Cigna Medical Coverage Policy

Subject **Tissue-Engineered Skin Substitutes**

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Coverage Policy

Cigna covers each of the following as medically necessary for wound closure:

- autologous skin graft (CPT® Codes 15040-15261)
- unprocessed allogeneic human, cadaver-derived skin graft (CPT® Codes 15271-15278)
- unprocessed allogeneic pig skin derived skin graft (CPT® Codes 15271-15278)

Cigna covers each of the following products as indicated:

Skin Substitute/ Platelet Derived Growth Factor	Indication	Criteria	Application CPT/HCPCS Codes	Product HCPCS Codes
AlloDerm®	Breast reconstruction	Covered as medically necessary when used in association with a covered, medically necessary breast reconstruction procedure	15271-15274 15777	Q4116
AlloMax™	Breast reconstruction	Covered as medically necessary when used in association with a covered, medically necessary breast reconstruction procedure	15271-15274 15777 C5271-C5274	C1781 Q4100
Apligraf®	Diabetic foot ulcer	Covered as medically necessary when ALL of the following criteria are met: • full-thickness diabetic foot ulcer of greater than three weeks duration for which standard wound therapy has failed • type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12% • treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70 When the above medical necessity criteria are met, the following conditions of coverage apply: • treatment is limited to one initial application • additional applications at a minimum of one week intervals, for up to a maximum of four in 12 weeks are considered medically necessary when evidence of wound healing is present (e.g., signs of epithelialization and reduction in ulcer size) Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.	15275-15278	Q4101
Apligraf®	Venous stasis ulcer	Covered as medically necessary when BOTH of the following criteria are met: • partial- or full-thickness venous stasis ulcer of greater than four weeks duration for which standard wound therapy has failed • treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70 When the above medical necessity criteria are met, the following conditions of coverage apply:	15271-15274	Q4101

Skin Substitute/ Platelet Derived Growth Factor	Indication	Criteria	Application CPT/HCPCS Codes	Product HCPCS Codes
		• treatment is limited to one initial application • additional applications at a minimum of one week intervals, for up to a maximum of four in 12 weeks when evidence of wound healing is present (e.g., signs of epithelialization and reduction in ulcer size) Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.		
Biobrane	Burn wound	Covered as medically necessary when used for temporary covering of a partial-thickness freshly debrided or excised burn wound	15271-15278 C5271-C5278	Q4100
Biobrane-L	Burn wound	Covered as medically necessary when BOTH of the following criteria are met: • temporary covering of a partial-thickness freshly debrided or excised burn wound • adjunct to meshed autograft	15271-15278 C5271-C5278	Q4100
Dermagraft®	Diabetic foot ulcer	Covered as medically necessary when ALL of the following criteria are met: • full-thickness diabetic foot ulcer of greater than six weeks duration for which standard therapy has failed • type I or type II diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12% • treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70 When the above medical necessity criteria are met, the following conditions of coverage apply: • treatment is limited to one initial application • additional applications for up to a maximum of eight in 12 weeks when there is evidence of wound healing (e.g., signs of epithelialization and reduction in ulcer size) Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.	15275-15278	Q4106
Epicel	Burn wound	Covered as medically necessary when used according to the U.S. Food and	15150-15157 C5271-C5278	Q4100

Skin Substitute/ Platelet Derived Growth Factor	Indication	Criteria	Application CPT/HCPCS Codes	Product HCPCS Codes
		Drug Administration (FDA)-approved Humanitarian Device Exemption (HDE) for an individual with deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30%		
EpiFix® Amniotic Membrane	Diabetic foot ulcer	Covered as medically necessary when ALL of the following criteria are met: • partial or full-thickness, diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed • type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12% • treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70 When the above medical necessity criteria are met, the following conditions of coverage apply: • treatment is limited to one initial application • additional applications may be applied at a minimum of one week intervals, for up to a maximum of four in 12 weeks are considered medically necessary when evidence of wound healing is present (e.g., signs of epithelialization and reduction in ulcer size) Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.	15275-15278	Q4131
EpiFix® Amniotic Membrane	Venous stasis ulcer	Covered as medically necessary when BOTH of the following criteria are met: • partial- or full-thickness venous stasis ulcer of greater than four weeks duration for which standard wound therapy has failed • treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70 When the above medical necessity criteria are met, the following conditions of coverage apply: • treatment is limited to one initial application	15271-15274	Q4131

Skin Substitute/ Platelet Derived Growth Factor	Indication	Criteria	Application CPT/HCPCS Codes	Product HCPCS Codes
		• additional applications at a minimum of one week intervals, for up to a maximum of four in 12 weeks when evidence of wound healing is present (e.g., signs of epithelialization and reduction in ulcer size) Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.		
FlexHD® Acellular Hydrated Dermis	Breast reconstruction	Covered as medically necessary when used in association with a covered, medically necessary breast reconstruction procedure.	15271-15274 15777 C5271-C5274	Q4128
GraftJacket® Regenerative Tissue Matrix	Diabetic foot ulcer	Covered as medically necessary when ALL of the following criteria are met: • partial or full-thickness, diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed • type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12% • treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70 When the above medical necessity criteria are met, one application is considered medically necessary.	15275-15278	Q4107
Integra® Dermal Regeneration Template Integra™ Bilayer Matrix Wound Dressing Integra™ Matrix Wound Dressing Integra™ Meshed Bilayer Wound Matrix	Burn wound	Covered as medically necessary when BOTH of the following criteria are met: • postexcisional treatment of a full-thickness or deep partial-thickness burn • sufficient autograft is not available at time of excision or is contraindicated	15271-15278 C5271-C5278	Q4105 Q4104 Q4108 C9363
NeoForm™ Dermis	Breast reconstruction	Covered as medically necessary when used in association with a covered, medically necessary breast reconstruction procedure	15275-15274 15777 C5271-C5274	C1781 Q4100
Oasis® Wound Matrix Oasis® Ultra Tri-	Diabetic foot ulcer	Covered as medically necessary when ALL of the following criteria are met: • partial or full-thickness, diabetic foot ulcer of greater than four weeks	15271-15278 C5275-C5278	Q4102 Q4124

Skin Substitute/ Platelet Derived Growth Factor	Indication	Criteria	Application CPT/HCPCS Codes	Product HCPCS Codes
Layer Matrix		duration for which standard wound therapy has failed • type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12% • treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70		
Oasis Wound Matrix Oasis® Ultra Tri-Layer Matrix	Venous stasis ulcer	Covered as medically necessary when BOTH of the following criteria are met: • partial or full-thickness, lower extremity venous stasis ulcer of four weeks duration for which standard wound therapy has failed • treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70	15271-15274 C5271-C5274	Q4102 Q4124
SurgiMend®	Breast reconstruction	Covered as medically necessary when used in association with a covered, medically necessary breast reconstruction procedure.	15271-15274 15777 C5271-C5274	C9358; C9360
TheraSkin®	Diabetic foot ulcer	Covered as medically necessary when ALL of the following criteria are met: • partial or full-thickness, diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed • type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12% • treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70 When the above medical necessity criteria are met, the following conditions of coverage apply: • treatment is limited to one initial application • additional applications may be applied at a minimum of one week intervals, for up to a maximum of four in 12 weeks are considered medically necessary when evidence of wound healing is present (e.g., signs of epithelialization and	15275-15278 C5275-C5278	Q4121

Skin Substitute/ Platelet Derived Growth Factor	Indication	Criteria	Application CPT/HCPCS Codes	Product HCPCS Codes
		reduction in ulcer size) Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.		
TheraSkin®	Venous stasis ulcer	Covered as medically necessary when BOTH of the following criteria are met: • partial- or full-thickness venous stasis ulcer of greater than four weeks duration for which standard wound therapy has failed • treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70 When the above medical necessity criteria are met, the following conditions of coverage apply: • treatment is limited to one initial application • additional applications at a minimum of one week intervals, for up to a maximum of four in 12 weeks when evidence of wound healing is present (e.g., signs of epithelialization and reduction in ulcer size) Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.	15271-15274 C5271-C5274	Q4121
Transcyte®	Burn wound	Covered as medically necessary when used for temporary covering of a surgically excised deep partial- or full-thickness burn wound as a covering prior to autografting.	15271-15278 C5271-C5278	Q4100

Cigna does not cover any of the products listed above for ANY unlisted indication because each is considered experimental, investigational, or unproven.

Cigna does not cover ANY of the following products* because each is considered experimental, investigational, or unproven for ANY indication (this list may not be all-inclusive):

Skin Substitute	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
Adherus Dural Sealant®	Dural repair	No specific code	Q4100
Allopatch HD™	Tendon augmentation	No specific code	Q4128
AlloSkin™	Wound care	15271-15278 C5271-	Q4115

Skin Substitute	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
		C5278	
AlloSkin™ RT	Wound care	15271-15278 C5271-C5278	Q4123
AmnioCare®	Tendon/nerve repair	No specific code	Q4100
AmnioExCel/BioDExCel™	Wound care Soft tissue repair	15271-15278 C5271-C5278	Q4137
Amniofix® Amniotic Membrane	Tendon/nerve repair	No specific code	Q4100
AmnioMatrix®	Wound care Soft tissue repair	15271-15278	Q4139 V2790
AmnioMTM Injectable	Wound care Soft tissue repair	N/A	Q4100
Architect™ Biomatrix	Wound care	15271-15278 C5271-C5278	Q4147
ArthroFlex™ (FlexGraft®)	Shoulder reconstruction Achilles tendon repair	No specific code	Q4125
BioDfactor™	Wound care Soft tissue repair	15271-15278 C5271-C5278	Q4100
BioDfence™	Surgical wrap/barrier Tendon repair	No specific code	Q4140
BioDfence™ DryFlex	Surgical wrap/barrier Tendon repair	No specific code	Q4138
Biodesign® (Surgisis®) AFP™ Anal Fistula Plug	Anal and rectal fistula repair	46707	C1781 Q4100
Biodesign® (Surgisis®) Hiatal Hernia Matrix	Hernia repair	No specific code	C1781 Q4100
Biodesign® (Surgisis®) Inguinal Hernia Matrix	Hernia repair	No specific code	C1781 Q4100
Biodesign® (Surgisis®) RVP™ Recto-Vaginal Fistula Plug	Recto-vaginal fístula repair	No specific code	C1781 Q4100
BioVance®	Wound Care	15271-15278 C5271-C5278	Q4100
Clarix® Regenerative Matrix	Surgical covering/wrap/barrier	No specific code	Q4100
Conexa™	Tendon repair	No specific code	C1781 Q4100
CorMatrix® ECM® for Cardiac Tissue Repair	Intracardiac patch	No specific code	Q4100
CorMatrix® ECM® for Carotid Repair	Carotid artery repair	No specific code	Q4100
CorMatrix® ECM® for Pericardial	Pericardial repair	No specific	Q4100

Skin Substitute	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
Closure		code	
CryoSkin®	Wound care	15271-15278 C5271-C5278	Q4100
Cymetra™	Integumental tissue repair	N/A	Q4112
Dermacell™	Wound care Breast reconstruction	15271-15278 15777 C5271-C5278	Q4122
DermaMatrix Acellular Dermis	Facial soft tissue defects Breast reconstruction	15271-15278 15777	C1781 Q4100
DermaSpan™	Wound covering Tendon repair	15271-15278	Q4126
Duraform™	Dural repair	No specific code	Q4100
DuraGen®	Dural repair	No specific code	Q4100
DuraGuard	Dural repair	No specific code	Q4100
DuraMatrix™	Dural repair	No specific code	Q4100
DuraSeal™ Dural Sealant System	Dural repair	No specific code	Q4100
DuraSeal™ Spine Sealant System	Dural repair	No specific code	Q4100
Durepair Regeneration Matrix®	Dural repair	No specific code	Q4100
Endoform Dermal Template™	Wound care	15271-15278	C9367
Epifix® Injectable	Wound care	N/A	Q4145
Excellagen®	Wound Care	15271-15278	Q4149
EZ Derm™	Wound care	15271-15278 C5271-C5278	Q4136
FloGraft™	Tendonites Soft tissue trauma	15271-15278 15777 C5271-C5278	Q4100
GammaGraft	Wound care	15271-15278 C5271-C5278	Q4111
GORE BIO-A® Fistula Plug	Anorectal fistulas	46707	C1781 Q4100
Grafix® Core	Wound Care	15271-15278	Q4132
Grafix® Prime	Wound Care	15271-15278	Q4133

Skin Substitute	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
GraftJacket® Xpress	Wound care	N/A	Q4113
hMatrix®	Integumental tissue repair	15271-15278	Q4134
Hyalomatrix® PA	Wound care	15271-15278 C5271-C5278	Q4117
HydroFix® Vaso Shield	Vessel guard	No specific code	Q4100
Integra™ Flowable Wound Matrix	Wound care	N/A	Q4114
MatriStem®	Wound care	15271-15278	Q4118 Q4119 Q4120
Matrix HD™	Wound care Tendon repair	15271-15278 C5271-C5278	Q4128
Mediskin™	Wound care	15271-15278 C5271-C5278	Q4135
MemoDerm™	Wound care Tendon repair	15271-15278	Q4126
Neox® Wound Matrix	Wound care	15271-15278 C5271-C5278	Q4148
NeuraGen® Nerve Guide	Peripheral nerve repair	No specific code	C9352
NeuraWrap™ Nerve Protector	Peripheral nerve repair	No specific code	C9353
NuCel™	Tendon repair	No specific code	Q4100
NuShield™ Orthopaedics	Tendon repair	No specific code	Q4100
NuShield™ Spine	Dura repair	No specific code	Q4100
Oasis® Burn Matrix	Burn wounds	15271-15278 C5271-C5278	Q4103
Orcel®	Burn wounds	15271-15278 C5271-C5278	Q4100
OrthADAPT™ Bioimplant	Soft tissue reinforcement	15777	C1781 Q4100
OsseoGuard®	Oral defects	15275-15278 C5275-C5276	Q4100
Ovation®	Wound healing	15271-15278 C5271-	Q4100

Skin Substitute	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
		C5278	
Peri-Guard® Repair Patch	Soft tissue repair Pericardial and intracardiac repair	15271-15278 C5271-C5278	C1781 Q4100
Peri-Strips® Dry	Staple line reinforcement	No specific code	Q4100
Permacol™	Soft tissue reinforcement/repair	15271-15278 15777	C9364
Preclude® Dura Substitute	Dural Repair	No specific code	Q4100
Preclude® Pericardial Membrane	Pericardial repair	No specific code	Q4100
PriMatrix™	Wound care	15271-15278	Q4110
Repriza®	Reconstructive surgery Breast reconstruction Abdominal wall repair	15271-15278 C5271-C5274	Q4143
Restore® Orthobiologic Soft Tissue Implant	Soft tissue reinforcement	15777	C1781 Q4100
Seamguard® Staple Line Reinforcement	Staple line reinforcement	No specific code	Q4100
SportMesh™	Soft tissue reinforcement	15777	C1781 Q4100
SteriShield™	Soft tissue reinforcement/repair	15271-15278 15777	Q4100
Strattice™ Reconstructive Tissue Matrix	Soft tissue reinforcement/repair	15271-15278 15777	C1781 Q4130
Talymed™	Wound care	15271-15278	Q4127
TenoGlide® Tendon Protector Sheet	Tendon repair	No specific code	C9356
TenSIX™	Wound care Tendon repair	15271-15278 C5271-C5278	Q4146
TissueMend	Soft tissue repair Tendon repair	15271-15278	C1781 Q4100
Tornier® BioFiber Absorbable Biological Scaffold	Soft tissue reinforcement/repair	15271-15278 15777	C1781 Q4100
Tornier® Collagen Coated BioFiber Scaffold	Soft tissue reinforcement/repair	15271-15278 15777	C1781 Q4100
Unite® Biomatrix	Wound care	15271-15278 C5271-C5278	Q4129
Vascu-Guard®	Peripheral vascular reconstruction	No specific code	Q4100

Skin Substitute	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
Veritas Collagen Matrix	Soft tissue reinforcement/repair	15271-15278 15777	Q4100 C9354
Veritas Collagen Matrix Peri-Strips Dry	Staple line reinforcement	No specific code	Q4100
XCM Biologic Vascular Patch	Soft tissue reinforcement/repair	15271-15278 15777 C5271-C5278	Q4142
XenMatrix™ Surgical Graft	Soft tissue reinforcement/repair	15271-15278 15777 C5271-C5278	C1781 Q4100
XenoSure® Biologic Vascular Patch	Cardiac reconstruction/repair Vascular reconstruction/repair	No specific code	C1781 Q4100

General Background

Autologous Skin Grafts and Cadaver-Derived Skin Grafts
Autologous skin grafts and the use of fresh, unprocessed allogeneic cadaver-derived skin grafts are established procedures for wound care. Autologous skin grafts, or autografts, refer to tissue transplanted from one location to another in the same individual. Autografts are referred to as partial-thickness or split-thickness graft. Autografts are ideal because there is no risk of rejection. In some cases, the area of healthy skin available for harvesting may be inadequate to cover the wound area. In these cases, the best choice is human skin taken from human cadavers, consisting of both epidermal and dermal skin layers. These unprocessed, allogeneic cadaver-derived skin grafts (allografts or homograft) are used for temporary coverage of excised wounds. Cadaver skin grafts may be kept fresh for up to 14 days or may be cryopreserved or glycerol-preserved (GPA). Unprocessed cadaveric skin is a widely used skin substitute. Fresh pig's skin that has been specially treated and contains only the dermis layer has been used for coverage of partial thickness burns and excised wounds prior to grafting. There are various ways to sterilize and preserve pigskin. In general, the pigskin is treated with a solution (e.g., providine-iodine), placed in normal saline with an antibiotic, soaked in a solution to sterilize it, rinsed and refrigerated or frozen. Fresh skin stored in normal saline is viable for up to 72 hours. When autografts, unprocessed human cadaver skin or unprocessed pig's skin graft are not available tissue-engineered skin substitutes which include processed human cadaver skin and pig skin may be an option (Ruszczak and Elston, 2013; Ahmad et al., 2010; Ge et al., 2010; Paul, 2008).

Tissue Engineered Skin Substitutes
Tissue-engineered skin substitutes (i.e., human skin equivalents [HSE]), also referred to as artificial skin, are bioengineered skin products and may be either acellular or cellular. Acellular (i.e., cadaveric human dermis with cellular material removed) products contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. The construction of the matrix allows easy access by host cells during the healing process. Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within a matrix may be allogeneic (i.e., obtained from another individual) or autologous (i.e., obtained from the same individual). Some products are derived from other species (e.g., bovine, porcine) and are referred to as a xenograft. Skin substitutes are generally comprised of epidermal cells, dermal cells or may be composites (i.e., a combination of dermal and epidermal). The substitutes can be used as either temporary or permanent wound coverings (Ho, et al., 2005; Sibbald, et al., 2005). Grafting techniques utilized to apply skin substitutes include autografting (i.e., tissue transplanted from one part of the body to another), allografting (i.e., transplant from one individual to another of the same species), and xenografting (i.e., a graft from one species to another unlike species). Skin substitutes have been proposed for the treatment of multiple conditions including breast reconstruction and chronic wounds nonresponsive to standard therapy.

During breast reconstruction, acellular dermal skin substitutes (i.e., AlloDerm, AlloMax) are primarily used in the setting of tissue expander and breast implant reconstruction. Patients should be in overall good health and have no underlying condition that would restrict blood flow or interfere with the normal healing process (e.g., uncontrolled diabetes, hypertension, previous surgery). These matrixes may be indicated when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required, as may be the case in a very thin patient; if there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis; or if there is a need to re-establish the inframammary fold and lateral mammary fold landmarks. When used in appropriate candidates, these skin substitutes are proposed to improve control over placement of the inframammary fold and final breast contour, enhance use of available mastectomy skin, reduce the number of expander fills necessary, reduce time to complete expansion and eventual implant exchange, potential improved management of a threatened implant, reduce the need for explantation and the potential for reduction in the incidence of capsular contracture. However, there are ongoing concerns regarding the increased risk of seroma and infection, a higher risk of an implant having to be removed, and tissue flap death (American Cancer Society, 2013; Nguyen, et al., 2011; Sbitany and Serletti, 2011).

A chronic wound is defined as a wound that does not heal in the time expected based upon the patient's age, comorbidities, and wound etiology. A wound that has not healed within 30 days to three months is considered chronic. Different types of chronic wounds include lower extremity diabetic neuropathic ulcers, venous ulcers and burn wounds. Treatment depends on the type of wound, wound location, and wound size. The wound should be free of infection, coagulum, sinus tracts, tunnels, cellulitis, eschar and necrotic tissue. There should be no exposure of joints, tendons, ligaments or bone. Adequate blood supply to the affected area should be evidenced by a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70.

