Medical Coverage Policy

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Coverage Policy Number..... 0068

Tissue-Engineered Skin Substitutes

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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request

should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses tissue engineered skin substitutes and the various proposed indications for their use in multiple conditions.

Coverage Policy

Each of the following skin grafts is considered medically necessary for wound coverage:

- autologous skin graft (CPT® Codes 15040-15261)
- unprocessed allogeneic human, cadaver skin graft (CPT® Codes 15271-15278; HCPCS Code Q4100)
- unprocessed xenogeneic pig skin graft (CPT® Codes 15271-15278; HCPCS Code Q4100)

Each of the following products is considered medically necessary as indicated:

Covered Indication Breast Reconstruction			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
AlloDerm®	15777	Q4116	Considered medically necessary when used in association with a covered, medically necessary breast reconstruction procedure.
AlloMax™	15777	Q4100 C1781	
Cortiva®	15777	Q4100 C9399	
DermACELL™	15777	Q4122	
FlexHD® Acellular Hydrated Dermis	15777	Q4128	

Covered Indication Burn wounds			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
Biobrane	15271-15278	Q4100 C9399	Considered medically necessary when used for temporary covering of a partial-

Covered Indication Burn wounds			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
	C5271-C5278		thickness freshly debrided or excised burn wound
Biobrane-L	15271-15278 C5271-C5278	Q4100 C9399	Considered 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
Epicel	15150-15157 C5271-C5278	Q4100 C9399	Considered medically necessary when used according to the U.S. Food and 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%
Integra® Dermal Regeneration Template Integra™ Bilayer Matrix Wound Dressing Integra™ Matrix Wound Dressing Integra™ Meshed Bilayer Wound Matrix	15271-15278	Q4105 Q4104 Q4108 C9363	Considered 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
Suprathel®	15271-15278	A2012	Considered medically necessary when used for the treatment of first- and second-degree burns.
Transcyte®	15271-15278	Q4182	Considered medically necessary when used for temporary covering of a surgically excised deep partial- or full-thickness burn wound as a covering prior to autografting.

Covered Indication Diabetic Foot Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
AlloPatch Pliable®	15275-15278	Q4128	Considered 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

Covered Indication Diabetic Foot Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
			• 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.
AmnioBand®	15275-15278	Q4151 Q4168	Considered 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.

Covered Indication Diabetic Foot Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
Apligraf®	15275-15278	Q4101	Considered 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.
DermACELL™ AWM For Breast Reconstruction see CP 0178	15275-15278	Q4122	Considered 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, treatment is limited to a total of two applications. Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.

Covered Indication Diabetic Foot Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
Dermagraft®	15275-15278	Q4106	Considered 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.
EpiFix® Amniotic Membrane	15275-15278	Q4186	Considered 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

Covered Indication Diabetic Foot Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
			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.
Geistlich Derma-Gide® Advanced Wound Matrix	15275-15278	Q4203	Considered medically necessary when ALL of the following criteria are met: • 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 at a minimum of one week intervals, for up to a maximum of eight 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
Grafix®	15275-15278	Q4132 Q4133	Considered 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

Covered Indication Diabetic Foot Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
			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 six 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.
GraftJacket NOW™, formerly GraftJacket® Regenerative Tissue Matrix	15275-15278	Q4107	Considered 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.
Integra® Dermal Regeneration Template/ Omnigraft Dermal Regeneration Matrix	15275-15278	Q4105	Considered medically necessary when ALL of the following criteria are met: • partial or full-thickness diabetic foot ulcer of greater than six 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

Covered Indication Diabetic Foot Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
			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.
Oasis® Wound Matrix Oasis® Ultra Tri-Layer Matrix	15275-15278 C5275-C5278	Q4102 Q4124	Considered 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 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.
PriMatrix™	15275-15278	Q4110	Considered medically necessary when ALL of the following criteria are met:

Covered Indication Diabetic Foot Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
			• partial or full-thickness diabetic foot ulcer of greater than six 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 three 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
TheraSkin®	15275-15278	Q4121	Considered 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

Covered Indication Diabetic Foot Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
			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.

Covered Indication Venous Stasis Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
AmnioBand®	15271-15278	Q4151 Q4168	Considered 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 lower extremity 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 12 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.
Apligraf®	15271-15278	Q4101	Considered 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

Covered Indication Venous Stasis Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
			• treated lower extremity 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.
EpiFix® Amniotic Membrane	15271-15278	Q4186	Considered 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 lower extremity 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.

