patients with chronic lower extremity wounds of various etiologies. *Wounds*. 2018 Mar;30(3):E36-E40.

Rosario-Quinones F, Magid MS, Yau J, et al. Tissue reaction to porcine intestinal Submucosa (CorMatrix) implants in pediatric cardiac patients: a single-center experience. *Ann Thorac Surg*. 2015 Apr;99(4):1373-7.

Santema TB, Poyck PP, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev*. 2016 Feb 11;2:CD011255.

Serena TE, Carter MJ, Le LT, et al; EpiFix VLU Study Group. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. *Wound Repair Regen*. 2014 Nov-Dec;22(6):688-93.

Serena TE, Yaakov R, DiMarco D, et al. Dehydrated human amnion/chorion membrane treatment of venous leg ulcers: correlation between 4-week and 24-week outcomes. *J Wound Care*. 2015 Nov;24(11):530-4.

Simman R, Mari W, Younes S, Wilson M. Use of hyaluronic acid-based biological bilaminar matrix in wound bed preparation: a case series. *Eplasty*. 2018 Feb 22;18:e10. eCollection 2018.

Sivak WN, Bourne DA, Miller MP, et al. Simplified calvarial reconstruction: coverage of bare skull with GammaGraft promotes granulation and facilitates skin grafting. *J Craniofac Surg*. 2016 Oct;27(7):1808-1809.

Snyder RJ, Shimozaki K, Tallis A, et al. A Prospective, randomized, multicenter, controlled evaluation of the use of dehydrated amniotic membrane allograft compared to standard of care for the closure of chronic diabetic foot ulcer. *Wounds*. 2016 Mar;28(3):70-7.

Tan M, Woo P. Injection laryngoplasty with micronized dermis: a 10-year experience with 381 injections in 344 patients. *Laryngoscope*. 2010Dec;120(12):2460-6.

Trippoli S, Caccese E, Tulli G, et al. Biological meshes for abdominal hernia: Lack of evidence-based recommendations for clinical use. *Int J Surg*. 2018 Mar 2; 52:278-284.

Troy J, Karlinski R, Downes K, et al. The Use of EZ Derm[®] in partial-thickness burns: an institutional review of 157 patients. *Eplasty*. 2013;13:e14.

Tsipopoulos K, Vasiliadis HS, Mavridis D. Injection therapies for plantar fasciopathy ('plantar fasciitis'): a systematic review and network meta-analysis of 22 randomised controlled trials. *Br J Sports Med*. 2016 Nov;50(22):1367-1375.

Vig K, Chaudhari A, Tripathi S, et al. Advances in skin regeneration using tissue engineering. *Int J Mol Sci*. 2017 Apr 7;18(4).

Walters J, Cazzell S, Pham H, et al. Healing rates in a multicenter assessment of a sterile, room temperature, acellular dermal matrix versus conventional care wound management and an active comparator in the treatment of full-thickness diabetic foot ulcers. *Eplasty*. 2016 Feb 4;16:e10.

Werber B. Amniotic tissues for the treatment of chronic plantar fasciosis and achilles tendinosis. *J Sports Med (Hindawi Publ Corp)*. 2015; 2015:219896.

Yang CK, Polanco TO, Lantis JC 2nd. A prospective, postmarket, compassionate clinical evaluation of a novel acellular fish-skin graft which contains Omega-3 Fatty Acids for the closure of hard-to-heal lower extremity chronic ulcers.wounds. 2016 Apr;28(4):112-8.

Zelen CM, Gould L, Serena TE, et al. A prospective, randomized, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. *Int Wound J*. 2015 Dec;12(6):724-32.

Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. *Foot Ankle Int*. 2013a;34(10):1332-1339.

Zelen CM, Serena TE, Denozziere G, et al. A prospective randomized comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *Int Wound J*. 2013b Oct;10(5):502-7.

Zelen CM, Serena TE, Fetterolf DE. Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: A long-term follow-up study. *Wound Medicine*. 2014a; 4:1-4.

Zelen CM, Serena TE, Gould L, Le L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. *Int Wound J*. 2016 Apr;13(2):272-82.

Zelen CM, Serena TE, Snyder RJ. A prospective, randomized comparative study of weekly versus biweekly application of dehydrated human amnion/chorion membrane allograft in the management of diabetic foot ulcers. *Int Wound J*. 2014b Apr;11(2):122-8.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2019	<ul style="list-style-type: none">• Updated list of applicable HCPCS codes to reflect annual code edits:<ul style="list-style-type: none">○ Added Q4186, Q4187, Q4195, and Q4196○ Removed Q4131 and Q4172• Archived previous policy version SURGERY 109.2 T2

INSTRUCTIONS FOR USE

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

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.