Standard wound therapy for a foot ulcer in a type 1 or type 2 diabetic includes avoidance of mechanical stressors on the ulcerated extremity (i.e., off-loading), wound cleansing and debridement, management of infection with antibiotic therapy and application of saline-soaked gauze. It is essential that routine medical management of diabetes and the presence of a hemoglobin A1C (HbA1C) of less than 12% be achieved to maximize complete healing of the wound.

The mainstay of conventional wound therapy for lower extremity venous stasis ulcers is compression therapy (e.g., compression stockings, Unna boots, elastic wraps). Surgical debridement of the wound, zinc paste gauze and non-weight bearing regimens may also be used. Skin substitutes may be indicated for the treatment of a wound that is not healing in response to conventional therapy. The underlying medical condition, such as hypertension, should be adequately managed to foster complete healing.

U.S. Food and Drug Administration (FDA)
Depending on the purpose of the product and how it functions, skin substitutes are regulated by the FDA premarket approval (PMA) process, 510(k) premarket notification process, or the FDA regulations for banked human tissue.

Products that are classified by the FDA as an interactive wound and burn dressing are approved under the PMA process as a class III, high-risk device and require clinical data to support their claims for use. These devices may be used as a long-term skin substitute or a temporary synthetic skin substitute. They actively promote healing by interacting directly or indirectly with the body tissues. Examples of these devices include Apligraf® (Organogenesis Inc., Canton, MA) and Dermagraft® (Advanced BioHealing, Inc., LaJolla, CA).

Other wound care devices are approved by the 510(k) process, and their primary purpose is to protect the wound and provide a scaffold for healing. They may or may not be integrated into the body tissue. Some devices are rejected by the body after approximately ten days to several weeks and removed prior to definitive wound therapy or skin grafting. Integra™ Bilayer Matrix Wound Dressing (BMWD) (Integra LifeSciences Corp., Plainsboro, NJ) and Oasis® Wound Matrix (Cook Biotech, Inc., West Lafayette, IN) are examples of these devices.

Donated skin that requires minimal processing and is not significantly changed in structure from its natural form is classified by the FDA as banked human tissue, is not considered a medical device, and does not require PMA or 510(k) approval. Donated skin is regulated by the American Association of Tissue Banks (AATB) and the FDA guidelines for banked human tissue. AATB oversees a voluntary accreditation program and the FDA focuses on preventing the transmission of communicable diseases by requiring donor screening and testing. Tissue

establishments must register with the FDA and list each cell or tissue produced. An example of a banked human tissue product is AlloDerm, an acellular dermal matrix (FDA, 2004; Department of Health and Human Services, 2001).

Skin Substitutes

The safety and efficacy of the skin substitutes listed below are supported by the evidence in the published peer-reviewed scientific literature and/or are established treatment options for the discussed indications.

AlloDerm® - Breast Reconstruction

AlloDerm (LifeCell Corporation, Branchburg, NJ) is a human acellular dermal matrix allograft classified as banked human tissue by the FDA because it is minimally processed and not significantly changed in structure from the natural material. AlloDerm is an established treatment option and is supported by the evidence in the published peer-reviewed scientific literature for tissue repair during postmastectomy breast reconstruction (Jansen and Macadam, 2011; Chun, et al., 2010; Spear, et al., 2008; Bindingnavele, et al., 2007; Breuing and Colwell, 2007; Zienowicz, et al., 2007; Salzberg, 2006; Breuing, et al., 2005; Nahabedian, 2005; Gamboa-Bobadilla, 2006). AlloDerm is available in two forms. One product is a Tissue Regeneration Matrix and the other is a Ready to Use matrix. The Ready to Use with a contour shape was specifically designed for breast reconstruction.

AlloDerm – Other Indications

AlloDerm has been proposed as a treatment option for various other conditions including: reconstruction after excision of skin and soft tissue malignancies, abdominal wall reconstruction and/or hernia repair, tympanoplasty, lower eyelid surgery, Frey's syndrome (a complication of parotid excision), cleft palate repair; various oral surgery procedures including gingival recession, empty nose syndrome, burns and postburn scar contractures and nasal contour deformities. In addition, AlloDerm has been investigated for placement over implantable cardioverter-defibrillators and cardiac pacemakers to prevent skin erosion, scalp reconstruction and hand resurfacing. Studies are primarily in the form of case series or retrospective reviews with small patient populations (n=6-58) and short-term follow-ups (e.g., 3–68 months). Comparative studies to established therapies with randomization are lacking. There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of AlloDerm for these indications.

Abdominal Wall Reconstruction: Case series (n=10) (DeMoya, et al., 2008) and retrospective reviews (Lee, et al., 2009; Bellows, et al., 2007; Patton, et al., 2007; Schuster, et al., 2006) (n=18-67) with 2–16 months follow-up have evaluated the use of AlloDerm during contaminated abdominal wall reconstructive surgery. Diagnosis included infected fascia with dehiscence, complex ventral hernia, and dehiscence and/or evisceration. Typically the wounds were contaminated or dirty. Hernia recurrence rates up to 64% were reported. Complication rates were as high as 43% and included wound infections, fistulas, wound dehiscence, graft infection, postoperative intra-abdominal bleeding, and evisceration. Some cases required repeat surgery and/or removal of the AlloDerm. The authors reported that 100% of the patients experienced either significant abdominal laxity or a hernia following the application of AlloDerm (De Moya, et al., 2008); due to the high overall rate of hernia recurrence when the wound was left open, they could not support the use of AlloDerm unless the wound could be closed postoperatively (Shuster, et al., 2006); ongoing studies are required to address further refinements of surgical technique and to analyze long-term outcomes related to the durability (Patton, et al., 2007); and lastly, long-term outcomes are unknown and are critical to "fully establish the durability and functional properties of remodeling of AlloDerm grafts when used as tissue prosthesis during abdominal wall repair" (Bellows, et al., 2007).

Cleft Palate Repair: A systematic review of the literature included nine nonrandomized studies (n=166) that evaluated AlloDerm for cleft palate repair during primary palatoplasty (n=92) and palatal fistula repair (n=74). There was insufficient evidence to support AlloDerm for this indication (Aldekhayel, et al., 2012).

Frey's syndrome: It has been proposed that AlloDerm can alleviate the gustatory sweating associated with Frey's syndrome following parotid excision (Zeng, et al., 2012; Sinha et al., 2003; Govindaraj, et al., 2001). Zeng et al. (2012) conducted a systematic review and meta-analysis of randomized and quais-randomized controlled trials to evaluate the effectiveness of AlloDerm for preventing Frey syndrome after parotidectomy. Five studies (n=409) met inclusion criteria. The primary outcome measure was the incidence of Frey syndrome (objective or subjective). Secondary outcomes included facial contour, wound infection, rejection, seroma or salivary fistula and facial nerve paralysis. Meta-analyses of 2–4 trials showed a significant reduction in objective incidence ($p<0.00001$) and subjective incidence ($p<0.00001$) of Frey syndrome and salivary fistula ($p=0.02$). There was no statistically significant reduction in the incidence of facial nerve paralysis ($p=0.51$), incidence of seroma/sialocele

(p=0.40) or improvement in facial contour. There were no significant differences in wound infection between the two groups and no cases of implant extrusion with AlloDerm. The authors noted that limitations of this study included: “the number of studies contributing substantial data to the meta-analysis was small; therefore, we could not fully assess the effects of important clinical factors that may have influenced outcomes”, possible problems with concealment, lack of blinding, loss of patients to follow-up and possible publication bias. Additional well-designed randomized controlled trials with large patient populations are needed to confirm the efficacy of AlloDerm for this subpopulation.

Hernia Repair: Case series (n=11–70) (Bluebond-Langner, et al., 2008; Misra, et al., 2008; Aycock, et al., 2007) and retrospective reviews (n=37–165) (Diaz, et al., 2009; Lee, et al., 2008; Jin, et al., 2007) evaluated the application of AlloDerm during hernia repairs (e.g., parastomal hernia, hiatal hernia, incisional hernia, ventral hernia). Follow-ups ranged from 8-37 months. Complication rates were as high as 44%. Diaz, et al. (2000) reported a 17.1% overall hernia recurrence rate, 40% surgical site infections, and 11.6% postoperative fistulas. Other studies reported postoperative ileus (24.2%), wound seroma (12.9%), and intrabdominal abscess (9.6%). In one study, seven of nine patients required reoperation due to postoperative abdominal wall laxity which was associated with infection and larger defects. Outcomes varied based on the type of surgical procedure performed, the type and number of AlloDerm sheets used, presence or absence of fecal contamination, and patient comorbidities (e.g., diabetes mellitus). The evidence in the published peer-reviewed scientific literature does not support the efficacy of AlloDerm for hernia repair.

Lower Eyelid Surgery: AlloDerm is proposed as an alternative to hard palate grafting used in the surgical repair of lower eyelid retraction following blepharoplasty. Two retrospective reviews compared the outcomes of hard palate mucosa to AlloDerm. Although not statistically significant, Li et al. (2005) (n=35) reported that hard palate patients had better elevation and lower failure rate than AlloDerm patients. Taban et al. (2005) (n=21) reported that no improvement was seen in five of the procedures. Sullivan and Dailey (2003) evaluated the graft contraction rate of AlloDerm compared with hard palate graft in 14 patients (19 grafts). A statistically significant difference in mean graft contraction between the AlloDerm group and the hard palate graft group was observed (57% and 16%, respectively; p<0.005). The mean one-year follow-up graft contraction rate was 57% with AlloDerm compared to 16% with the hard palate graft. Five patients with a mildly contracted socket treated with AlloDerm either failed or had partial success due to graft contraction. The authors concluded that AlloDerm contracts significantly more than hard palate grafts resulting in less successful outcomes.

Oral Surgery: AlloDerm has been proposed for closure of oral harvest sites, oral cavity reconstruction, and the treatment of gingival recession. Studies are primarily in the form of case reports or case series with small patient populations. Published randomized controlled trials have included small, heterogeneous patient populations (e.g., n=10–23) and short-term follow-ups. Overall, studies have not reported a significant difference with the use of AlloDerm for these indications. Jamal et al. (2010) conducted a randomized controlled trial to compare AlloDerm (n=10) closure to primary closure (n=10) of oral harvest sites for buccal mucosa grafts for urethroplasty. A single graft was harvested from one cheek. Based on questionnaire scores, there were no significant differences in postoperative oral pain, neurosensory deficits, or mouth tightness between the two groups. Although the difference was not statistically significant, there was a trend in the AlloDerm group toward more difficulty with mastication at three weeks, and three-, six-, and 12-month follow-ups. A significant difference was reported in cheek swelling at three weeks with 80% of the AlloDerm group compared to 30% of the primary closure group (p=0.01). The authors noted that AlloDerm “proved to be an effective means of closing the harvest site, but offered no significant advantages when compared with primary closure” and its use appeared to be “an unnecessary step”.

In a prospective nonrandomized study, Girod et al. (2009) compared the efficacy of AlloDerm (n=22) to split thickness skin graft (STSG) (n=12) in patients who underwent surgical resection of oral cavity tumors followed by reconstruction. The surgeries were performed by two different surgeons. The time from date of surgery to enrollment in the study was 22 months for the AlloDerm group and 12 months for the STSG group. There was a higher pre- and post-operative prevalence of radiotherapy exposure in the AlloDerm (45%) compared to the STSG group (17%). A higher graft failure rate was seen in the AlloDerm group (14% vs. 0%), but was not statistically significant. There was a significant difference in the distribution of graft sites with more tongue patients in the AlloDerm group and more floor-of-mouth patients in the STSG group. AlloDerm grafts resulted in a more normal appearing mucosal surface. Although the AlloDerm patients scored higher on the Global Health Status, Functional, and Symptom scores on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items/Head and Neck 35 (EORTC QLQ-C30/H&N35) tool, the differences

were not significant. Histopathology comparisons (n=12) showed less fibrous tissue and keratinization of the epithelium in the AlloDerm patients.

Mahajan et al. (2007), in a randomized controlled trial, evaluated the effectiveness of AlloDerm in the treatment of gingival recession. Fourteen patients were randomly assigned to the AlloDerm group (AlloDerm and coronally positioned flap [CPF]; n=7) or the CPF group (CPF alone; n=7). The defect coverage in the AlloDerm group was 97.14% compared to 77.42% in the CPF group, which was statistically significant ($p<0.05$). CPF produced statistically significant better results ($p<0.03$) in patient comfort. There were no significant differences between the two groups in the remaining clinical outcomes and overall patient satisfaction.

A randomized study by Rahmani and Lades (2006) compared AlloDerm to conventional grafting. Fourteen patients with 20 gingival recessions of Miller's grade I and II were included in the study. Outcomes were measured at baseline and at six months after surgery and included: recession height, recession width, probing depth, attached gingiva, keratinized gingiva, and clinical attachment level. Differences in the mean change between the two groups were not significant in any of the parameters.

Gapski et al. (2005) conducted a systematic review and meta-analysis to compare the efficacy of acellular dermal matrix (ADM) (AlloDerm) based root coverage increase in keratinized tissues to commonly used mucogingival surgeries for the treatment of gingival recession and to increase the width of attached gingiva. Eight randomized controlled trials met inclusion criteria. Four studies were eligible for comparisons between ADM-based root coverage and free autogenous connective tissue graft (CTG): two for comparisons between ADM based root coverage and coronally advanced flap (CAF) and two for comparisons between ADM-based augmentation of keratinized gingiva (KG) and free gingival graft (FGG). "There were no statistically significant differences between groups for any of the outcomes measured (recession coverage, keratinized tissue formation, probing depths, and clinical attachment levels)". Due to the heterogeneity in study design and analysis and lack of data, meta-analysis' could not be performed. Based on this analysis, the authors noted that it was "difficult to draw anything other than tentative conclusions from this meta-analysis of ADM for mucogingival surgery.

AlloMax™

AlloMax Surgical Graft (Bard Davol, Inc. Warwick, RI) is an acellular non-cross-linked human dermis allograft. Because AlloMax is a natural human product it is classified as banked human tissue and does not require FDA approval. It is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. The AlloMax Surgical Graft for Breast Reconstruction (previously marketed as NeoForm™) is proposed for post-mastectomy breast reconstruction and is an established skin substitute for this indication (Bard, 2013).

The AlloMax Surgical Graft for Hernia and Abdominal Wall Repair is proposed for hernia or other complex abdominal wall repairs when a synthetic prosthesis is contraindicated or inappropriate. There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of AlloMax for hernia and abdominal wall repair. Studies have primarily been in the form of case reports for hernia repair (e.g., hiatal hernia, incisional hernia) and abdominal wall reconstruction (Bard, 2013).

Apligraf®

Apligraf (Organogenesis Inc., Canton, MA) (also known as Graftskin), a bilayered living skin equivalent with bovine reagents, is FDA PMA approved for use in conjunction with compression therapy for the treatment of non-infected, partial and full-thickness skin ulcers due to venous insufficiency and for full-thickness neuropathic diabetic foot ulcers nonresponsive to standard wound therapy. Based on the results of clinical trials, Apligraf may be appropriate when used for the treatment of type I and type 2 diabetics when the patient is under routine medical management and has a hemoglobin A1C (HbA1C) less than 12%. The ulcer should be free of sinus tracts, tunnels, cellulitis, eschar and necrotic tissue. Adequate blood supply to the treated foot (i.e., palpable pedal pulse or an ankle-brachial index [ABI] of ≥ 0.70) is necessary for healing to occur. One application of Apligraf is initially indicated. If Apligraf coverage is less than 100% and the wound is not progressing, up to a total of four applications in a twelve week period of time may be used. The safety and efficacy of more than five applications has not been reported in the published peer-reviewed literature (Organogenesis, 2010; FDA, 2000).

Apligraf is an accepted treatment modality for chronic noninfected, full-thickness lower extremity venous stasis ulcers of at least one month duration that are nonresponsive to medical management. The ulcer should be free of cellulitis, eschar, sinus tracts, tunnels, necrotic tissue and osteomyelitis and have adequate arterial blood supply to support healing as determined by a palpable pedal pulse or an ankle-brachial index (ABI) of ≥ 0.70. Apligraf is

used in conjunction with standard wound care therapy. One initial application is used and the wound is observed to see if the graft adheres to the skin. If less than 50% adherence is observed, additional applications may be indicated for up to a maximum of four applications in 12 weeks. Any underlying medical condition that may deter healing should be adequately managed (Organogenesis, 2010; FDA, 1998).

Systematic reviews and randomized controlled trials (DiDomenica, et al., 2011; Steinberg, et al., 2010; Edmonds, et al., 2009; Curran and Plosker, 2002; Veves, et al., 2001; Falange, et al., 1999; Falange et al., 1998) support the safety and efficacy of Apligraf for these indications.

Biobrane®/Biobrane®-L
Biobrane/Biobrane-L (Smith and Nephew, Inc., Largo, FL) are synthetic, bilaminate, collagen-based composites. Under the FDA PMA approval, Biobrane is indicated for use as a temporary covering of partial-thickness, freshly debrided or excised burn wounds in the absence of coagulum, eschare and necrotic tissue. Biobrane-L is also a temporary covering used as an adjunct until autografting is clinically appropriate. Biobrane L is a less complex nylon fabric for use when less aggressive adhesion is needed (UDL Laboratories, 2013). Randomized controlled trials and retrospective reviews support the safety and effectiveness of Biobrane for the treatment of partial-thickness burns (Lang, et al., 2005; Lal, et al., 2000).

Biobrane has also been proposed for the treatment of toxic epidermal necrolysis, paraneoplastic pemphigus, dermabrasion, skin graft harvesting, laser resurfacing, and other types of chronic wounds that cannot be immediately closed (e.g., open sternotomy, venous ulcers), but there is insufficient evidence to support Biobrane for these indications (Whitaker, et al., 2008).

Dermagraft®
Dermagraft (Advanced Tissue Sciences., LaJolla, CA) is a cryopreserved dermal substitute approved by the FDA PMA process for the treatment of lower extremity full-thickness diabetic foot ulcers on the fore foot, toes or heal, of longer than six weeks' duration, that extend through the dermis, and are refractory to standard wound care management. Dermagraft is used as an adjunct to standard wound therapy for type 1 and type 2 diabetics who have an A1C of less than 12% and are being managed by routine medical care. The ulcer should be free of sinus tracts, tunnels, infection, redness, underlying osteomyelitis, cellulitis, eschar, necrotic tissue. Adequate blood flow to the affected foot (i.e., palpable pedal pulse or ankle-brachial index [ABI] of ≥ 0.70) should be present in order for healing to occur. When Dermagraft is indicated, treatment is limited to one initial application. If evidence of healing is seen (e.g., signs of epithelialization and reduction in ulcer size) a maximum of eight applications for up to a total of 12 weeks are considered appropriate (Advanced Biohealing, 2013; FDA, 2001). The FDA Humanitarian Device Exemption (HDE) process for the treatment of dystrophic epidermolysis bullosa (EB) was withdrawn by the manufacturer. Randomized controlled trials and case series have demonstrated improved outcomes when Dermagraft was used for the treatment of these ulcers (Marston, 2005; Marston, et al., 2003, Gentzkow, et al., 1999).

Epicel
Epicel (Genzyme Biosurgery, Cambridge, MA) is a cultured epidermal autograft (CEA) that is FDA approved under the HDE process for patients who have deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30%. It may be used in conjunction with split-thickness autografts or alone in patients for whom split-thickness autografts may not be an option (FDA, 2007). Epicel is FDA approved as a Humanitarian Device Exemption (HDE) device. Prospective comparative studies and case series support Epicel for the treatment of burns (Carsin, et al., 200; Munster, 1996).

Epifix® Membrane
EpiFix Amniotic Membrane Allograft (MiMedx Group, Kennesaw, GA) is an amnion/chorion membrane (dHAM) processed by a patented Purion® Process. These processes are regulated by the FDA regulations and American Association of Tissue Banks (AATB) standards. The allograft contains active growth factors (i.e., epidermal growth factor [EGF], transforming growth factor [TGF-α, TRF-β], fibroblast growth factor [bFGF], platelet derived growth factor [PDGF], and vascular endothelial growth fact [VEGF]), cytokines (e.g., interleukin I receptor antagonist [IL-1ra], interleukin 4 [IL-4] and interleukin 10 [IL-10]), and structural extracellular matrix proteins (e.g., collagen types [I7, III7, IV7, V7, and VII8], fibronectin7, laminins7, and proteoglycans). EpiFix is proposed to promote cellular migration to enhance soft tissue repair in acute and chronic wounds free of necrotic tissue and infection; partial- and full-thickness wounds; venous, diabetic, pressure, and chronic vascular ulcers; trauma wounds, including burns; and surgical wounds. EpiFix membranes/sheets come in 14 mm and 16 mm disks as

well as, 2X3 cm, 4X4 cm and 5X6 mm sheets. Randomized controlled trials support EpiFix for the treatment diabetic foot ulcers and venous status ulcers reported significantly greater reduction in wound size and faster healing time (Zelen, et al., Feb 2014; Serena, et al., 2014; Zelen, et al., Apr 2014; Zelen et al., 2013).

Epifix® also comes in a micronized powder. There is insufficient evidence to support the safety and efficacy of Epifix Micronized Powder nor is its use an established standard of care.

FlexHD® Acellular Hydrated Dermis: FlexHD Acellular Hydrated Dermis (Musculoskeletal Transplant Foundation, Edison, NJ and Ethicon Inc., Somerville, NJ) is a matrix derived from donated human allograft skin. The product is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. The dermis is indicated for the replacement of damaged or inadequate integumental tissue or for the repair, reinforcement or supplemental support of soft tissue defects. Flex HD is available in multiple sizes. Case series and retrospective reviews support the safety and efficacy of FlexHD for use during postmastectomy breast reconstruction. FlexHD is an established skin substitute for this indication (Liu, et al., 2014; Seth, et al., 2013; Seth, et al., 2012; Brooke, et al., 2012; Rawlani, et al., 2011; Cahan, et al., 2011; Topol, et al., 2008).

The implantation of FlexHD has also been reported to aid in the rehabilitation of patients with empty nose syndrome in an attempt to provide resistance for breathing and decrease the sensation of suffocation (Ethicon, 2013; Chhabra and Houser, 2009). Data supporting the safety and efficacy of FlexHD from published clinical trials are lacking. Studies have primarily been in the form of retrospective reviews and case series with small patient populations.

Bochicchio et al. (2013) conducted a prospective, time-interrupted, comparison study (n=95) of FlexHD and AlloDerm for ventral hernia repair. Subjects were age ≥ 18 years and had a symptomatic (pain, discomfort) complicated ventral hernia > 200 CM^2. The initial 55 patients were repaired with Alloderm and two years later, 40 patients with the same criteria were repaired with FlexHD. Three different surgical techniques were used based on the surgeon's discretion. Follow-up occurred for one year with a primary outcome of hernia recurrence. At the one year follow-up all of the AlloDerm patients underwent repair for recurrence of hernia compared to 11 FlexHD patients, which was statistically significant ($p<0.001$). The incidence of seroma was similar between the groups but postoperative wound infection/abscess formation was higher in the AlloMap group although not statistically significant. Limitations of the study include the lack of randomization, the use of three different surgical approaches, two year delay between study groups, and small patient populations.

GraftJacket® Regenerative Tissue Matrix (RTM)
GraftJacket Regenerative Tissue Matrix (RTM) (Wright Medical Technology, Inc., Arlington, TN) is an acellular human dermal collagen template indicated for the repair or replacement of damaged or inadequate integumental tissue. GraftJacket Regenerative Tissue Matrix is regulated by the FDA as human tissue for transplantation and indicated for the treatment of diabetic foot ulcers. GraftJacket Regenerative Tissue Matrix MaxForce Extreme and GraftJacket Matrix Maxstrip are variations of the size and thickness of this tissue matrix. There are also products specific for hand surgery and shoulder surgery (Wright Medical Technologies, 2011). Randomized controlled trials support the use of GraftJacket for the treatment of diabetic foot ulcers. Compared to standard wound care, more patients healed within 6-12 weeks with Graftjacket (Reyzelman, et al., 2009; Brigido, 2006).

GraftJacket has also been investigated for use during tendon/rotator cuff repair. Published studies have been primarily in the form of case reports, case series, and retrospective reviews. Barber et al. (2012) conducted a randomized controlled trial (n=42) to evaluate the safety and effectiveness of Graftjacket used in arthroscopic repair of large rotator cuff tears. Patients underwent repair of two-tendon rotator cuff tears measuring greater than three centimeters (cm) with (n=22) (group 1) and without Graftjacket (n=20) (group 2). Exclusion criteria included: irreparable massive rotator cuff tears measuring greater than five cm; subscapularis tendon disruptions; revision surgery; inflammatory or autoimmune diseases; evidence of active infection, cancer, or highly communicable diseases; and smokers. Follow-up ranged from 12–38 months (mean 24 months). The primary outcome measure was the presence of retears independently seen on gadolinium-enhanced magnetic resonance imaging (MRI) at least 12 months postoperatively. Secondary endpoints were clinical outcomes measured by the American Shoulder and Elbow Surgeons (ASES) scores, Constant scores and the University of California, Los Angeles (UCLA) scores. MRIs showed intact cuffs in 85% of group 1 (n=17) and 40% of group 2 (n=6), statistically significant ($p<0.01$). With Graftjacket, there was a significant improvement in the ASES score ($p=0.035$) and the Constant score ($p=0.08$). There were no significant differences in the UCLA scores between the two groups. No adverse events were attributed to the use of Graftjacket. Operative time was increased 30–60

minutes with Graftjacket application. Limitations of the study include the small patient population, short-term follow-up, and loss of patients to MRI follow-up.

Integra®
Integra Dermal Regeneration Template (Integra LifeSciences Corp., Plainsboro, NJ) is a bovine, collagen-based temporary epidermal substitute that is FDA PMA approved for use in postexcisional treatment of life-threatening, non-infected full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable because of the physiological condition of the patient (FDA, 2002). Integra™ Bilayer Matrix Wound Dressing, Integra™ Matrix Wound Dressing, and Integra™ Meshed Bilayer Wound Matrix, are substantially equivalent skin substitutes that are FDA 510(k) approved for the management of partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree bums, and skin tears) and draining wounds (FDA, 2008).

Results of randomized controlled trials, case series and retrospective reviews support the safety and efficacy of Integra Dermal Regeneration Template as a treatment option for burn patients (Lee, et al., 2008; Branski, et al., 2007; Fette, 2005; Groos, et al., 2005; Klein, et al., 2005; Heitland, et al., 2004; Heimbach, et al., 2003).

Case reports, case series, pilot studies and retrospective reviews have reported the application of Integra for the treatment of other conditions including: diabetic wounds, chronic wounds, giant congenital melanocytic nevi, scalp reconstruction, burn scar revision, tendon coverage, and dermatologic procedures (e.g., removal of squamous cell carcinoma, malignant melanomas, and keloids). Studies included small patient populations (n=8-30), short-term follow-ups and did not compare Integra to standard methods of treatment. There is insufficient evidence in the published peer-reviewed scientific literature to support Integra for the treatment of these conditions.

Neoform™ Dermis
Neoform Dermis (Mentor Corp., Santa Barbara, CA) is a solvent-dehydrated, gamma-irradiated preserved human allograft dermis indicated for use as a soft tissue graft for horizontal and vertical soft tissue augmentation of thickness and length, such as breast reconstruction. NeoForm is classified as banked human tissue by the FDA. Although evidence in the published, peer-reviewed scientific literature supporting the use of this product in breast reconstruction is limited, Neoform Dermis is an established skin substitute used for tissue expansion in breast reconstruction following a mastectomy. Neoform is no longer available for distribution.

Oasis® Wound Matrix
Oasis Wound Matrix (Cook Biotech Inc., West Lafayette, IN) is a porcine-derived, acellular collagen matrix. Oasis is 510(k) FDA approved for the management of partial and full thickness wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears), and draining wounds (FDA, 2006). The Oasis Ultra Tri-Layer Matrix incorporates three layers of the same structural components as the single layer matrix and is used in the treatment of larger wounds.

Oasis is an established treatment option for partial or full-thickness diabetic foot ulcers of greater than four weeks duration. The diabetic patient should be participating in ongoing medical management and have an A1C of less than 12%. Oasis may also be used to treat venous stasis ulcers of one month duration that do not respond to standard wound care. The ulcer should be free of sinus tracts, tunnels, cellulitis, eschar and necrotic tissue. Viable tissue around the edges of the ulcer and the presence of adequate arterial blood supply therapy (i.e., palpable pedal pulse or an ankle-brachial index [ABI] of ≥ 0.70) are necessary for healing to occur.

Randomized controlled trials and case series support Oasis for the treatment of chronic partial and full-thickness lower extremity venous or diabetic foot ulcers when conventional wound therapy fails. The studies compared Oasis to standard wound therapy, Regranex Gel or hyaluronic acid dressing. Treatment with Oasis resulted in better outcomes and lower recurrence rates (Romanelli, et al., 2010; Romanelli, et al., 2007; Niezgoda, et al., 2005; Mostow, et al., 2005; Demling, et al., 2004).

SurgiMend®: SurgiMend or SurgiMend Collagen Matrix (TEI Biosciences Inc., Boston, MA) is an acellular dermal tissue matrix derived from fetal or neonatal bovine dermis. The matrix acts as a scaffold that is

progressively integrated, remodeled, and replaced by the functional host tissue. Approved as a Class II, FDA 510(k) device, SurgiMend is "intended for implantation to reinforce soft tissue where weakness exists and for the surgical repair of damage or ruptured soft tissue membranes" specifically for plastic and reconstructive surgery, muscle flap reinforcement, and hernia repair (e.g., abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, incisional) (FDA, 2009). SurgiMend products include SurgiMend Collagen Matrix and SurgiMend PRS for breast reconstruction. Results of case series reviews in the peer-reviewed literature support the safety and efficacy of SurgiMend for use during postmastectomy breast reconstruction. SurgiMend is an established skin substitute for this indication. SurgiMend is available in multiple sizes and thicknesses (Butterfield, et al., 2013, Gaster, et al., 2013, Ohkuma, et al., 2013; Endress, et al., 2012; Craft, et al., 2011; Cromwell, et al., 2009; TEI Biosciences, 2013)

SurgiMend is proposed for reconstructive surgery other than breast. Studies, primarily in the form of case reports and retrospective reviews, have evaluated SurgiMend for the treatment of necrotic heel decubitus ulcers; repair of recurrent ventral hernia, enterocutaneous fistula, Achilles tendon, rupture of tibialis anterior tendon, posterior tibiotalar ligament, damaged cartilage; tendon-lengthening procedures; foot and ankle tendon reattachment procedures; and to promote biologic regeneration of tendon tissue around a supporting suture to prevent a large tissue gap (Cromwell, et al., 2009; TEI Biosciences, 2013). There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of SurgiMend for these other indications. SurgiMend e3.0 is a collagen matrix specifically designed for application in ventral hernia repair and is available in one size, 10 cm X 25 cm X 3mm.

TheraSkin®
TheraSkin (LifeNet Health, Inc., Virginia Beach, VA) is a human skin allograft with epidermis and dermis layers. As a human skin product, TheraSkin is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. Proposed indications for TheraSkin include ulcers (i.e., diabetic foot ulcers, venous stasis ulcers, stage II and greater pressure ulcers) and dehisced surgical burns with or without exposed tendon, muscle or bone. It is also proposed for the treatment of wounds that might otherwise require autografts. The allograft is to be used in conjunction with conventional therapies (Soluble Solutions, 2013). Randomized controlled trials have reported significant improvement following treatment of diabetic foot ulcers with TheraSkin (Sanders, et al., 2014; DiDomenica, et al., 2011). TheraSkin is an established human skin allograft for the treatment of diabetic and venous stasis lower extremity ulcers.

There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of TheraSkin for any other indications including dehisced surgical wounds and pressure sores.

TransCyte
TransCyte (Smith & Nephew Inc., Largo, FL) (originally known as Dermagraft-TC) is a human, bilaminate, temporary skin substitute that is FDA PMA approved for the treatment of full- or partial-thickness burns. It is used as a temporary wound covering until autograft is possible. The wound is surgically excised prior to application of TransCyte. Randomized controlled trials and prospective case series support the safety and efficacy of TransCyte for the treatment of this type of burns (Amani, et al., 2006; Kumar, et al., 2004, Lukish, et al., 2001).

Other Skin Substitutes
Additional skin substitutes have been proposed for the treatment of multiple conditions as discussed below, but the evidence in the published peer-reviewed scientific literature does not support the safety and efficacy of the use of these substitutes. The number of available studies is limited and involves small, heterogeneous patient populations, short-term follow-ups, minimal comparisons to the established treatment method for the condition, and/or lack of a control group. In some cases, reported outcomes are inconsistent, and a consensus on patient selection criteria and the appropriate surgical approach and techniques that should be used have not been established.

Adherus Dural Sealant®
The Adherus Dural Sealant system (HyperBranch Medical Technology, Inc. Durham, NC) is a synthetic hydrogel sealant proposed for use as an adjunct to standard methods of dural repair (e.g., sutures) to prevent spinal fluid leakage in cranial and spinal surgery. The sealant is also proposed to minimize dural adhesions and scarring. It is designed for neurosurgical procedures when only a small amount of material is required to close a durotomy. The product comes in a syringe and is reconstituted prior to use. The hydrogel is absorbed by the body over a 90 day period as healing occurs. Adherus™ sealants also include the Adherus AutoSpray Dural Sealant. According

to the manufacturer, a randomized clinical trial has been completed and will be submitted to the FDA as part of the PMA process (HyperBranch, 2013). There is insufficient evidence to support the safety and efficacy of Aherus dural sealants nor are they FDA approved.

Allopatch HD™
Allopatch HD (Musculoskeletal Transplant Foundation [MTF], Edison, NJ) is an extracellular matrix (ECM) scaffold derived from human allograft skin for tendon augmentation. The Musculoskeletal Transplant Foundation (MTF), which acquires and processes the tissue, is registered with the FDA (MTF, 2012). There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of Allopatch.

AlloSkin™ and AlloSkin RT
AlloSkin (Allosource, Centennial, CO) is a cryopreserved, allograft composed of epidermal and dermal cadaveric tissue proposed for use with partial and full thickness wounds and is regulated by the American Association of Tissue Banks (AATB) and the FDA guidelines for banked human tissue (AlloSource, 2013). AlloSkin products include the AlloSkin Wound Care, AlloSkin RT Wound Care at Room Temperature, and the AlloWrap Natural Wound cover. The difference in these grafts includes whether they are frozen or irradiated and whether they are single layered or double layered. Published data supporting the safety and efficacy of AlloSkin are lacking. According to the manufacturer, Alloskin AC (Q4141) is not commercially available.

AmnioCare®, AmnioMatrix®, and FloGraft™
AmnioGenic Therapy™ (Applied Biologics™ LLC. Phoenix, AZ) includes various amniotic membrane products proposed for various indications. These products are regulated by the FDA guidelines for banked human tissue. AmnioMatrix® is a cryopreserved, allograft liquid wound covering and is most commonly used as a filling agent for soft tissue injuries, hollow regions of bone, and as an anti-inflammatory wound dressing. Other proposed uses include the treatment of skin and soft tissue ulcerations, plantar fasciitis, muscle tears, repetitive motion/overuse injuries, tendinopathies, bone injuries resistant to healing, arthritis, and failed back surgery syndrome due to epidural scar formation. AmnioGenic Therapy™ amniotic products also include AmnioCare® which is a patch proposed as a wound covering for tendons and nerves at the surgical site. FloGraft™, a cryopreserved tissue matrix, is proposed for use as a soft tissue defect filler. FloGraft is proposed for the treatment of tendinitis, tendinosis, soft tissue trauma and defects, plantar fasciitis, Charcot, ligament tears and strains and other orthopedic injuries. Studies are primarily in the form of case reports and case series with small patient populations (n=≤20) (Applied Biologics, 2013). There is insufficient evidence in the published peer reviewed literature to support the safety and efficacy of AmnioGenic Therapy or amniotic membrane for these indications.

AmnioExCel and AmnioMTM
AmnioExCel or BioDExCel™ (AmnioGenix™, LLC. Collierville, TN) is a non-crosslinked, human amniotic extracellular matrix that acts as a scaffold for cellular attachment. The product includes EGF, TGF-ß, FGF, PDGF A & B, VEGF, IFG 1 & 2 growth factors. AmnioExCel is a FDA-registered device regulated as a human tissue product. Proposed applications include: wound covering, ridge augmentation, soft tissue repair, periodontal defects, boney defects and sinus coverage. AmnioMTM™ is the injectable form of the amnion allograft (AmnioGenix, 2011). There is insufficient data in the published clinical trials to support the safety and efficacy of AmnioExCel and AmnioMTM.

AmnioFix® Amniotic Membrane
AmnioFix (MiMedx Group, Kennesaw, GA) is an amniotic membrane extracellular collagen allograft comprised of an epithelial layer and two fibrous connective tissue layers with growth factors. It is a wrap proposed for nerve and tendon protection to enhance healing. Amniotic membrane is a banked human tissue regulated by the AATB and does not require FDA approval. Surgical Biologics uses a Purion® process to prepare AmnioFix specifically for spinal surgeries including: anterior lumbar interbody fusion (ALIF); anterior cervical discectomy and fusion (ACDF), laminectomy, discectomy posterior lumbar interbody fusion (PLIF) and transforaminal lumbar interbody fusion (TLIF) (MiMedx, 2013). AmnioFix also comes in an injectable form.

Other AmnioFix products include: AmnioFix injectable which is a powder form intended for treatment of “tendon and soft tissue injuries, such as patellar tendon inflammation, tendonitis, tendonosis, plantar fasciitis, tennis elbow”. AmnioFix Sports Med and AmnioFix Wrap are for nerve and tendon protection (MiMedx, 2013). There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of Amniofix products.

Zelen et al. (2013) conducted a single-center randomized controlled trial to examine the effectiveness of AmnioFix injectable amniotic membrane for the treatment of refractory plantar fasciitis (n=45). Recruited patients were 18 years or older and were recalcitrant to three of the following treatments: rest, ice, compression, and elevation (RICE); corticosteroid injection; stretching exercises; nonsteroidal oral antiinflammatory agents; and orthotics. Patients were randomized to standard care, 2 cc injection of 0.5% Marcaine plain, then 1.25 cc saline (controls) or 0.5 cc AmnioFix, or 1.25 cc AmnioFix (n=15 per group). Follow-ups occurred for eight weeks. At one week significant improvement in plantar fasciitis symptoms was observed in patients receiving Amniofix injection compared to those receiving saline injections. There was a significant improvement in the American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot scores at 1 week and at eight weeks follow-up ($p<0.001$, each). No significant treatment response was reported in patients injected with saline. No adverse events related to AmnioFix were reported. Limitations of the study include the short-term follow-up and small patient population.

Architect™ Biomatrix
Architect Biomatrix (Harbor MedTec, Inc., Irvine, CA) is an equine, pericardial, extracellular collagen matrix. It was approved by the FDA 510 (k) process in 2013 as Harbor MedTech BriDGE Extracellular Collagen Matrix Wound Dressing. FDA approved indication is for the local management of moderately to heavy exudating wounds including: partial and full thickness wounds, draining wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds and surgical wounds. Architect is processed by a proprietary patented BriDGE™ process. The matrix is available in four sizes in standard and fenestrated sheets (FDA, 2013; Harbor MedTec, 2014). Evidence supporting the safety and efficacy of Architect is lacking. Studies are primarily in the form of case reports.

ArthroFlex™ Acellular Bio-Implant for Soft Tissue Repair
ArthroFlex or FlexGraft® (LifeNet Health, Virginia Beach, VA) is a decellularized human allograft dermis implant proposed for soft tissue repair including shoulder reconstruction, fat pad repair of the foot and Achilles tendon repair. The allograft is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. Based on the size and thickness the product may be referred to as Aflex100, Aflex101, or Aflex200 (LifeNet Health, 2011). Data in the peer-reviewed scientific literature supporting the safety and effectiveness of Arthroflex are lacking.

BioDfactor™/BioDfence™/BioDfence™ DryFlex
Amedico Corporation (Salt Lake City, UT) provides three products proposed for use as physical barriers between the dura and soft tissue of the paraspinal muscles to reduce fibroblast infiltration into the epidural space and postoperative scarring. The products are human amniotic tissue allografts that are resorbed into the body during healing. They are regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. BioDfactor is a cryopreserved liquid form of the allograft extracellular matrix and comes in 0.25 ml, 0.5 ml and 1.25 ml. BioDfence Resorbable Adhesion Barrier comes in sheets 1X2 cm, 2X2cm, 2X6Cm and 4X4 cm. BioDfence DryFlex comes in sheets 2X3 cm, 2X6 cm, 4X4 cm and 4X8 cm. There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of these products.

Biodesign® (Surgisis®) AFP™ Anal Fistula Plug
The Biodesign (Surgisis) AFP Anal Fistula Plug (Cook Biotech Inc., West Lafayette, IN) is a porcine-based acellular matrix and is contraindicated in patients who are sensitive to porcine materials (Cook Biotech Inc., 2009). The Surgisis AFP (i.e., SIS Fistula Plug) received 510(k) approval from the FDA in March 2005 for "implantation to reinforce soft tissue where a rolled configuration is required, for repair of anal, rectal, and enterocutaneous fistulas."

Evidence in the published peer-reviewed scientific literature does not support the safety and efficacy of the Surgisis AFP. Studies have primarily been in the form of case series and retrospective reviews with small, heterogeneous patient populations, and short-term follow-ups. Randomized controlled trials have reported no significant difference with the use of Surgisis AFP or worse outcomes. Appropriate candidates for AFP have not been established. Outcomes varied based on the type of fistula, the presence of single vs. multi-track fistula, and whether or not the patient had undergone previous fistula surgical procedures. Poorer results were reported in patients who were smokers, diabetics, and/or had Crohn's disease. Failure rates were reported as high as 59% and recurrence rates as high as 75%. Some studies reported a decline in the success rate over time. One of the most common reasons for failure was due to plug expulsion. Studies also reported the occurrence of postoperative sepsis as high as 89%.

Van Koperen et al. (2011) conducted a double-blinded, multicenter, randomized controlled trial to compare Surgisis Anal Fistula Plug (n=31) to a mucosal advancement flap (n=29) for the treatment of cryptoglandular high transsphincteric perianal fistulas. At the 11-month median follow-up, the recurrence rate was not significantly different (p=0.126) between the two groups with fistula plug patients and 15 mucosal advancement flap patients experiencing recurrence. There were also no significant differences in postoperative pain, pre- and postoperative incontinence scores, soiling and quality of life. There were no intraoperative complications and one postoperative complication in a fistula plug patient and two complications in advancement flap patients. Limitations of the study include the small patient population and short-term follow-up.

In a randomized controlled trial, Ortiz et al. (2009) compared the outcomes of Surgisis AFP (n=16) to endorectal advancement flap (ERAF) (n=16) for the treatment of patients with high fistula in ano of cryptoglandular etiology. Sixteen patients had previously undergone ERAF. Recruitment was stopped because of the high recurrence rate following AFP. Follow-up evaluations were performed by an independent observer for up to one year postoperatively. Within the first postoperative year, a statistically significant difference was seen in 12 AFP patients who had fistula recurrence compared to two ERAF patients ($p<0.001$). Nine of 16 patients who had undergone previous surgery, experienced fistula recurrence, and eight of the nine were in the AFP group. Postoperatively, one AFP patient experienced recurrence with abscess, three had plug dislodgement, and eight had persistent leakage around the plug. Two ERAF patients experienced recurrences. In this study, AFP was associated with a low rate of healing especially in patient with previous fistula surgery.

Schwandner et al. (2009) prospectively evaluated the efficacy of the Surgisis AFP in 60 patients with single transsphincteric anorectal fistulas. Vessel loop drainage was applied for at least eight weeks prior to plug insertion. Follow-up occurred for up to 12 months. Complete healing was observed in 37 cases (62%). At 26 weeks, 38% had unhealed fistulas. There were no significant differences in preoperative and postoperative continence scores. Two plugs were expelled on postoperative day one and reinserted without further complications.

In a prospective case series, Zubaidi and Al-Obeed (2009) evaluated the efficacy of the Surgisis AFP in patients (n=22 patients; 23 fistulas) with chronic and/or complicated anorectal fistulas that were not amenable to fistulotomy. Most of the fistulas were primary in nature and had not undergone previous surgical intervention. A draining seton was used in 11 cases. The plugs were sutured in place. Follow-up ranged from 6–18 months (mean 12 months). At the final follow-up, 19 of 22 (86%) patients had successful closure. Three fistulas failed to close.

Additional prospective case series have reported mixed outcomes. Garg, (2008) reported complete healing in 15 of 23 patients (71.4%) in 6–18 months. Better outcomes were reported in single track fisulas vs. multi-track fistulas. With a median follow-up of 6.5 months, Ky et al. (2008) (n=45) reported that plug success declined over time, dropping from 84% to 54.6% at 12 months. Outcomes were significantly better in simple fissure closures compared to complex fissure closures ($p<0.02$), with first plug closures compared to repeat closures ($p=0.001$), and with patients without Crohn's disease ($p<0.02$). Schwandner et al. (2008) conducted a prospective study to analyze the efficacy of the Surgisis AFP for the closure of cryptoglandular and Crohn's disease-associated transphincteric anorectal fistulas. The overall success rate was 61% (12 of 18). The success rate for the cryptoglandular fistulas was 45.5% (5 of 11) and 85.7% (6 of 7) for the Crohn's associated fistulas. The failure rate was 27.8% at nine months.

Thekkinkattil et al. (2008) conducted a prospective case series (n=43) for the treatment of anorectal, rectovaginal and pouch vaginal fistula. Complete healing occurred in 44% of patients. Nonhealing in ten patients (22%) was due to dislodgement of the plug. Van Koperen et al. (2007) conducted a prospective, two-center clinical study in patients (n=17) with complex high perianal fistulas. This data suggested a 41% success rate using the anal fistula plug to treat complex high perianal fistulas. The most common reason for recurrence was plug expulsion (7 of the 10 recurrences).

Biodesign® (Surgisis®) Hiatal Hernia Graft

Surgisis Hiatal Hernia Graft is derived from a porcine source and proposed for implantation to reinforce soft tissue where weakness exists including paraesophageal/hiatal hernias. Per the FDA 510(k) (2006) approval for SIS Hernia Repair Device and Surgisis Gold Hernia Repair Graft, the devices are "intended to be implanted to reinforce soft tissue where weakness exists. Indications for use include the repair of a hernia and body wall defect." There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and

efficacy of Surgisis Hiatal Hernia Graft. Studies are primarily in the form of case reports, retrospective reviews and case series with small patient populations (n=5-6) and short-term follow-ups, reporting a high hernia recurrence rate.

Oelschlager et al. (2006) conducted a randomized controlled trial to compare the outcomes of paraesophageal hernia repair with primary repair (n=57) to primary repair with Surgisis (n=51). At the six-month follow-up, four SIS patients and 12 primary repair patients developed a recurrent, > 2 centimeter hernia (p=0.04). There were no significant differences in operative times and perioperative complications. Both groups experienced significant improvement in heartburn, regurgitation, dysphagia, chest pain, early satiety, postprandial pain and improved quality of life symptoms following surgery with no significant differences between the groups. Limitations of the study include the small patient population, short-term follow-up and the lack of follow-up data on 18 patients (i.e., seven incomplete questionnaire data and eleven did not have an x-ray).

Biodesign® (Surgisis®) Inguinal Hernia Graft
The Biodesign (Surgisis) Inguinal Hernia Matrix (SIS Hernia Repair Device, Surgisis Gold Hernia Repair Graft) (Cook Biotech Inc., West Lafayette, IN) is a porcine derived device. Per the FDA 510(k) (2006) approval for SIS Hernia Repair Device and Surgisis Gold Hernia Repair Graft, the device is "intended to be implanted to reinforce soft tissue where weakness exists. Indications for use include the repair of a hernia and body wall defect." There is insufficient data from clinical trials to support the efficacy of this matrix. Studies are primarily in the form of case reports and case series with small patient populations (n=5-67) and short-term follow-ups.

Ansaloni et al. (2009) conducted a blinded, randomized controlled trial to compare the safety and efficacy of the use of Inguinal Hernia Matrix (SIHM) (n=35) to polypropylene mesh (n=35) in Lichtenstein's repair of noncomplicated, primary inquinal hernias in men. The primary endpoint was the degree of postoperative pain using a visual analogue scale or a simple verbal scale. The investigators were unaware of the mesh used. The first 24 postoperative hours a significant number of patients in the SIHM group developed self-subsiding hyperpyrexia (temperature > 38°) compared to the polypropylene group ($p<0.05$). During the three year follow-up period, a significant decrease in the incidence of postsurgical pain was not seen in the SIHM group, but a significantly lower degree of pain was detected at rest and on coughing at 1, 3, and 6 months, on movement at 1, 3, and 6 months and 1, 2, and 3 years, and use of pain medication at 1, 3, and 6 months ($p<0.05$, each). No significant differences were noted in pain localization and irradiation. One recurrence was noted in the polypropylene group. Both groups experienced hematomas and seromas that resolved without treatment within the first three postoperative months. The SIHM group had a trend in higher incidence of complications (especially seromas), but compared to the polypropylene group the difference wasn't significant The authors noted that their sample size was "too small to prove absolute efficacy in terms of low recurrence rate", Additional prospective studies are needed to establish the safety and efficacy of Inguinal Hernia Matrix.

Biodesign® (Surgisis®) RVP™ Recto-Vaginal Fistula Plug™
Biodesign (Surgisis) RVP Recto-Vaginal Fistula Plug (Cook Biotech Inc., West Lafayette, IN) is a surgical mesh skin substitute manufactured from porcine small intestinal submucosa. It is supplied in a tapered configuration with a button to allow increased retention. The button eventually falls off leaving the plug to seal the opening between the rectum and the vagina. The Plug is FDA-510(k) approved for "implantation to reinforce soft tissue for repair of recto-vaginal fistulas" (FDA, 2006). There is insufficient evidence in the published peer-reviewed scientific literature to establish the safety and efficacy of Surgisis RVP. Studies are primarily in the form of case series with small patient populations and short-term follow-ups (1–21 weeks). Failure rates were as high as 65% due to dislodgement of the plug (Gonsalves, et al., 2009).

BioVance®
BioVance (Alliqua™ Biomedical, Langhorne, PA) is a dehydrated amniotic membrane allograft proposed for the treatment of acute and chronic wounds including burns, diabetic ulcer, venous leg ulcers, pressure ulcers and surgical wounds. The product is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. BioVance is available in four sizes (Alliqua Biomedical, 2014). There is insufficient evidence in the published peer-reviewed literature to support the efficacy of BioVance. Studies are primarily in the form of case series with small patient populations.

Clarix® Regenerative Matrix
Clarix Regenerative Matrix (Amniox Medical, Inc., Marietta, GA) is an amniotic membrane processed by Amniox's patented Cryotek™ Process that utilizes a deep freezing technique (cryopreserved) to preserve the

membrane. The membrane is proposed for surgical covering, wrap or barrier. Based on the size of the membrane, it comes in two different products. Clarix is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. There are two preparation of the matrix based on the thickness and size: Clarix 1K (4 sizes) and Clarix 100 (3 sizes) (Amniox, 2014). There is insufficient evidence in the published peer-reviewed literature to support the efficacy of Clarix. Studies are primarily in the form of case reports.

Conexa™ Reconstructive Matrix
Conexa Reconstructive Matrix (Tornier, Inc., Edna, MN) is a porcine dermis tissue substitute that is FDA 510(k) approved as LifeCell Tissue Matrix (LTM) Surgical Mesh (LifeCell Corporation, Branchburg, NJ). According to the FDA (2008) the matrix is intended "for the reinforcement of soft tissue repaired by sutures or suture anchors during tendon repair surgery including reinforcement of rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Indications for use also include the repair of body wall defects which require the use of reinforcing or bridging material to obtain the desired surgical outcome. The device is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Sutures, used to repair the tear, and sutures or bone anchors used to attach the tissue to the bone, provide biomechanical strength for the tendon repair." Based on the thickness of the matrix, this product is available as Conexa 100 and Conexa 200 (Tornier, 2013). There is insufficient evidence in the published peer-reviewed scientific literature supporting the safety and effectiveness of Conexa as studies have primarily been in the form of individual case reports (Stover, et al., 2009).

CorMatrix® ECM®
CorMatrix ECM products are a porcine, small intestinal submucosa (SIS) extracellular matrix. There are three CorMatrix FDA approved products. The CorMatrix ECM® for Pericardial Closure is FDA 510(k) approved as a pericardial patch for the "reconstruction and repair of the pericardium" (FDA, 2005). The CorMatrix ECM Patch for Cardiac Tissue Repair is FDA 510(k) approved for "use as an intracardiac patch or pledget for tissue repair (i.e., atrial septal defect [ASD], ventricular septal defect [VSD], etc.) and suture-line buttressing (FDA, 2007). The CorMatrix ECM for Carotid Repair received FDA 510(k) approval in July of 2011. This patch is "intended for use as a patch material for vascular reconstruction and repair of the carotid artery, including patch closure following carotid endarterectomy and. suture line buttressing and will be available to repair the carotid artery including patch closure following endarterectomy procedures" (FDA, 2011).

There is a paucity of evidence supporting the safety and effectiveness of the CorMatrix products. Published studies are primarily in the form of case reports, case series and retrospective reviews with small, heterogeneous patient populations and short-term follow-ups. Quarti et al. (2011) prospectively reported on 26 patients, ages 8 days–32 years, who underwent congenital heart repair using CorMatrix for cardiac tissue repair and pericardial closure. The patch was used for repair in ten pulmonary artery patch arterioplasties, nine valve leaflet extensions, four ascending aortic patch aortoplasties and three aortic arch reconstructions. In four cases, the procedure involved pericardial closure using the same patch. At a mean 13.2 month follow-up (range 4–25 months), there were no reported patch-related complications. The authors noted that studies with longer follow-up are needed "to understand the full potential" of CorMatrix.

Cryoskin®
Cryoskin (Altrika Ltd, Sheffield, United Kingdom) is a frozen mono-layer sheet of undifferential allogenic keratinocysed attached to a silicone backing. The product includes growth factors and cytokines. It is proposed as a treatment option for burns and hard to heal wounds or as an adjunct to meshed grafting to enhance closure and reduce scarring. It has also been used as a covering for donor sites. Altrika is licensed by the UK Medicines and Healthcare Products Regulatory Agency (MHRA). Per the manufacturer "Cryoskin® is available as an unlicensed medicine under specific circumstances" (Altrika, 2011). It is also available in a spray form from Regenrys Ltd. (Sheffield, United Kingdom) who acquired Altrika. Data supporting the safety and efficacy of Cryoskin are lacking.

Cymetra™
Cymetra (LifeCell Corporation, Branchburg, NJ) is a micronized form of AlloDerm. It is processed from human tissue obtained from tissue banks and is therefore, classified by the FDA as human tissue for transplantation. The allograft tissue is processed into a particulate acellular dermal matrix, dried and placed in a syringe. It is to be used in transplantation for the repair or replacement of damaged or inadequate integumental tissues (e.g., injection laryngoplasty) (LifeCell, 2010). Cymetra is proposed for the treatment of vocal fold scars, presbyphonia,

Parkinson-related dysphonia, and medialization of vocal folds following thyroplasty. Due to resorption, repeated injections may be indicated (Simpson, et al., 2008; Remacle and Lawson, 2007; Simpson, 2006). Cymetra is also proposed for use for smoothing deep wrinkles, nasolabial lines, lip enhancement, and repair of acne scarring.

Studies evaluating the efficacy of Cymetra injections for vocal fold immobility are primarily in the form of case studies or retrospective reviews with small patient populations (n=6–34) and short-term follow-ups. Milstein et al. (2005) conducted a retrospective review of 20 patients treated with Cymetra for unilateral vocal fold paralysis. Following injections, significant improvements were seen in glottal closure ($p<0.001$), dysphonia ($p<0.001$), and self-perceived voice quality ($p<0.01$). Improvements following the injections were temporary for five patients, lasting three months for three patients. Eight patients had results that lasted one year or longer. Further investigation is warranted to assess long-term benefits.

Dermacell™
Dermacell (LifeNet Health®, Virginia Beach, VA) is an acellular human dermis allograft collagen scaffold proposed for the treatment of second and third degree burns, breast reconstruction, chronic non-healing wounds, dehisced wound sites and cosmetic reconstruction after traumatic burn injuries. LifeNet Health is registered with the FDA as an establishment producing tissue- and cellular-based products. Arthrex® processes and distributes DermACELL® for the treatment of diabetic foot ulcers and chronic nonhealing wounds. MatrACELL® is a patented process that renders Demacell acellular (Arthrex, 2013; LifeNet Health, 2012). There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of Demacell.

DermaMatrix Acellular Dermis
DermaMatrix (Synthes Inc., West Chester, PA) is an allograft derived from human skin and is classified by the FDA as banked human tissue. This dermal collagen matrix is proposed for repair of facial soft tissue defects, eyelid or anophthalmic reconstruction, nasal reconstruction, septal perforation, parotidectomy, cleft palate repair, oral resurfacing, vestibuloplasty, radial forearm free flap repair, breast reconstruction postmastectomy, and abdominal wall repair. There is insufficient evidence in the published peer-reviewed scientific literature to establish the efficacy of DemaMatrix for tissue repair and reconstruction. Studies are primarily in the form of retrospective reviews with small patient populations.

Becker et al. (2009) conducted a retrospective review to compare the outcomes of DermaMatrix (n=25) to AlloDerm (n=25) in patients who underwent immediate expander-based breast reconstruction following unilateral (n=20) or bilateral mastectomy (n=10). The median follow-up for the AlloDerm group was 15 months and 13.5 months for the DermaMatrix group. The only significant difference in the operative and reconstructive course between the two groups was that the AlloDerm patients had drains in place 11 mean number of days compared to 13 mean number of days in the DermaMatrix group ($p=0.02$). The DermaMatrix group had one incidence of seroma and one infection/cellulites. There were no complications in the AlloDerm group.

DermaSpan™
DermaSpan (BioMet® Biologics Inc., Warsaw, IN) is an acellular dermal matrix derived from allograft human skin. The product is regulated by the FDA's American Association of Tissue Banks and regulatory process for testing and donor screening and prepared by a Biologics proprietary process. DermaSpan is proposed for repair or replacement of damaged or inadequate integumental tissue (wound coverage), and as supplemental support, protection, reinforcement or covering of tendons (BioMet, 2013). There is insufficient evidence to support the safety and efficacy of DermaSpan.

Duraform™
Duraform Dural Graft Implant (Codman & Shurtleff, Inc., Raynham, MA) is a collagen-based biocompatible implant approved by the FDA 510(k) process for "use in procedures where the repair or substitution of the patient's dura mater is needed (FDA, 2004). The overlay is proposed to prevent spinal fluid leakage. There is insufficient evidence in the peer-reviewed published literature to support the safety and efficacy of Duraform.

DuraGen®
DuraGen (Integra LifeSciences Corp., Plainsboro, NJ) is a family of collagen absorbable implants or onlay grafts proposed for repair of dural defects. The grafts are made from bovine achilles tendon. The DuraGen Plus® Dural Regeneration Matrix - Spinal Matrix and the Integra™ SpinalMend™ Dural Regeneration Matrix are FDA 510(k) approved "as a dura substitute for the repair of dura mater" (FDA, 2010). There is insufficient evidence to support

the safety and efficacy of Duragen implants. Studies are primarily in the form of case reports and retrospective reviews.

Williams et al. (2013) conducted a randomized controlled trial (n=34) to compare the efficacy of DuraGen (n=16), a sutureless device to Dura-Guard (n=18), a suturable device. The objective of the study was to determine if suturing the dural patch was essential for reduction of complications or whether sutureless patches correlated to worse outcomes. The authors also completed a cost analysis. Subjects were age 18 years and older with a clinical diagnosis of Chiari Malformation I (CM I). Follow-up occurred for three months. Postoperatively, there were no significant differences in complications, pseudomeningocele, meningitis, CSF leak, readmissions or emergency room visits and no patients had a wound infection. SF−36 Quality of Life Questionnaire scores showed no significant differences in patient's physical health ($p<0.005$) and function ($p<0.005$) were significantly improved. All patients showed a significant improvement in their outcome response ($p=0.0112$). Limitations of the study include the small patient population and short-term follow-up.

Dura-Guard®
Dura-Guard (Synovis® Surgical Innovations, St. Paul, MN) is prepared from a bovine pericardium cross-linked with glutaraldehyde. It is a membraneous implant sutured to the surrounding dura. The device is FDA 510 (k) approved for closure of dura mater during neurosurgical procedures. The product is available in five different sizes (Synovis, 2010; FDA, 1998). There is insufficient evidence to support the safety and efficacy of Dura-Guard. As noted above in DuraGen, Williams et al. (2013) compared DuraGen to Dura-Guard and found no significant differences between the products.

DuraMatrix™
DuraMatrix Collagen Dura Substitute Membranes and DuraMatrix-Onlay™ (Collagin Matrix, Inc., Franklin Lakes, NJ) are resorbable matrices made from collagen derived from bovine Achilles tendon. The devices are FDA 510(k) approved for "use as a dural substitute for the repair of dura mater" (FDA, 2006). The membrane can be applied either as an inlay or sutured in place. Due to the lack of evidence in published clinical trials, the safety and efficacy of DuraMatrix implants have not been established.

DuraSeal™ Dural Sealant System
The DuraSeal Dural Sealant System (Confluent Surgical, Inc., Waltham, MA) consists of synthetic absorbable sealant materials and an applicator used to apply the sealant to an incision site. The sealant is approved by the FDA premarket approval (PMA) process "for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure. DuraSeal should only be used with autologous duraplasty." The sealant is composed of a polyethylene glycol (PEG) ester solution and a trilysine amine solution that are mixed together to form a gel. The gel is applied to the suture site to prevent cerebrospinal fluid leakage and is proposed to be absorbed in four to six weeks (FDA, 2009; FDA, 2005).

Osbun et al. (2012) conducted a multicenter, randomized controlled trial to assess the safety and efficacy of DuraSeal Dural Sealant System (n=120) compared to a control group treated with standard procedure based on the surgeon's judgment (e.g., application of additional sutures; soft tissue patches from muscle, pericardium or fasicia;vacularized grafts of muscle and pericranium; off-label use of various biological products including fibrin glues, gelatin and collagen sponges, dural substitutes, and/or hemostatic agents) (n=117). Patients underwent infratentorial or supratentorial procedures. There were significant differences in sealing methods between the two approaches. Some patients in both groups required autologous duraplasty. There were no significant differences between the groups in neurosurgical complications, reoperation/unplanned interventions, surgical wound complications, central nervous system events, cerebral spinal fluid leaks or surgical site infections within the first 30 postoperative days. The authors noted that a limitation of the study included a significantly greater number of infratentorial procedures were performed in the control group ($p=0.04$). Other limitations include the use of two different surgical approaches and the short-term follow-up. Additional randomized controlled trials are needed to validate the safety and efficacy reported in this study.

DuraSeal™ Spine Sealant System
DuraSeal™ Spine Sealant System (Covidien, Waltham, MA) is FDA PMA approved "for use as an adjunct to sutured dural repair during spinal surgery to provide watertight closure" to prevent CSF leakage through the suture pinholes and gaps between stitches. The system is composed of two solutions, a PEG ester solution and a Trilysine amine solution. When mixed together, the precursors polymerize to form the hydrogel sealant. The

sealant is sprayed or layered on the sutured site. Since the sealant is more than 90% water, it is absorbed within four to eight weeks following surgery. The hydrogel may swell up to 50% of its size in any dimension (FDA 2009).

Kim and Wright (2011) conducted a multicenter, randomized controlled trial to assess the safety and efficacy of DuraSeal Spinal Sealant (n=102) compared to standard methods (n=56) (control group). Examples of control group procedures included sutures or sutures plus fibrin glue. Postoperative follow-ups occurred at 30 and 90 days. Nine patients required a second application of DuraSeal for continued leakage on Valsalva. In the control group, 20 patients had a nonwatertight closure and 16 received no further treatment per the surgeon's discretion. Patients treated with DuraSeal had a significantly higher rate of watertight closure compared to the control group ($p<0.001$). No statistically significant differences were reported in postoperative cerebrospinal fluid leakage (CSF) ($p=1.00$), infection, and wound healing. No neurologic deficits were seen attributable to the sealant. Study limitations noted by the authors included the choice of the intraoperative watertight dural closure with Valsalva as the primary end point instead of postoperative CSF leak and in the control group some investigators chose not to attempt second treatment method per protocol but instead used another adjunctive therapy. Other limitations of the study are the unequal number of patients in the groups and the short-term follow-up. Additional studies are needed to support the safety and efficacy of DuraSeal Spinal Sealant.

Durepair® Regeneration Matrix
Durepair Regeneration Matrix (Medtronic Neurosurgery, Goleta, CA) is a biological fetal bovine collagen implant that is FDA 510(k) approved for the repair of defects in the dura mater. The scaffold is proposed to prevent cerebrospinal fluid leakage and allow healing of openings in the dura by the ingrowth of fibroblasts and blood vessels on the scaffold (FDA, 2004). Evidence from the published peer-reviewed scientific literature supporting the safety and efficacy of Durepair is lacking.

Endoform Dermal Template™
Endoform Dermal Template (Mesynthes Ltd, Wellington, New Zealand) is an ovine (sheep)-derived extracellular matrix that is FDA 510(k) approved for single use in the treatment of "partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree bums; and skin tears) and draining wounds" (FDA, 2010). The template is a temporary matrix that is completely replaced by the patient's own tissue over time. There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Endoform.

Epifix® Injectable
Epifix Injectable (MiMedx Group, Kennesaw, GA) is a micronized powder form of Epifix amniotic membrane discussed above. The particulate form is available in 40 mg, 100 mg and 160 mg preparations. There is insufficient evidence to support the safety and efficacy of Epifix Micronized Powder nor is its use an established standard of care.

Excellagen®
Excellagen (Tissue Repair Company, San Diego, CA) is a bovine collagen gel FDA approved by the 510 (k) process. The device is composed of formulated, 2.6% fibrillar bovine dermal collagen (Type 1) that is topically applied. Excellagen is intended for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic avascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds and draining wounds. The gel is packaged in a single-use 1.0 cc syringe containing 0.5cc of collagen (Cardium Therapeutics, 2014; FDA, 2011). There is insufficient evidence to support the safety and efficacy of Excellagen. Studies are primarily in the form of case series (n=3) and case reports.

EZ Derm™
EZ Derm (Brennen Medical, Inc., St. Paul, MN) is a porcine-derived, biosynthetic xenograft. The product is FDA 510 (k) approved as a collagen, wound dressing. The manufacturer's recommended indications for use are as a temporary wound covering for partial-thickness burns, donor sites, autograft sites and ulcers. Evidence in the published peer-reviewed scientific literature is insufficient to make a determination regarding the efficacy of EZ Derm.

GammaGraft
GammaGraft (Promethean Lifesciences Inc., Pittsburg, PA) is an irradiated human skin allograft harvested from cadaveric donors and contains epidermal and dermal layers of skin. It is a temporary graft proposed for the

treatment of venous stasis ulcers; diabetic foot ulcers; full-thickness ulcers; Mohs surgery sites; skin graft donor sites; partial thickness wounds; burns; areas of dermabrasion; temporary coverage of exposed abdominal viscera, including small bowel and liver; exposed pericranium and cranium; fasciotomy sites; as a test on a wound bed before autografting; and areas of excision which are not closed pending final pathology report. GammaGraft is regulated by the FDA as human tissue because it is donated human skin and not an engineered product (Promethean Lifesciences, 2008). Evidence in the published peer-reviewed scientific literature does not support the efficacy of GammaGraft.

GORE BIO-A® Fistula Plug
The GORE BIO-A Fistula Plug (W.L. Gore & Associates, Inc., Elkton, MD) is FDA approved as a Class II, 510(k) synthetic bioabsorbable scaffold intended for use in the reinforcement of soft tissue for repair of anorectal fistulas. Cell migration into the scaffold and tissue is generated as the body gradually absorbs the synthetic material (FDA, 2009). There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of this device.

Grafix®
Grafix Cellular Repair Matrix (Osiris Therapeutics, Inc., Columbia, MD) is an extracellular matrix that includes growth factors and mesenchymal stem cells (MSC) and is proposed for the treatment of acute and chronic wounds (e.g., diabetic foot ulcers, burns). Grafix is regulated by the FDA as banked human tissue and Osiris is accredited by the American Association of Tissue Banks (AATB) (Osiris, 2012). Osiris also markets Grafix Multipotent Cellular Repair Matrix ($Grafix_{PRIME™}$, $Grafix_{CORE™}$) proposed to promote healing and tissue repair for chronic wounds, limb salvage procedures, tendon repair and burns. There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of these Osiris products for any indication.

GraftJacket® Xpress
GraftJacket Xpress (Wright Medical Technology, Inc., Arlington, TN), a flowable soft-tissue scaffold, is a powdered form of the GraftJacket tissue matrix. Using saline, it is reconstituted and injected into a wound. The scaffold is proposed for filling deep tunneling-type chronic wounds such as those found in chronic diabetic foot ulcers. The skin substitute is packaged in a syringe and intended for one time use. This product is regulated by the FDA as human tissue for transplantation.

There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of GraftJacket Xpress. Studies have primarily been in the form of retrospective reviews with small patient populations and short-term follow-ups (Brigido, et al., 2009).

hMatrix®
hMatrix Acellular Dermis (Bacterin International Holdings Inc., Belgrade, MT) is an acellular dermal scaffold processed from donated human skin. The dermis is processed using a proprietary method and the matrix is packaged and sterilized using low-dose gamma irradiation. hMatrix is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. The product is stored and supplied frozen. Bacterin offers three hMatrix preparations: hMatrix Acellular Dermis for wound applications; hMatrix PR for breast augmentation, abdominal wall repair, and facial reconstruction; and SportMatrix onlay for tendon augmentation (Bacterin, 2013). There is insufficient evidence to support the safety and efficacy of hMatrix as a skin substitute.

Hyalomatrix PA®
Hyalomatrix PA (Anika Therapeutics, S.r.l., Padova, Italy) is a bilayered, biodegradable acellular dermal skin substitute composed of hyaluronic acid and a semipermeable silicone membrane that acts as a scaffold for cellular invasion and capillary ingrowth. The matrix is FDA 510(k) approved "for the management of wounds including: partial and full-thickness wounds; second and third-degree bums; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undetermined wounds; surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, skin tears); and draining wounds" (FDA, 2007). There is insufficient evidence in the peer-reviewed scientific literature to support the safety and effectiveness of Hyalomatrix PA. Studies have primarily been in the form of case series and retrospective reviews. Prospective randomized controlled trials comparing Hyalomatrix PA to standard therapy are indicated.

Gravante et al. (2007) conducted a prospective case series (n=300) to assess the outcomes of a "bridge" treatment for deep-partial thickness burn patients. The treatment involved removing necrotic debris by

dermabrasion followed by the application of Hyalomatrix PA on the third to fifth hospital day. Dressings were changed every seven days and areas without signs of recovery on day 21 were removed with escharectomy and covered with thin skin grafts. A total of 183 patients required only one treatment, 67 required more than one treatment and 50 patients required escharectomy. A total of 83% of patients healed within 21 days. A limitation of the study is the lack of a control or comparison group. Prospective randomized controlled trials are needed to validate the outcomes of this study.

HydroFix® Vaso Shield
HydroFix Vaso Shield (the "Vaso Shield") (MiMedx® Group, Inc., Marietta, GA) is a vessel guard made of hydrogel material using proprietary technology. Protection of veins and arteries is a common issue associated with many types of surgeries. Protection of the aorta, vena cava, iliac vessels and other anatomy is particularly important in anterior spine surgery. HydroFix® Vaso Shield was designed to help physicians protect vessels during anterior vertebral surgery. The Shield is FDA 510(k) approved "as a cover for vessels during anterior vertebral surgery". Intended uses include: fusion surgery, adjacent level surgery, artificial disc implantation, implant or hardware removal, trauma, and vascular surgery in the spine (FDA, 2011). Data in the form of clinical trials supporting the safety and effectiveness of HydroFix are lacking.

Integra™ Flowable Wound Matrix
Integra Flowable Wound Matrix (Integra Lifesciences Corp., Plainsboro, NJ) is an acellular bovine tendon collagen device that is 510(k) FDA approved for the treatment of advanced wound care. It is considered "substantially equivalent in function and intended use to Integra Matrix Wound Dressing" and is approved for the treatment of "partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds" (FDA, 2007). The skin substitute is packaged in a syringe and intended for one time use. There is insufficient evidence in the published peer-reviewed scientific literature supporting the efficacy of Integra Flowable Wound Matrix.

MatriStem®
MatriStem (Acell®, Inc., Columbia, MD), also called urinary bladder matrix (UBM), is an acellular device derived from the urinary bladder of pigs. The matrix is FDA 510(k) approved for the "management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second degree burns, skin tears) and draining wounds" (FDA, 2009). The matrix is resorbed and replaced with new tissue. MatriStem has also been proposed for the treatment of alopecia. Product types include the MatriStem Wound Care Matrix, MatriStem Plastic Surgery Matrix, MatriStem Burn Matrix, MatriStem Hernia Matrix, and MatriStem Micromatrix®, which consists of micronized particles that are sprinkled onto the wound and covered with a moist dressing. There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of MatriStem. ECRI conducted a literature review on MatriStem Surgical Matrix and Matristem MicroMatrix and concluded that although the products seem to work as intended studies are primarily in the form of case series with small patient populations and various wound types. No data was found that compared MatriStem to established methods of wound management (ECRI, 2014).

Matrix™ HD
Matrix HD (RTI Biologics, Inc., Alachua, FL), an acellular allograft human dermis of collagenous connective tissue, is proposed to support cellular revascularization and repopulation by the host tissue. Regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue, the matrix has been used in the repair of the deltoid muscle, patellar tendon, Achilles tendon, and shoulder capsule, as well as elbow capsule reconstruction, and fascia repair in the calf. It is also proposed as a wound covering (RTI Biologics, 2011). Evidence supporting the safety and efficacy of Matrix D from published clinical trials is lacking.

Mediskin™
Mediskin (Brennen Medical, Inc., St. Paul, MN) is a frozen porcine xenograft with a dermal and epidermal layer. The xenograft is 510(k) approved by the FDA as a collagen wound dressing. Per the manufacturer proposed uses include: temporary coverage prior to autograft, partial thickness skin loss, protect meshed autografts, outpatient skin loss, donor sites, skin ulcerations and abrasions (Brennen Medical, 2012). Due to the lack of evidence in published clinical trials, the safety and efficacy of Mediskin has not been established.

Memoderm™
MemoDerm (Memometal, Inc., Memphis, TN) is a sterile acellular dermal matrix derived from human allograft skin tissue and is regulated by AATB and FDA requirements for tissue processing. The matrix is proposed for use in various orthopedic procedures involving rotator cuff, anterior shoulder capsule, flex/extension tendons, ulnar collateral ligament, Achilles tendon, or lateral ankle complex, as well as for treatment of chronic diabetic foot ulcers (Memometal, 2011). There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of Memoderm

Neox™ Wound Matrix
Neox Wound Matrix, previously Neox 1K, (Amniox Medical™, [partner with Bio-Tissue, Inc.], Marietta, GA) is an amniotic membrane graft proposed for use as a wound covering for dermal ulcers and defects. The product, classified as a human tissue and cell-based product regulated by the AATB, is prepared using the Cryoteck™ process. It is proposed for single use as a surgical covering, wrap or barrier. Neox Cord1K is available in 4 sizes and Neox 100 quick peal is available in three sizes (Amniox Medical, 2014). The safety and efficacy of these products has not been established in randomized controlled trials.

NeuraGen® Nerve Guide and NeuraWrap™ Nerve Protector
NeuraGen Nerve Guide (Integra Life Sciences Corp., Plainsboro, NJ) is an absorbable, Type I collagen tubular matrix designed for peripheral nerve repair. The collagen tube is proposed to act as an interface between the nerve and surrounding tissue to promote healing across a nerve gap, therefore, replacing the need for a nerve graft. The NeuraWrap Nerve Protector is also an absorbable collagen implant that is proposed to provide an encasement and protection for injured peripheral nerves to isolate the nerve during the healing process (Integra LifeSciences, 2010). NeuraGen Nerve Guide is FDA 510(k) approve “for repair of peripheral nerve discontinuities where gap closure can be achieved by flexion of the extremity”. NeuraWrap is 510(k) approved “for the management of peripheral nerve injuries in which there has been no substantial loss of nerve tissue”.

There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of NeuraGen and NeuraWrap. Studies are primarily in the form of case series and retrospective reviews with small patient populations (n=8–96).

NuCel™/NuShield™ Spine/NuShield™ Orthopaedics
NuShield Spine (Nutech Medical, Birmingham, AL) is a bioabsorbable amniotic membrane proposed for use in various spinal surgeries including: decompression, foraminotomy, microdiscectomy, anterior lumbar interbody fusion (ALIF); laminectomy, discectomy, posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF) and lateral lumbar interbody fusion (XLIF).It is a biologic scaffold used as a barrier interface between the dura and surrounding musculature. Nutech Medical is registered as a tissue bank with the U.S. Food and Drug Administration (FDA). NuShield Orthopaedics, an amniotic membrane, is proposed for use as a scaffold for cellular migration and as a protective barrier for tendons and nerves following tendon repair. NuCel is a liquid form of amniotic membrane proposed for use in situations where a patch covering is “inadequate or inconvenient”. The product is mixed with the patient’s own blood and applied to the surgical site. NuTech noted that “there are no studies specifically related to the spine and/or orthopedics” using NuCel for these conditions (ECRI, 2012; Nutech Medical, 2012). Due to the lack of evidence in published clinical trials, the safety and efficacy of NuShield Spine, NuShield Orthopaedics and NuCel have not been established.

Oasis® Burn Matrix
Oasis Burn Matrix (Cook BioTech, Inc., West Lafayette, IN) is a porcine-derived acellular collagen matrix that is FDA 501(k) approved under the Oasis Wound Matrix device approval. The Burn Matrix is indicated for the treatment of partial-thickness burns. It is not indicated for the treatment of third degree burns (FDA, 2006). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Oasis Burn Matrix for the treatment of burns. Studies have primarily been in the form of case reports.

OrCel™
OrCel (Forticell Bioscience, Inc., New York, NY) (formerly called Composite Cultured Skin [CCS]) is an allogeneic, bilayered cellular matrix, Type I bovine collagen sponge with FDA PMA approval for the treatment of split-thickness donor site wounds in burn patients. There is limited evidence to support the efficacy of Orcel compared to the standard of care for the treatment of split-thickness donor sites. Therefore, OrCel is considered investigational for this indication. FDA-HDE approval was granted for OrCel for use as an adjunct in the

treatment of mitten-hand deformity surgery of epidermolysis bullosa. Published studies are in the form of case series with small patient populations (n=7). There is insufficient evidence to support the use of Orcel for any indication.

In a matched-pairs study conducted by Still et al. (2003), the use of OrCel was compared to treatment with Biobrane L. Eighty-two severely burned patients each had two designated split-thickness donor sites of equivalent surface area and depth. Sites were randomized to receive a single treatment of either OrCel or the standard dressing, Biobrane-L. Sites were evaluated for wound closure. The researchers found a statistically significant decrease in healing time with the use of OrCel compared to Biobrane L. There was a decrease in scarring associated with the use of OrCel, although it was not statistically significant. Additional clinical trials are needed to validate the findings of this study.

OrthADAPT™ Bioimplant
OrthADAPT Bioimplant (Pegasus Biologics, Inc., Irving CA) is a decellularized, biologic scaffold made from equine pericardium (xenograft). It is FDA 510(k) approved "to reinforce soft tissue including but not limited to: defects of the abdominal and thoracic wall, muscle flap reinforcement, rectal and vaginal prolapse, reconstruction of the pelvic floor, hernias, suture-line reinforcement and other reconstructive procedures. The device is also intended for the reinforcement of soft tissues repaired by sutures or suture anchors during tendon repair surgery including reinforcement of rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons" (FDA, 2007; Coons and Barber, 2006).

OsseoGuard®
The OsseoGuard Membrane (Biomet, Inc., Palm Beach Gardens, FLA) is a protective barrier made from bovine Type I Achilles tendon collagen proposed for the regeneration of hard and soft tissue in various dental defects including: localized ridge augmentation/future site preparation, peri-implant bone defects, extraction sockets, bone regeneration after root resection and sinus window coverage. The Osseo Guard Flex® Membrane is a resorbable collagen matrix made from Type I and Type III bovine dermis collagen. It is intended for use in oral surgical procedures as a resorbable membrane for: peri-implant defects in immediate or delayed extraction sockets, localized and alveolar ridge reconstruction, filling of bone defects, guided bone regeneration in dehiscence defects, and guided tissue regeneration in periodontal defects (Biomet, 2013). Biomet also provides OsseoGurad Flex™ Membrane which is proposed for defects in which more drapability is indicated. Data are primarily in the form of case reports and insufficient to establish the safety and efficacy of these products.

Ovation®
Ovation, an allograft product, is an injectable cellular repair suspension proposed for tissue repair. The product is regulated by the FDA under regulations for human cell, tissues and cellular and tissue-based products. Ovation is a three-dimensional collagen scaffold proposed to enhance wound healing. There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of Ovation.

Peri-Guard® Repair Patch
Peri-Guard Repair Patch (Peri-Guard) (Synovis® Surgical Innovations, St. Paul, MN; previously Biovascular, Inc.) is prepared from bovine pericardium cross-link with glutaraldehyde and manufactures with Synovis" exclusive Apex Processing®. Per the FDA 510(k) approval, Peri-Guard is "intended for repair of pericardial structures and for use as a prosthesis for the surgical repair of soft tissue deficiencies which include: defects of the abdominal and thoracic wall, gastric binding, muscle flap reinforcement, and hernias (including diaphragmatic, femoral, incisional, inguinal, lumbar, paracolostomy, scrotal, and umbilical hernias). Peri-Guard is also intended for use as patch material for intracardiac defects, great vessel, septal defect and annulus repair, and suture-line buttressing. Supple Peri-Guard Patch is a similar product proposed for procedures that require a more flexible and compliant patch (Synovis, 2010; FDA, 2012)

There is insufficient evidence in the peer-reviewed literature to support Peri-Guard Repair Patch for any indication. Studies evaluating the Patch include case reports, case series and retrospective reviews with small patient populations (n=5–92). Reported uses of the Patch included post-mastectomy breast reconstruction, chest wall reconstruction (e.g., due to secondary incisional herniation development following lung transplantation or malignant disease with chest wall infiltration) and diaphragmatic repair.

Peri-Strips Dry

Peri-Strips Dry (Synovis® Surgical Innovations, St. Paul, MN) is a proposed staple line reinforcement used with a surgical stapler. The device is composed of two primary components: the Peri-Strips Dry plastic mounting unit and the PSD Gel. The mounting unit has two strip of dehydrated bovine pericardium on each side of a foam spacer by the plastic mounting unit. The PSD adhesive hydrogel is placed on the strips to create a temporary bond between the strips and the surfaces of a surgical stapler and also promotes rehydration of the strips. The stapler is positioned on the tissue to be excised, fired and removed. There is insufficient evidence to support the safety and effectiveness of Per-Strips Dry.

Stamou et al. (2011) conducted a prospective comparative study (n=187) to determine if staple-line reinforcement with Peri-Strips Dry (PSD) reduces surgical complications of laparoscopic sleeve gastrectomy. Group A (n=96) received PSD and group B (n=91) did not receive PSD. Reinforcement with PSD significantly reduced the occurrence of bleeding from the staple line (p=0.012) and intra-abdominal collections (p=0.026). The leak rate was not significantly different between the two groups. Patients in group A required fewer days of hospitalization than group B (481 days vs. 524 days). Two leaks were observed in group A, one due to malfunction of the stapling device. In group B, three patients required transfusion. Number of stapler loads was 5–8 per operation. Limitations of the study include the small patient population, lack of randomization, and allocation primarily determined by insurance coverage and product availability.

Angrisani et al. (2004) conducted a randomized controlled trial to compare extraluminal bleeding with (group A) (n=50) or without (group B) (n=48) staple-line reinforcement with Peri-Strips Dry during laparoscopic Roux-en-Y gastric bypass in morbidly obese patients. Outcome measures included: mortality, intraoperative and postoperative complications, operating time, number of hemostatic clips used, and blood transfusion. There were no recorded incidents of intra- or postoperative mortality and no patients were re-operated or transfused because of extraluminal bleeding. Intra-operative methylene blue test was positive in six group B patients compared to zero group A patients ($p<0.001$). The mean number of clips ($p<0.001$) and operating time ($p<0.01$) were significantly lower in group A. Conversion to laparotomy was required in one group A patient and two group B patients. No adverse clinical or surgical event was related to Peri-Strip. A limitation of the study is the small patient population and lack of reporting of inclusion and exclusion criteria.

Miller et al. (2001) conducted a two-center, randomized controlled trial (n=80) to determine if Peri-Strip used as a buttress along the lung staple line would decrease air leaks and hospital stays after lobectomy and segmentectomy. Patients were randomized to Peri-Strip (n=40) or no Peri-Strip (n=40). There were no statistical differences in the mean intensive care unit length of stay (p=0.09), number of days with a chest tube (p=0.6), or total length of stay (p=0.24). Patients treated with Peri-Strip had a 2 day mean duration of air leak and 5.9 day mean time to chest tube removal compared to three days and 6.3 days, respectively, for patients without Peri-Strip.

Stammberger et al. (2000) conducted a three-center randomized controlled trial to compare the effects of Peri-Strips Dry (PSD) (n=32) vs. no PSD (control group) (n=33) to reduce air leaks and shorten hospital length of stay on patients who underwent bilateral lung volume reduction surgery by video-assisted thoracoscopy using endoscopic staplers for severe emphysema. Number of cartridges used in the treatment group ranged from 8–24 and 10–26 in the control group. The median duration of air leaks ($p<0.001$) and the median drainage time ($p<0.045$) was significantly shorter in the PSD group. Four patients in the non-PSD group and three PSD patients required reoperation for persistent air leak and pneumothorax. There was no significant difference between the groups in the length of hospital stay. In three patients, PSD detached from the stapler before it was fired. Limitations of the study include the small patient population, short-term follow-up and heterogeneous emphysema morphology.

Permacol™

The Permacol Crosslinked Porcine Dermal Collagen Surgical Mesh (Tissue Sciences Laboratories PLC, Hants, United Kingdom), a xenograft, is a fibrous flat sheet comprised of acellular porcine dermal collagen and elastin. It is 510(k) FDA approved for “use to provide soft tissue repair or reinforcement in plastic and reconstructive surgery of the face and head” (FDA, 2002). Permacol is also proposed for use in inguinal hernia repair, abdominal wall repair, and colorectal surgery. In 2004, 510(k) FDA approval was given for Permacol® Surgical Implant “for use as a soft tissue patch to reinforce soft tissue where weakness exists and for the repair of damaged or ruptured soft tissue membranes. It is specifically indicated for the repair of abdominal wall defects and hernias, including but not limited to parastomal hernias. The Permacol® Surgical Implant T-piece is shaped for use in rectal intussusception repair and the Permacol® Surgical Implant Rectocele-pieces are shaped for use

in rectocele repair (FDA, 2005). Other Permacol products include ENDURAGen™ (distributed by Porex Corporation, Newnan, GA) specifically indicated for plastic and reconstructive surgery of the head and face, and Permacol™ Biologic Implant (distributed by Covidien, Mansfield, MA), a biologic mesh for hernia repair. The Permacol™ Injection agent is also available from Covidien.

The application of Permacol products has been investigated for multiple conditions including various types of hernia repairs, Frey's syndrome, nasal septal perforation, fecal incontinence and urodynamic stress incontinence. Case series, case reports and retrospective reviews with small patient populations (n=15-65) and short-term follow-ups lack the data needed to support the efficacy of Permacol in the treatment of these conditions (Sileri, et al., 2012; Wahed, et al., 2012; Hammond, et 2008, Shaikh, et al., 2007).

Maeda et al. (2010) conducted a systematic review investigating perianal injectable bulking agents for the treatment of fecal incontinence. Two randomized controlled trials using Permacol injection agent with a total of 12 patients were identified. There is insufficient data to support Permacol for the treatment of fecal incontinence.

Frey's Syndrome: In a prospective case series, Papadogeorgakis et al. (2008) investigated the use of Permacol (n=19) in the prevention of Frey's syndrome and face-contouring deformities following parotid tumor surgery. Vacuum suction drains were used in all patients. Follow-up visits ranged from 28–36 months. None of the patients developed Frey's syndrome or complained of sweating, heat, or redness of the skin. All patients experienced "satisfactory aesthetic results with full facial contouring." Three patients developed salivary mucoceles and one case of facial nerve paralysis was reported following removal of the facial nerve.

Urodynamic Stress Incontinence: Bano et al. (2005) conducted a randomized controlled trial to compare the use of Permacol injection (n=25) to silicone injection (Macroplastique) (n=25) in the treatment of urodynamic stress incontinence in women. Following injection, two women treated with Permacol had urinary retention requiring catheterization for one week compared to three women in the Macroplastique injection group requiring catheterization for 24 hour to three days. Regarding pad loss at six months, 15 Permacol patients remained dry (62.5%), seven were unchanged, one was worse and one relapsed. In the Macroplastique group, nine were dry, seven were unchanged, five were worse and two relapsed. Fourteen Permacol patients had a reduction in the Stamey scoring system and 14 in the King's College Hospital Quality of Health Questionnaire scores compared to ten and seven, respectively, in the Macroplastique.

Other Indications: Permacol has also been investigated for use in lip augmentation; facial augmentation; nasal wall deformity; orbital floor implants; as a substitute for tendon graft to repair rotator cuff tears; abdominal compartment syndrome; inquinal, Littre's, and paraesophageal hernia repairs; hernias in contaminated fields; as well as, various urological, gynecological and plastic surgery indications (Bachman and Ramshaw, 2008; Hammond, et al., 2008; Hsu, et al., 2008; Papadogeorgakis, et al., 2008; Teicher, et al., 2008). The studies were primarily case reports or small case series (n≤10).

Preclude Dura Substitute

Gore Medical (Flagstaff, AZ) produces three dura products for repair of dura matter during neurosurgery. The devices are FDA 510 (k) approved as dura substitutes. Preclude® Dura is a smooth surface barrier proposed to minimize tissue attachment to allow easy re-operation following craniectomy procedures. Preclude® MVP® is for procedures in which immediate, watertight closure is needed during dura repair and reconstruction techniques. Preclude PDX Dura Substitute, a temporary or permanent prosthesis, is proposed to minimize cerebrospinal fluid leakage and tissue attachment during duraplasty procedures. PDx consists of a polytetrafluoroethylene (ePTFE) and elastomeric fluoropolymer three-layer construct. There is insufficient evidence in the published peer-reviewed literature to support the efficacy of these products.

Preclude® Pericardial Membrane

Preclude Pericardial Membrane (Gore Medical, Flagstaff, AZ) is FDA 510 (k) approved for the reconstruction or repair of the pericardium. The membrane is a biocompatible, expanded polytetrafluoroethylene and is proposed for use with left ventricular assist devices and artificial hearts. Preclude is available in 6 sizes and lengths. There is insufficient evidence to support the safety and efficacy of Preclude. The manufacturer's information warns that "the safety and efficacy of PRECLUDE® Pericardial Membrane in preventing adhesion formation between tissues or between tissue and a mechanical circulatory assist device has not been proven. Clinical trial data are currently unavailable".

PriMatrix
PriMatrix (TEI Biosciences, Inc., Boston, MA) is an acellular dermal tissue matrix derived from fetal bovine dermis. It is 510(k) FDA approved for the "management of wounds that include: "partial and full thickness wounds; pressure, diabetic, and venous ulcers; second-degree burns; surgical wounds-donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds-abrasions, lacerations, and skin tears; tunneled/undermined wounds and draining wounds" (FDA, 2008). There is insufficient evidence in the published peer-reviewed scientific literature supporting the efficacy of Primatrix. Studies are primarily in the form of retrospective reviews (Hayn, 2013; Lullove, 2012; Strauss, et.al., 2012; Karr, 2011).

Kavros et al. (2014) conducted a nine-center, prospective case series (n=55) to evaluate PriMatrix for the treatment of chronic diabetic ulcers. Subjects were age 18 years or older, type 1 or type 2 diabetics, with a 1–20 cm^2 size foot ulcer of at least four weeks' duration. Subjects also had an HBA1C ≤ 10% and adequate vascular perfusion as measured by ankle brachial index (between 0.75 and 1.2), toe pressure (950mmHg), TcPo2 (930mmHg), or Doppler waveform. Follow-ups occurred for up to 12 weeks or until complete wound closure. The primary outcome was the number of complete wound closures at 12 weeks. Secondary outcomes included mean time to closure, area reduction, number and frequency of PriMatrix applications. Patients were treated for 14 days with the institutions' standard protocol (e.g., debridement, moist wound therapy, pressure off-loading) prior to application of PriMatrix. Of the 46 patients who completed treatment, 35 (76%) healed by week 12. Of the 11 who did not heal, average wound reduction was 71.4%. Mean time to healing was 53.1 days. The number of Primatrix applications was 2 ± 1.4. A single application was sufficient for healing in 59.1% of subjects and 22.9% of subjects received two applications. Limitations of the study includes the small patient population, subjects lost to follow-up (n=9) and lack of a comparator.

Repriza® Acellular Dermal Matrix
Repriza (Promethean Lifesciences Inc., Pittsburg, PA) is a human skin, acellular dermal matrix. The product is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. Repriza is membrane free and proposed for implantation for reconstructive surgery including breast reconstruction, abdominal wall reconstruct and augmentation of soft tissue irregularities. The matrix is provided in 4X12 cm and 6X16 cm sheets. It can also be custom made. The product is marketed by Specialty Surgical Products, Inc. (SSP) (SSP, 2014). There is insufficient evidence to support the safety and efficacy of Repriza for reconstructive surgery.

Restore® Orthobiologic Soft Tissue Implant
Restore Orthobiologic Soft Tissue Implant (Depuy Orthopaedics, Inc., Warsaw, IN) is an FDA 510(k) porcine small intestinal submucosa (SIS) device. Per the FDA it is "intended to reinforce soft tissue where weakness exists, specifically for the reinforcement of soft tissue repaired by sutures or suture anchors during tendon repair surgery, including reinforcement of the rotator cuff, patella, Achilles, biceps, quadriceps, and other tendons." It may also be used during general tissue reconstruction of the periosteum. The device is proposed to be reabsorbed and replaced by the patient's own tissue (FDA, 2007). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Restore. Published studies consist primarily of case reports and in vitro studies.

Seamguard® Staple Line Reinforcement Material
Seamguard Staple Line Reinforcement Material (Gore® and Associates, Inc., Flagstaff AZ) is a bioabsorbable membrane of synthetic polyglycolic acid and trimethylene carbonate copolymer for use in surgical staplers. The material is FDA 510(k) approved for use in surgical procedures in which soft tissue transection or resection with staple line reinforcement is needed (e.g., hysterectomy, lung resection, liver resection, bladder reconstruction, bronchial, bariatric, colon, colorectal, esophagus, gastric, mesentery, pancreas, small bowel, and spleen procedures) (Gore and associates, 2014; FDA, 2005).

There is insufficient evidence to support the use of Seamguard for staple line reinforcement. A randomized controlled trial (Senagore, et al., 2014) compared outcomes with Seamguard vs. no reinforcement (n=258) with a colorectal, coloanal, or ileoanal anastomosis. The study was terminated at the first planned interim analysis because of insufficient power to detect an intergroup difference in anastomotic leak rate between the two groups.

SportMesh™
SportMesh (Biomet Sports Medicine, Warsaw, IN) is a synthetic device made from Artelon® (Artimplant, AB, Vastra Frolunda, Sweden) fibers. The device is a biodegradable temporary scaffold that is proposed to allow the

body's cells to regenerate and heal. SportMesh is FDA 510(k) approved for "use in general surgical procedures for reinforcement of soft tissue where weakness exists" and "for reinforcement of soft tissues that are repaired by suture or suture anchors, limited to the supraspinatus, during rotator cuff repair surgery" (FDA, 2006). A second product, SportsMesh or Artelon Tissue Reinforcement mesh, is also FDA 510(k) approved based on the SportMesh predicate device for the same indications. Data supporting the safety and efficacy of SportMesh is lacking. Studies have primarily been in vitro or in the form of case reports with small patient populations (n=4) and short-term follow-ups (i.e., two weeks) (Huss, et al., 2008).

SteriShield™
SteriShield and SteriShield II (Bone Bank® Allografts, San Antonio, TX) are constructed from amniotic membrane and proposed as a wound covering, nerve protector, barrier for scar tissue adhesion, cover for implanted hardware and for use in various surgical procedures including bariatric surgery, orthopedic surgery and dental surgery. The products are processed in accordance to the FDA guidelines for banked human tissue and the American Association of Tissue Banks. SteriShield is a single layer preparation that comes in four sizes and SteriShield II is a dual layer patch that comes in eight different sizes. There is insufficient evidence to support SteriShield for these indications.

Strattice™ Reconstructive Tissue Matrix
Strattice Reconstructive Tissue Matrix (LifeCell Corporation, Branchburg, NJ) is an acellular, xenographic tissue matrix derived from porcine dermis. It is FDA 510(k) approved as LTM-RC surgical mesh "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. The implant is intended for the reinforcement of soft tissues repaired by sutures or suture anchors, during rotator cuff surgery. Indications for use also include the repair of hernias and/or body wall defects which require the use of reinforcing or bridging material to obtain the desired surgical outcome" (FDA, 2007).

Strattice is proposed for use during postmastectomy breast reconstruction to support medial repair for breast pocket size and position. It is also proposed to provide support to primary suture repair during abdominal wall reconstruction. Studies are primarily in the form of retrospective reviews (Glasberg and Light, 2012; Patel, et al., 2012; Shah, et al., 2011) and case series with small patient populations (n=25-45) (Guerra, et al., 2014; Ciclioni, et al., 2012). There is insufficient evidence in the published peer-reviewed scientific literature supporting the efficacy of Strattice. The manufacturer notes that their comment that Strattice "allows for tissue regeneration by supporting rapid revascularization, white cell migration and cell repopulation, all of which may lead to increased resistance to infection at the surgical site" has only been shown in an animal model.

Fleshman et al. (2013) conducted a multicenter, randomized controlled (n=113) to assess the safety and efficacy of Strattice dermal matrix for parastomal reinforcement in patients undergoing standard end-stoma reconstructions for permanent abdominal wall ostomy. Strattice was applied in the study group (n=55) but not in the control group (n=58). The primary outcome measure was the occurrence of parastomal hernia by the 24-month follow-up. Secondary outcome measures included a comparison of early (≤30 days) and late (>30 days) stoma-related complication, as well as quality-of-life measurements. At the 24-month follow-up, there was no significant difference in the incidence of parastomal hernias between the two groups, intraoperative complications and blood loss and quality of life scores. Strattice did not significantly reduce the incidence of parastomal hernia. Limitations of the study include the inclusion of ileostomy and colostomy patients, heterogeneity of operative procedures and loss of patients to follow-up (n=12).

Itani et al. (2012) conducted the Repair of Infected or Contaminated Hernias (RICH) prospective, multicenter study (n=80) to evaluate the clinical outcomes of open repair of ventral incisional hernia of contaminated abdominal defects using Strattice. Patients were age ≥ 18 years with hernias ≥ 9 centimeters^2 (cm^2) and reparable using a single sheet (up to 20 X 20 cm) of Strattice. Hernia defects were 'clean-contaminated' (n=39), 'contaminated' (n=39), or 'dirty' (n=2), and the defects were classified as grade 3 (n=60) or grade 4 (n=20). The midline was restored, and primary closure was achieved in 64 patients; the defect was bridged in 16 patients. Strattice was placed in the retrorectus or intraperitoneal space as an underlay and as an on-lay in three patients. The primary outcome was the incident of wound events (e.g., inflammation, seroma, hematoma, dehiscence, reoperation). At 24 months postoperative, 95 wound events were experienced by 53 patients including 22 seromas. There were 28 unique, infection-related events in 24 patients. There were 15 hernia recurrences at 12 months and 22 at 24 months. Seven patients underwent repair within the study period. Limitations of the study include the small heterogeneous patient population, short-term follow-up and lack of a comparator.

Talymed™
Talymed (Marine Polymer Technologies, Inc., Danvers, MA) is a wound healing matrix comprised of shortened fibers of poly-N-acetyl glucosamine (pGlcNAc) isolated from microalgae. The dressing is FDA 510(k) approved and "indicated for the management of wounds including: diabetic ulcers, venous ulcers, pressure wounds, ulcers caused by mixed vascular etiologies, full thickness and partial thickness wounds, second degree burns, surgical wounds-donor sites/grafts, post-Mohs' surgery, post-laser surgery, and other bleeding surface wounds, abrasions, lacerations, traumatic wounds healing by secondary intention, chronic vascular ulcers, and dehisced surgical wounds" (Marine Polymer Technologies, 2013; FDA 2010).

Kelechi et al. (2011) conducted a multicenter, randomized, pilot study (n=82) to evaluate the safety and efficacy of Talymed for the treatment of partial-thickness venous leg ulcers. Patients were randomized into four groups. The control group (n=20) was treated with standard wound care and three treatment groups (n=62) were randomized to standard care with Talymed. The three treatment groups included: group A (n=20), received Talymed once; group B (n=22), received Talymed every other week; and group C (n=20), received Talymed every third week. Standard wound care included: cleaning the wound with saline; applying a moisture-barrier product, applying a nonadherent absorptive primary dressing, and wrapping the leg in a zinc oxide pressure dressing. In the study groups, Taylmed was applied to the wound immediately before the primary absorptive dressing. At 20 weeks, nine patients in group A, 19 patients in Group B, and 13 patients in Group C had completely healed wounds compared to nine patients in the control group. Only Group B had significantly more healed wounds compared to the control group (p=0.005). Limitations of the study include the small patient population and the number of patients lost/withdrawn/discontinued intervention in the study group (n=11).

TenoGlide® Tendon Protector Sheet
TenoGlide (Integra LifeSciences Corp. Plainsboro NJ) is an absorbable tendon protector sheet comprised of a crosslinked bovine Type I collagen and glycosaminoglycan. The device can be wrapped around the affected area or slid between the tendon and adjacent tissue. It is proposed for use with severed tendons after primary repair, partially injured tendons and tendons damaged by compression trauma. TenoGlide was FDA 510(k) approved as Tendon Wrap™ and indicated "for the management and protection of tendon injuries in which there has been no substantial loss of tendon tissue". (Integra LifeSciences, 2010). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Tenoglide.

TenSIX™ Acellular Dermal Matrix
TenSIX Acellular Dermal Matrix (Solana Surgical, LLC, Memphis, TN) is derived from donated human tissue and sterilized via a Gamma Precision Dose Sterilization proprietary process. The product is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. TenSIX has a basement membrane and dermal sides. The matrix is proposed for repair or replacement of tissue lost from foot ulcers or amputation or for protection, reinforcing and covering tendons. TenSIX is available in meshed (4X4 cm, 4X8 cm) and non-meshed forms (2X4 cm, 4X7 cm, 5X10 cm). There is insufficient published evidence to support the safety and efficacy of TenSIX. Studies are primarily in the form of case reports Solana Surgical, 2014).

TissueMend Soft Tissue Repair Matrix
TissueMend Soft Tissue Repair Matrix (TEI Biosciences, Inc., Boston, MA), an acellular bovine collagen matrix, is 510(k) FDA approved for "reinforcement of soft tissues repaired by sutures or suture anchors, during tendon repair surgery, including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps or other tendons". It is a remodelable scaffold replaced by the patient's own soft tissue during the healing process (FDA, 2006; Coons and Barber, 2006). Data from clinical trials to establish the efficacy of this matrix are lacking.

Tornier® BioFiber™ Scaffold and Tornier® Collagen Coated BioFiber Scaffold
There are two Tornier BioFiber Scaffolds (Tornier, Inc. Edina MN). The Tornier Collagen Coated BioFiber Scaffold is a bi-layer, synthetic absorbable reinforced woven fabric made from poly (4-hydroxybutyrate) fibers. The device is FDA 510(k) approved for "use where temporary wound support is required to reinforce soft tissues where weakness exists or for the repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result". The 510(k) FDA approved predicate device is the BioFiber Absorbable Biological Scaffold for soft tissue repair and reinforcement. BioFiber is an orthopedic absorbable polymer soft tissue scaffold proposed for reinforcement of suture-tendon interface and tendon repair. Biofiber is proposed for a wide range of orthopedic indications including repairs of the shoulder, knee, hip, and foot/ankle (Tornier, Inc. 2013; FDA, 2012). There is insufficient evidence supporting the safety and efficacy of the Tornier BioFiber Scaffolds.

Unite® Biomatrix
Unite Biomatrix (Synovis®, Irvine, CA) is a non-reconstituted collagen xenograft derived from native equine pericardium. The matrix is FDA 510(k) approved "for the management of moderately to severely exudating wounds, including: partial and fill thickness wounds, draining wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, partial thickness [second degree] burns, skin tear, surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, dehisced surgical incisions) (FDA, 2011). Because studies are primarily in the form of case reports, there is insufficient data to support the safety and efficacy of Unite Biomatrix.

Vascu-Guard®
Vascu-Guard (Synovis® Surgical Innovations, St. Paul, MN, previously Bio-Vascular, Inc.) is a bovine pericardium cross-linked matrix with glutaraldehyde. It is 510(k) FDA approved as an intracardiac patch and proposed for use in peripheral vascular reconstruction including the carotid, renal, iliac, femoral, profunda and tibial blood vessels and arteriovenous access revisions. Vascu-Guard may be sutured, clipped, or stapled to the edge of the host tissue or vessel. The patches come in four different sizes (Baxter Biosurgery, 2013). There is insufficient evidence in the published peer-reviewed literature supporting the safety and efficacy of Vascu-Guard. Studies are primarily in the form of retrospective reviews.

Veritas Collagen Matrix
Veritas Collagen Matrix (Synovis® Surgical Innovations, St. Paul, MN) is an implantable noncrosslinked biologic mesh made from bovine pericardium. Veritas is FDA approved as a surgical mesh under the 510(k) process for use as an implant for surgical repair of soft tissue deficiencies including: buttressing and reinforcing staple lines during lung resection and other incision and excisions of the lung and bronchus; reinforcement of gastric staple line during bariatric surgical procedures; abdominal and thoracic wall repair; muscle flap reinforcement; rectal and vaginal prolapse repair; urinary incontinence treatment; reconstruction of pelvic floor and hernia repairs. There is also a Veritas Collagen Matrix Dry product that is FDA approved as a predicate device for the conventional Collagen Matrix (FDA, 2008; FDA, 2006).

Synovis also offers Per-Strips Dry with Veritas Collagen Matrix which is proposed for staple line reinforcement. Peri-Strips Dry with Veritas is a remodelable, thinner staple line reinforcement. The product is vacuum-dried and delivered in a plastic mounting unit. The plastic mounting unit contains two strips of dehydrated bovine pericardium secured on each side of a foam spacer in a plastic mounting unit. The PSD adhesive hydrogel is placed on the strips to create a temporary bond between the strips and the surfaces of a surgical stapler and also promotes rehydration of the strips. The stapler is positioned on the tissue to be excised, fired and removed. The number of Peri-Strips Dry with Veritas firings required for a surgery varies according to the amount of tissue excised (Synovis, 2010). According to Stamou et al. (2011) PSD is a nonabsorable material without an industrially standardized thickness. The authors also pointed out that the manufacturers of stapler devices do not officially support the use of buttressing materials and will not take responsibility if the stapler malfunctions.

Peri-Strips Dry with Veritas is FDA 510 (k) approved for the following indications: 1) "as a prosthesis for the surgical repair of soft tissue deficiencies using surgical staplers when staple line reinforcement is needed; 2) for reinforcement of staple lines during lung and bronchus resections and during bariatric surgical procedures; 3) for reinforcement of staple lines during gastric, small bowel, mesentery, colon, and colorectal procedures; 4) for reinforcement of suture lines and staple-lines (i.e., occlusion of the left atrial appendage during open chest procedures) during cardiac surgery"

There is insufficient evidence to support the use of Veritas Collagen Matrix and Peri-Strips with Veritas. The limited number of published studies investigating is primarily in the form of retrospective reviews.

XCM Biologic Vascular Patch
XCM Biologic Vascular Patch (Kenny Nash Corp., Exton PA) is a non-cross-linked 3-D matrix derived from porcine dermis using the Optrix™ process. The dermis is composed of cells and extracellular matrix (ECM). The matrix is FDA 510(k) approved as Medeor Matrix (Kenny Nash Corp., Exton PA) and indicated **"**for the reinforcement and repair of soft tissue where weakness exists including, but not limited to: defects of the thoracic wall, suture line reinforcement, muscle flap reinforcement, hernia repair, soft tissue reconstructive procedures including plastic and reconstructive surgical applications, and reinforcement of the soft tissues, which are repaired by suture or suture anchors, including but not limited to, rotator cuff, patellar, Achilles, biceps,

quadriceps and other tendons. Medeor Matrix is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Sutures, used to repair the tear, and sutures or bone anchors used to attach the tissue to the bone, provide biomechanical strength for the tendon repair". The product is distributed by Syntheses® (Syntheses, 2013; FDA, 2011). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of XCM Biologic.

XenMatrix™ Surgical Graft
XenMatrix (C.R. Bard, Inc. Covington, GA) is an acellular non-crosslinked regenerative porcine collagen matrix proposed for hernia and abdominal wall repair. The grafts are created using a patented AquaPure™ Process that removes the cells, leaving an open collagen scaffold. Brennan Medical received FDA 510(k) approval for porcine dermal matrix "intended for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue membranes. XenMatrix is specifically indicated for: plastic and reconstructive surgery; muscle flap reinforcement; hernia repair including abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, and incisional hernias; suture-line reinforcement; reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Porcine Dermal Matrix is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff, patellar Achilles, biceps, quadriceps, or other tendons (C.R. Bard, 2013; FDA, 2011). Clinical trials with data supporting the safety and efficacy of Xenmatrix are lacking. Studies are primarily in the form of retrospective reviews and in vitro studies.

XenoSure® Biologic Vascular Patch (formerly PeriPatch)
XenoSure Biologic Vascular Patch (LeMaitre Vascular, Inc., Ontario, Canada), a processed bovine pericardial patch was FDA approved as PeriPatch™ (PM Devices Inc., British Columbia, Canada). The device is intended for use as a surgical patch for cardiac and vascular reconstruction and repair as well as, soft tissue repair and reinforcing suture lines during general surgical procedures. Per LeMaitre applications include carotid endarterectomy, iliac artery stenting, femoral, illiac, renal and tibial patching, profundaplasty, and arteriovenous access revisions (LeMaitre Vascular, 2014; FDA, 2004). There is insufficient evidence to support the safety and efficacy of Xenosure.

Literature Review – Systematic Review and Meta-Analysis
Abdominal Wall Reconstruction: Following a systematic review of 40 studies (37 retrospective reviews), Janis et al. (2012) concluded that there is a lack of high-level data to define the precise role of acellular dermal matrix and guidelines for its use for abdominal reconstruction guidelines. Hernia recurrence, the primary outcome measure, ranged from 0–80%. Limitations of the studies included small, heterogeneous patient populations (n=5–240); short-term follow-ups (0–68 months); heterogeneity in surgical techniques; variable starting points of the studies; wide variety of clinical indications for reconstruction (e.g., ventral hernia; incisional hernia, abdominal compartment syndrome, tumor resection, fascial defects, contaminated abdominal wall); variety of positions of matrices; conflicting reports regarding superiority of underlay vs. overlay techniques; variety in the number of matrix layers used; and use of matrices in combinations with other techniques making it difficult to evaluate the benefit of the matrix alone.

Zhong et al. (2011) conducted a systematic review to evaluate the evidence on acellular dermal matrix (ADM) used during abdominal wall reconstruction. Thirty case series (n=4) and retrospective reviews (n=26) met inclusion criteria. No randomized controlled trials or systematic reviews were found. Studies included the use of porcine acellular dermal matrix and human acellular dermal matrix. The outcomes studied included hernia recurrence, abdominal wall laxity, delayed wound healing, infection and seroma. The incidence of postoperative/recurrent hernia ranged from 0%–80%, and the incidence of abdominal wall laxity was largely unreported. Delayed healing occurred in up to 64% of patients with infection-related complications (e.g., surgical site infections, cellulitis, deep/intrabdominal abscesses) reported as high as 40%. Types of ADM, technique, and types of fascia repair and suture used varied. The authors concluded that there was a paucity of high-level evidence comparing ADM with other methods interfering with the ability of physicians to make data-driven recommendations on clinical indications, surgical techniques and outcomes following ADM assisted abdominal wall reconstruction.

Breast Reconstruction: Kim et al. (2012) conducted a systematic review and metaanalysis to evaluate complication outcomes from human acellular dermal matrix (ADM) used as an adjunct to traditional submuscular tissue expander/implant breast reconstruction. Forty eight uncontrolled cohort studies met inclusion criteria. Thirteen studies had information only on human ADM matrix-based reconstruction, 29 had information only on

submuscular-based reconstructions, and six reported complications on human ADM and submuscular techniques. A total of 2037 human ADM reconstructions and 12,847 submuscular reconstructions were included in the metaanalysis. A total of 877 human ADM and 3464 muscular reconstructions from six studies were used to calculate relative risks. Average follow-up time was 13.8 months in the human ADM group and 28.3 months in the submuscular cohort. There was an increased rate of total complications, 15.4% vs. 14.0%; seroma, 4.8% vs. 3.5%; infection, 5.3% vs. 4.7%; and flap necrosis, 6.9% vs. 4.9% in the human ADM cohort compared to the submuscular reconstruction cohort. The rate of hematomas was greater in the submuscular cohort 1.5% vs. 1% in the human ADM. Metaanalysis revealed an increase in the risk of total complications (relative risk, 2.05; 95 percent confidence interval, 1.55 to 2.70), seroma (relative risk, 2.73; 95 percent confidence interval, 1.67 to 4.46), infection (relative risk, 2.47; 95 percent confidence interval, 1.71 to 3.57), and reconstructive failure (relative risk, 2.80; 95 percent confidence interval, 1.76 to 4.45) in the human ADM cohort. There was a trend toward increased risk of hematoma (relative risk, 2.06; 95 percent confidence interval, 0.86 to 4.95) and flap necrosis (relative risk, 1.56; 95 percent confidence interval, 0.85 to 2.85) in the human acellular dermal matrix cohort, but the results were not statistically significant. The majority of pooled complication analyses showed significant heterogeneity. The metaanalysis suggested that the use of human ADM increases complication rates compared to submuscular approach.

Nguyen et al (2011) conducted a systematic review of the literature to assess the quality and quantity of evidence regarding the use of acellular dermal matrices (ADM) (e.g., AlloDerm) in prosthetic breast reconstruction. Eighteen articles in the form of case reports, prospective cohort studies and retrospective reviews met inclusion criteria. The authors analyzed the evidence for the following proposed advantages of ADM: decrease or eliminate the need for expanders to create a tissue pocket for an implant; reduction in postoperative pain; decrease in operative time; increased initial fill volumes; fewer expansions; precise control of over the lateral and inframammary fold; ability to use more of the mastectomy skin flaps; faster time to completion of reconstruction; improved lower pole expansion; decreased incidence of capsular contractures; decreased rate of revisions; improved aesthetic outcome of the breast. The authors concluded that there was insufficient data to support any of the above proposed benefits of ADM for breast reconstruction due to the paucity of actual data and conflicting data. Some studies did not formally quantify or report applicable data; evidence was inconsistent due to the variations in size of the matrix, type of mastectomy, size and viability of the mastectomy flaps and surgeon judgment; and data was conflicting due to variations in surgical technique, patients' physical characteristics, and number of expansions used.

Diabetic Foot and Venous Leg Ulcers: Game et al. (2012) conducted a systematic review of interventions used to enhance healing of chronic diabetic ulcers of the foot. Forty-three studies met inclusion criteria including three studies (i.e., two randomized controlled trials and one case series) using bioengineered skin and skin grafts. Overall, the number of controlled studies was small and the majority were of poor methological quality with wide variation in the selection of outcome measures (e.g., time to healing, amputation). The authors concluded that there was "little published evidence to justify the use of newer therapies".

Fistula Plugs: In a systematic review, O'Riordan et al. (2012) identified 56 articles that investigated anal fistula plugs for the treatment of Crohn's (n=42) and non-Crohn's disease (n=488). Eight studies were retrospective, ten were prospective cohorts, and two were randomized controlled trials. Patient population ranged 4–60 patients. Included studies involved patients with and without Crohn's disease that could be differentiated and a mean or median follow-up of three months or greater. The longest follow-up was 24.5 months. Patients with rectovaginal, anovaginal, rectourethral, or ileal-pouch vaginal fistulas were excluded. Overall, plug extrusion rate was 8.7% (n=46). In patients with non-Crohn's disease, fistula closure ranged from 0.2–0.86. The overall success rate for patients with Crohn's was 54.8% (23 of 42 patients) and 54.3% of patients (265 of 488 patients) without Crohn's. Limitations of the study included: heterogeneity of operative technique, perioperative care; operative position, and anesthesia type; and the retrospective and non-comparative study designs.

Frey Syndrome: Li et al. (2013) conducted a systematic review of randomized controlled trials (RCTs) to evaluate the safety and efficacy of grafts for the prevention of Frey syndrome following parotidectomy. Fourteen randomized controlled trials (n=1098) met inclusion criteria. Subjects were age 9–85 years and had undergone various parotidectomy procedures using various types of acellular dermal. Follow-ups ranged from 3–60 months. Meta-analysis of nine studies showed that an acellular dermis matrix graft vs. no graft significantly reduced the risk of Frey syndrome ($p<0.0001$). Six studies showed that a muscle flap graft versus no graft also significantly reduced the risk of Fey syndrome compared to no graft ($p<0.001$). When the superficial musculoaponeurotic system (SMAS) graft was introduced as active treatment, there was no significant difference between the groups.

One study reported no statistical difference between the study and control groups when acellular dermas matrix was compared to a muscle flap graft. (p=0.70). No serious adverse events were reported. Frey syndrome had an incidence of 8.3% in the acellular dermis group and 11.1% in the muscle flap group. Limitations of the analysis include a discrepancy in the number of subjects with Frey syndrome dependent on whether a subjective vs. objective assessment was made. Very mild Frey syndrome cannot be detected by a subjective assessment. Other limitations include heterogeneity in the types of parotid lesions and surgical procedures, small patient populations and possibility of selection bias of the included studies. More RCTs with large, homogeneous patient populations and long-term follow-up are needed to valid that grafts are effective in preventing Frey syndrome.

Hernia Repairs: In a 2014 systematic review, Cross et al. reported that the data for biological mesh products in ventral hernia repair in contaminated fields were limited. Sixteen studies (n=554) met inclusion criteria. All of the studies were case series with the largest patient population being 116. Six different mesh products were used. The authors recommended that caution be used when considering the use of biological meshes because there is a paucity of controlled trials and none of the products are FDA approved for this indication.

Ferzoco (2013) conducted a systematic review to assess outcome in patients who underwent repair of contaminated or infected ventral incisional hernias using a biologic mesh. The eleven studies that met inclusion criteria used the following products: AlloDerm (n=7), Surgisis (n=2); CollaMend (n=2), Permacol (n=2), Strattice (n=1), and Veritas (n=1). All studies were retrospective chart reviews and included a total of 677 patients. Reported hernia recurrence varied widely and ranged from 0%–50%. Wound dehiscence rates varied from 0%–35.5% and mesh explantation ranged from 0%–23%. Occurrence rates for seroma, fistula, evisceration, intrabdominal bleeding, repeat surgery, hematoma were typically not reported. The most commonly reported reasons for a secondary surgical procedure included repair of recurrent hernia, mesh removal, drainage of seroma, and drainage of surgical site abscess. Prospective studies are needed to investigate the efficacy of biologic mesh in the treatment of infected ventral incisional hernias.

Beale et al. (2012) conducted a systematic review to evaluate the use of biological mesh in the repair of ventral hernias in adults. Twenty-nine studies met inclusion criteria (n=1257). Four studies used Permacol (n=64), three used Surgisis (n=87) and 23 used AlloDerm (n=1106). Primary outcomes were hernia recurrence and surgical site occurrences (hematoma, seroma, wound infection, dehiscence or graft removal). There was a 20.8% AlloDerm, 10.9% Permacol and 8.0% Surgisis recurrence rate and a 31.4% AlloDerm, 25% Permacol and 40.2% Surgisis surgical site occurrence rate (e.g., hematoma, seroma, wound, infection, dehiscence, or need for graft removal). The authors noted that it was difficult to identify a uniformly accepted technique for the placement of the biologic mesh. Limitations of the studies included: retrospective study design (n=27 studies), heterogeneity of surgical technique and placement of the product, lack of reporting of hernia recurrence and complication rates, paucity of data and older studies. Well designed, prospective randomized controlled trials with large patient populations and long-term follow-up are needed to evaluate biological mesh for ventral hernia repair.

Kissane and Itani (2012) conducted a systematic review to evaluate acellular demal matrix for complex ventral incisional hernia repair. Eight single center studies (n=635) met inclusion criteria and used either AlloDerm (n=461), Surgisis (“Sis-ECM” mesh) (n=91) or Strattice (n=80). One study was prospective and used Strattice in a one-stage repair of infected or contaminated hernias. Seven studies were retrospective in design. There was a recurrence rate of 21 percent after 25.8 months with the highest rate being in the AlloDerm patients. Total percentage of complications (e.g., wound-related, eventration, mesh rejection) in the AlloDerm hernia repairs was 40.4 percent. Other complications included: seroma formation, postoperative peritonitis, subfascial abscesses, intraabdominal hematoma, and mesh reaction. Because of the heterogeneity of the patient population, ventral incisional hernia grades, type of meshes used, surgical techniques, and length of follow-up, a meta-analysis could not performed. Other limitations of the studies included: minimal reporting of patient inclusion criteria and demographics; diverse patient comorbidities; retrospective study designs; lack of controls; and short-term follow-up (mean 25.8 months).

Smart et al. (2012) conducted a systematic review to assess the clinical outcomes of biological meshes used in abdominal wall hernia repairs. Forty-five randomized controlled trials, case series and retrospective reviews met inclusion criteria including: 23 studies on AlloDerm, seven on Surgisis, ten on Permacol and seven on other meshes. Most articles were retrospective reviews or uncontrolled prospective case series with small heterogeneous, patient populations, poorly described methodology and short-term follow-ups (3–52 months). AlloDerm recurrence rates ranged from 0%–100% and were inferior compared to polypropylene and Surgisis. In infected fields, recurrence rates were high at short and medium-term follow-up. Concerns were reported

regarding bulging at the repair site and stretching of the graft. “There is little evidence to support the use of AlloDerm in most of the situation where a biological mesh is indicated.” The recurrence rates with Permacol were 0%–15%. Outcomes in Permacol studies were conflicting and “important methological weaknesses exist” representing a low level of evidence. Outcomes with Surgisis were also conflicting. Some studies reported a recurrence rate of 0%–5.3% regardless of whether the surgery was performed in a clean or infected field, while other studies reported a recurrent rate as high as 39% in dirty fields. One study was terminated early due to the high recurrence rates in a Surgisis group with clean cases. According to the authors, insufficient or minimal data in the form of retrospective reviews were found for Veritas, Xenmatrix, CollaMend and Strattice and only case reports were found for Allomax, FlexHD, FortaGen, Peri-Guard, SurgiMend and Tutopatch.

Tendon and Ligament Repairs: Chen et al. (2009) conducted a systematic review of biological and synthetic scaffolds used for tendon and ligament repairs. Out of 378 identified articles, 47 clinical trials met inclusion criteria. Of the 47 articles, 16 clinical trials included four commercial biological scaffolds (i.e., five included the use of Restore, six used GraftJacket, four used Zimmer (formerly Permacol), and one study included both Restore and GraftJacket. After review of the data, the authors reported the following:

- Restore – “Restore or scaffolds from small intestine submucosal are ineffective in the reinforcement of large rotator cuff tears and currently not recommended for use in cuff tendon repair.” They identified other scaffolds made from small intestine submucosal (i.e. Oasis, Surgiss, and CuffPatch™ [Organogenesis, Inc., Canton, MA]) and stated that “extra care should be taken to monitor adverse events when applied in patients.”
- GraftJacket – “Satisfactory results have been described using GraftJacket for skin lesion and abdominal wall repair”. No reports of inflammatory response, edema or postoperative infection have been reported and patients seemed to tolerate it well. However, recurrent tears were noted in 30% of patients in two studies.
- Zimmer (Permacol) – Two retrospective reviews (n=10 each) reported increased pain relief and range-of-motion following implantation, but two other smaller studies reported recurrent tears, aggravated pain and decrease range-of-motion. Foreign body reaction was noted in several of the patients.
- TissueMend – No published animal or clinical studies were found. They noted that TissueMend has been reported to contain higher genetic materials compared to other products which raise concern re human application.
- OrthADAPT – No published animal or clinical studies could be found

According to Chen et al., the studies in this systematic review were primarily in the form of case reports, case series, or retrospective reviews and limited by small patient populations (n=1–30), short term follow-ups (3 months–5 years) and lack of comparison to established methods of treatment. One of the major concerns with these products is biocompatibility and inflammatory response associated with foreign body rejection. The authors also noted that many scaffolds were FDA approved without proper animal studies or evidence-based clinical trials.

Technology Assessments

Agency for Healthcare Research and Quality (AHRQ): AHRQ (2013) conducted a technology assessment on the effectiveness of treatment modalities (i.e., advanced wound dressings, systemic antibiotics, or venous surgery) for chronic venous ulcers. Sixty studies met inclusion criteria. Patients had venous leg ulcers for six weeks or longer and signs of preexisting venous disease. Patients with arterial ulcers, pressure ulcers, postsurgical ulcers, and neuropathic ulcers were excluded from the review. Three studies evaluated acellular human skin equivalents. Four studies evaluated biological or cellular dressings. AHRQ concluded with moderate confidence (i.e., evidence reflects the true effect. Further research may change confidence in the estimate of the effect and may change the estimate) that cellular human skin equivalents (allogenic bilayered cultured skin substitute vs. compression dressing) resulted in a more rapid and higher proportion of healing, especially in patients who had failed previous therapy and had the ulcer for over a year. However, there were no effects on post-treatment recurrence. Low level of confidence showed that collagen dressings healed a greater proportion of ulcers than compression alone, and cellular (autologous keratinocytes in a fibrin sealant) vs. compression. Due to the insufficient evidence, AHRQ was unable to draw conclusions regarding the effectiveness of acellular human skin equivalent dressings vs. compression, cellular (cryo-preserved human fibroblast-derived dermal substitute vs. compression) or cellular human skin equivalent dressings vs. other dressings. The evidence was insufficient to support freeze-dried intestinal pig mucosa (n=1 study). There was no effect on post-treatment recurrence and systematic assessment of harms or adverse events were not found.

AHRQ published a 2012 systematic review that included 57 skin substitutes for the treatment of chronic wounds (i.e., pressure ulcers, diabetic foot ulcers, venous leg ulcers, or arterial leg ulcers). Complete wound healing was the primary outcome. Other outcomes measures included time to complete wound closure, wound infection, wound reoccurrence, need for amputation and hospitalization. The following skin substitutes were considered in this report:

ACell UBM Hydrated Wound Dressing	Graftjacket® Regenerative Tissue Matrix
ACell UBM Lyophilized Wound Dressing	HA Absorbent Wound Dressing
AlloDerm Regenerative Tissue Matrix	Helicoll
Allopatch HD™	Hyalomatrix® KC Wound Dressing (Laserskin®)
Alloskin™	Hyalomatrix® Wound Dressing
Aongen™ Collagen Matrix	Jaloskin®
Apligraf®/Graftskin	Integra™/Bilayer Matrix Wound Dressing
Arthroflex®	Integra™ Flowable Wound Matrix
Atlas Wound Matrix	LTM Wound Dressing
Avagen Wound Dressing	Matristem
Collagen Sponge (Innocoll)	MatriStem® Wound Matrix
Collagen Wound Dressing (Oasis Research)	Matrix Collagen Wound Dressing
Collaguard®	Matrix HD™
CollaSorb™	Medline Collagen Wound Dressing
CollaWound™	Memoderm™
Collexa®	Oasis®
Collieva®	Primatrix™
Coreleader Colla-Pad	Primatrix™ Dermal Repair Scaffold
Cymetra® Micronized AlloDerm	Puros Dermis®
Dermacell®	Repliform®
Dermagraft®	SIS Wound Dressing II
Dermadapt™ Wound Dressing	SS Matrix™
DressSkin	Stimulen Collagen
E-Z Derm	Suprathel
EndoForm Dermal Template™	Talymed®
Excellagen	TheraForm Standard/Sheet
Flex HD®	TheraSkin®
FortaDerm™ Wound Dressing	Unite Biomatrix® (Synovis)
GammaGraft®	Unite™ Biomatrix (Pegasus Biologics)

Eighteen randomized controlled trials met inclusion criteria – 12 included diabetic foot ulcers, six included venous leg ulcers. Seven skin substitutes were represented. The one study that included pressure ulcers did not meet inclusion criteria. All studies reported some benefit of skin substitutes over the control group when the number of completely healed wounds was measured between 8–16 weeks, but results varied widely across studies.

The level of evidence for evaluating complete wound healing of diabetic foot ulcers at 12 weeks was graded as low for the comparisons of Graftjacket vs. moist wound products, Apligraf vs. a nonadherent dressing and Graftskin vs. saline-moistened gauze. The strength of evidence for the comparison of Dermagraft vs. saline-moistened gauze (3 studies; 530 patients) was also considered low because of a moderate risk of bias. Likewise, the strength of evidence was low for complete healing of venous or mixed ulcers at 12 weeks comparing Apligaf plus compression to compression alone and Oasis Wound Matrix plus compression to compression alone. The strength of the evidence was insufficient for other comparisons for diabetic foot ulcers and venous or mixed ulcers. A grade of low meant that there was “low confidence that the evidence reflects the true effect of skin

substitutes on complete wound healing", and "additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect".

The authors reported that there was no clinical efficacy data from RCTs for the large majority of the skin substitute products included in the report. It was also noted that the "results of the available studies cannot be extended to other skin substitute products because of differences in active components in the various products. Additionally, the results from studies of diabetic foot ulcers do not extrapolate to studies of vascular leg ulcers or pressure ulcers because of differences in wound pathophysiology and etiology". Limitations of the studies included: lack of blinding of wound assessment; poor reporting of comorbidities; risk of bias; variation in wound severity prior to initiation of treatment; imprecise reported treatment effect (percentage increase in completely healed wounds); and poorly reported comorbidities and secondary outcomes (e.g., amputation, return to function, pain relief). Because patients were generally in good health, under glycemic control and had adequate blood flow to the wound area, available studies are not generalizable to the broader patient population that is not healthy. Studies comparing skin products to each other are lacking.

Canadian Agency for Drugs and Technologies: In a Rapid Respond Report on biological mesh, the Canadian Agency for Drugs and Technologies in Health (CADTH) (2010) presented a summary of findings on biological mesh for breast reconstruction, pelvic organ prolapse, mucogingival surgery, inguinal hernia repair, urethroplasty, diabetic foot ulcers, and decompressive hemicraniectomy. The report included systematic reviews, meta-analyses, technology assessments, randomized and non-randomized clinical trials, economic studies and guidelines. CADTH stated that "overall, there was insufficient clinical evidence to thoroughly assess the comparative efficacy of biological and synthetic mesh product. " "In addition to the complexity of having many indications and few studies, there is an abundance of different mesh products available and an absence of evidence regarding differences in safety and efficacy." In conclusion, CADTH stated "there is insufficient evidence to clearly establish the place in therapy of biological mesh products." Examples of commercially available products noted by CADTH included:

- AlloDerm
- FlexHD®
- GraftJacket
- DermaMatrix
- Repliform® (LifeCell Corp, Branchburg, NJ)
- Suspend® (Mentor, Santa Barbara, CA)
- Tutoplast® (Tutogen Medical Inc., West Paterson, NJ)
- Permacol™
- CollaMend™ (Bard Davol, Inc., Warwick, RI)
- XenMatrix™ (Brennen Medical, St. Paul, MN)
- Strattice®
- Pelvicol™ (CR Bard, Inc., Murray Hill, NJ
- FortaGen (Organogenesis, Canton, MA
- Surgisis®
- SurgiMend™
- Veritas® Collagen Matrix (Synovis Surgical Innovations, St. Paul, MN)
- Tutopatch® (Tutogen Medical Inc., West Paterson, NJ)
- UroPatch™ (Shelhigh, Inc. Union, NJ)

Professional Societies/Organizations
New England Regional Society of the American Society of Colon: Based on data from a prospective, multicenter registry of 245 patients who underwent surgical intervention for anal fistula, the New England Regional Society of the American Society of Colon and Rectal Surgeons (Hyman, et al., 2009) reported that the best healing rates occurred following fistulotomy (87%) and the worse healing rates occurred following anal fistula plug (32%) (p=0.001). They stated that randomized controlled trials comparing various treatment options for anal fistulas "are clearly needed."

Use Outside of the US
Tissue-engineered skin substitutes are offered outside the US by several companies. For example, DuralSeal dural sealant systems are available in Canada and Europe. Medtronic offers products in Canada, Europe, Asia,

Japan, Middle East, Africa, Latin America, Australia and New Zealand and Biomet 3i™ also offers products worldwide.

In a 2011 guidance document, the National Institute for Health and Clinical Excellence (NICE) (United Kingdom) stated that current evidence on closure of anal fistula using a suturable bioprosthetic plug raises no major safety concerns, but the evidence on efficacy is inadequate in quantity and quality. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. In the 2011 guidance document on inpatient management for diabetic foot problems, NICE recommends that dermal or skin substitutes not be used for treatment unless it is part of a clinical trial.

Summary
There are numerous tissue-engineered skin substitute products available on the market. Various products are approved by the U.S. Food and Drug Administration (FDA) for specific indications (e.g., diabetic foot ulcers, temporary covering of partial-thickness or full-thickness burn wounds, and wounds from dystrophic epidermolysis), and are supported by evidence in the published peer-reviewed scientific literature.

Although the published evidence supporting the role of AlloDerm, AlloMax, FlexHD, Neoform Dermis and SurgiMend in breast reconstruction procedures is not robust, limited data from several small studies, as well as acceptance and limited use of these products by certain specialists in the practicing community indicate that these products may improve outcomes in a carefully selected subset of breast reconstruction patients. Based on the current peer-reviewed literature, the role of these products for any other indication has not been established.

Due to the limited number of studies with small heterogeneous patient populations, variable outcomes and study designs, and a lack of comparison to established treatment options, evidence in the published peer-reviewed scientific literature does not support the safety and efficacy of other skin substitutes for any indication. Overall, studies are primarily in the form of case reports, case series and retrospective reviews. Some studies have reported that outcomes were worse using tissue engineered skin substitutes. For many indications randomized controlled trials comparing the skin substitute to established treatment modalities have not been conducted and/or published in the peer-reviewed literature.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Autologous Skin Grafts, Unprocessed Allogeneic Cadaver Derived or Pig Skin Derived Grafts

Covered when medically necessary:

CPT®* Codes	Description
15040	Harvest of skin for tissue cultured skin autograft, 100 sq cm or less
15050	Pinch graft, single or multiple, to cover small ulcer, tip of digit, or other minimal open area (except on face), up to defect size 2 cm diameter
15100	Split-thickness autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)
15101	Split-thickness autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15110	Epidermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15111	Epidermal autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15115	Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children

15116	Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15120	Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)
15121	Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15130	Dermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15131	Dermal autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15135	Dermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15136	Dermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15150	Tissue cultured skin autograft, trunk, arms, legs; first 25 sq cm or less
15151	Tissue cultured skin autograft, trunk, arms, legs; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
15152	Tissue cultured skin autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15155	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 25 sq cm or less
15156	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
15157	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15200	Full thickness graft, free, including direct closure of donor site, trunk; 20 sq cm or less
15201	Full thickness graft, free, including direct closure of donor site, trunk; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
15220	Full thickness graft, free, including direct closure of donor site, scalp, arms, and/or legs; 20 sq cm or less
15221	Full thickness graft, free, including direct closure of donor site, scalp, arms, and/or legs; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
15240	Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; 20 sq cm or less
15241	Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
15260	Full thickness graft, free, including direct closure of donor site, nose, ears, eyelids, and/or lips; 20 sq cm or less
15261	Full thickness graft, free, including direct closure of donor site, nose, ears, eyelids, and/or lips; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area

15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15777	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk) (List separately in addition to code for primary procedure)
15778	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

AlloDerm®

Covered when medically necessary:

CPT®* Codes	**Description**
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15777	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk) (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
Q4116	Alloderm, per square centimeter

AlloMax™

Covered when medically necessary:

CPT®* Codes	**Description**
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children

15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15777	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk) (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
C1781	Mesh (implantable)
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
Q4100[†]	Skin substitute, not otherwise specified

[†]**Note: Covered when medically necessary when used to report a tissue-engineered skin substitute as covered in this policy.**

Apligraf® (Graftskin)

Covered when medically necessary:

CPT®* Codes	**Description**
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits,

	genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
Q4101	Apligraf, per square centimeter

Biobrane®/Biobrane L®

Covered when medically necessary:

CPT®* Codes	Description
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	Description
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list

	separately in addition to code for primary procedure)
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
Q4100†	Skin substitute, not otherwise specified

†Note: Covered when medically necessary when used to report a tissue-engineered skin substitute listed as covered in this policy.

Dermagraft®

Covered when medically necessary:

CPT®* Codes	**Description**
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
Q4106	Dermagraft, per square centimeter

Epicel®

Covered when medically necessary:

CPT®* Codes	**Description**
15150	Tissue cultured skin autograft, trunk, arms, legs; first 25 sq cm or less
15151	Tissue cultured skin autograft, trunk, arms, legs; additional 1 sq cm to 75 sq cm (List

	separately in addition to code for primary procedure)
15152	Tissue cultured skin autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15155	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 25 sq cm or less
15156	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
15157	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
Q4100[†]	Skin substitute, not otherwise specified

[†]Note: Covered when medically necessary when used to report a tissue-engineered skin substitute as covered in this policy.

EpiFix® Amniotic Membrane

Covered when medically necessary:

CPT®* Codes	**Description**
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area

15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
Q4131	EpiFix, per square centimeter

FlexHD® Acellular Hydrated Dermis

Covered when medically necessary:

CPT®* Codes	**Description**
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15777	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (ie, breast, trunk) (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area

	up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
Q4128	FlexHd, Allopatch HD, or Matrix HD per square centimeter

GraftJacket® Regenerative Tissue Matrix

Covered when medically necessary:

CPT®* Codes	**Description**
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
Q4107	Graftjacket, per square centimeter

Integra® Dermal Regeneration Template, Integra™ Bilayer Matrix Wound Dressing, Integra™ Matrix Wound Dressing and Integra™ Meshed Bilayer Wound Matrix

Covered when medically necessary:

CPT®* Codes	**Description**
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C9363	Skin substitute (Integra Meshed Bilayer Wound Matrix), per square cm
Q4104	Integra bilayer matrix wound dressing (bmwd), per square centimeter
Q4105	Integra dermal regeneration template (drt), per square centimeter
Q4108	Integra matrix, per square centimeter

NeoForm Dermis™

Covered when medically necessary:

CPT®*	**Description**

Codes	
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15777	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk) (List separately in addition to code for primary procedure)

HCPCS Codes	Description
C1781	Mesh (implantable)
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
Q4100†	Skin substitute, not otherwise specified

†**Note: Covered when medically necessary when used to report a tissue-engineered skin substitute as covered in this policy.**

Oasis® Wound Matrix

Covered when medically necessary:

CPT®* Codes	Description
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area

15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
Q4102	Oasis wound matrix, per square centimeter
Q4124	Oasis ultra tri-layer wound matrix, per square centimeter

SurgiMend®

Covered when medically necessary:

CPT®* Codes	**Description**
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in

	addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children

HCPCS Codes	**Description**
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C9358	Dermal substitute, native, nondenatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm
C9360	Dermal substitute, native, nondenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm

Theraskin

Covered when medically necessary:

CPT®* Codes	**Description**
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)

15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
Q4121	TheraSkin, per square centimeter

Transcyte®

Covered when medically necessary:

CPT®* Codes	**Description**
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater

	than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS Codes	**Description**
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
Q4100[†]	Skin substitute, not otherwise specified

[†]**Note: Covered when medically necessary when used to report a tissue-engineered skin substitute as covered in this policy.**

Other Tissue-Engineered Skin Substitutes

Experimental/Investigational/Unproven/Not Covered when used to report a tissue-engineered skin substitute not covered in the policy statement above:

CPT®* Codes	Description
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15777	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk) (List separately in addition to code for primary procedure)
46707	Repair of anorectal fistula with plug (eg: porcine small intestine submucosa [SIS])

HCPCS Codes	Description
C1781	Mesh (implantable)
C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq

	cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C9352	Microporous collagen implantable tube (NeuraGen Nerve Guide), per square centimeter
C9353	Microporous collagen implantable slit tube (NeuraWrap Nerve Protector), per square centimeter
C9354	Acellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm
C9356	Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per square centimeter
C9364	Porcine implant, permacol, per square centimeter
C9367	Skin substitute, endoform dermal template, per square centimeter
Q4100	Skin substitute, not otherwise specified
Q4103	Oasis burn matrix, per square centimeter
Q4110	Primatrix, per square centimeter
Q4111	Gammagraft, per square centimeter
Q4112	Cymetra, injectable, 1cc
Q4113	Graftjacket express, injectable, 1cc
Q4114	Integra flowable wound matrix, injectable, 1cc
Q4115	Alloskin, per square centimeter
Q4117	Hyalomatrix, per square centimeter
Q4118	MatriStem micromatrix, 1 mg
Q4119	MatriStem wound matrix, per square centimeter
Q4120	MatriStem burn matrix, per square centimeter
Q4122	Dermicel, per square centimeter
Q4123	Alloskin RT, per square centimeter
Q4125	Arthroflex, per square centimeter
Q4126	Memoderm, per square centimeter
Q4127	Talymed, per square centimeter
Q4128	FlexHd, Allopatch HD, or Matrix HD per square centimeter
Q4129	Unite Biomatrix, per square centimeter
Q4130	Strattice tm, per square centimeter
Q4132	Grafix core, per square centimeter
Q4133	Grafix prime, per square centimeter
Q4134	hMatrix, per square centimeter
Q4135	Mediskin, per square centimeter
Q4136	E-Z Derm, per square centimeter
Q4137	Amnioexcel or biodexcel, per square centimeter
Q4138	Biodfence dryflex, per square centimeter
Q4139	Amniomatrix or biodmatrix, injectable, 1 cc
Q4140	Biodfence, per square centimeter
Q4141	Alloskin AC, per square centimeter
Q4142	Xcm biologic tissue matrix, per square centimeter
Q4143	Repriza, per square centimeter
Q4145	Epifix, injectable, 1 mg
Q4146	Tensix, per square centimeter
Q4147	Architect extracellular matrix, per sq cm
Q4148	Neox 1k, per square centimeter
Q4149	Excellagen, 0.1 cc

V2790	Amniotic membrane for surgical reconstruction, per procedure

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