Covered Indication Venous Stasis Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
Grafix®	15271-15278	Q4132 Q4133	Considered 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 lower extremity 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 six 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.
Oasis Wound Matrix Oasis® Ultra Tri-Layer Matrix	15271-15278 C5271-C5278	Q4102 Q4124	Considered 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 lower extremity 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

Covered Indication Venous Stasis Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
			epithelialization and reduction in ulcer size) Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.
PriMatrix™	15271-15278	Q4110	Considered 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 lower extremity 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 three 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.
TheraSkin®	15271-15278	Q4121	Considered 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 lower extremity 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:

Covered Indication Venous Stasis Ulcers			
Skin Substitute	**Application CPT®/HCPCS Codes**	**Product HCPCS Codes**	**Criteria**
			• 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.

Each of the products listed above for ANY unlisted indication is considered not medically necessary.

Each of the following products listed below is considered experimental, investigational, or unproven for ANY indication:

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
AC5® Advanced Wound System	Wound healing	15271-15278 C5271-C5278	A2020
Actigraft®	Wound healing	15271-15278 C5271-C5278	Q4100 C9399
Actishield™ Amniotic Barrier Membrane	Soft and/or hard tissue repair	15271-15278 C5271-C5278	Q4100 C9399
Actishield™CF Amniotic Barrier Membrane	Soft and/or hard tissue repair	15271-15278 C5271-C5278	Q4100 C9399
ActiveBarrier®	Wound care	15271-15278 C5271-C5278	Q4100 C9399
ActiveMatrix® flowable	Connective tissue repair	No specific code	Q4100 C9399
Acuseal Cardiovascular Patch	Cardiovascular reconstruction	No specific code	C1768

Not Covered Products	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 C9399
Affinity	Wound care	15271-15278	Q4159
DermaMatrix ® Acellular Dermal Matrix	Soft tissue repair	No specific code	Q4100 C1762
Allopatch HD™	Tendon augmentation	No specific code	Q4128
Allowrap™ DS and Dry	Wound care	15271-15278	Q4150
AmnioAMP-MP™	Wound care	15271-15278 C5271-C5278	Q4250
AmnioBand® Particulate	Wound care	15777	Q4168
AmnioCare®	Tendon/nerve repair	No specific code	Q4100 C9399
AmnioClear®	Wound care Surgical barrier	15271-15278 C5271-C5278	Q4100 C9399
AmnioClear LTC flowable	Knee pain and inflammation	No specific code	J3590
AmnioCore™	Wound care	15271-15278	Q4227
Amniocyte™ Flowable Matrix	Connective tissue repair	No specific code	J3590
AmnioEffect™	Wound care Surgical barrier	15271-15278 C5271-C5278	Q4100 C9399
AmnioExCel/AmnioExcel Plus/BioDExCel™	Wound care Soft tissue repair	15271-15278	Q4137
Amniofix® Amniotic Membrane	Tendon/nerve repair	No specific code	Q4100 C9399
Amniofix® Injectable	Tendon repair Soft tissue repair	No specific code	J3590
AmnioHeal® Plus	Wound care	15271-15278 C5271-C5278	Q4100 C9399
Amnio-Maxx	Wound care	15271-15278	Q4239
AmnioMatrix®	Wound care Soft tissue repair	15271-15278 C5271-C5278	Q4139
AmnioMTM Injectable	Wound care Soft tissue repair	No specific code	Q4100 C9399

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
AmnioPro Membrane	Wound care	15271-15278 C5271-C5278	Q4100 C9399
AmnioPro Flow	Wound care	No specific code	Q4100 C9399
Amniorepair/Altiply	Wound care	15271-15278	Q4235
Amnios®/Amnios® RT	Wound care	No specific code	Q4100 C9399
Amniovo™	Soft tissue repair Tendon repair	No specific code	Q4100 C9399
Anu RHEO™	Connective tissue repair	No specific code	Q4100 C9399
Artacent® ac, powder	Wound care	No specific code	Q4189
Arthrex Amnion™ Matrix	Orthopedic barrier or wrap	No specific code	Q4100 C1762
Arthrex Amnion™ Viscous	Orthopedic barrier or wrap	No specific code	J3590
ArthroFlex™ (FlexGraft®)	Shoulder reconstruction Achilles tendon repair	No specific code	Q4125
ARTIA™ Reconstructive Tissue Matrix	Soft tissue repair	No specific code	C1763
Avance Nerve Graft	Peripheral nerve repair	64912 64913	Q4100 C9399
Avive® Soft Tissue Membrane	Soft tissue repair	No specific code	Q4100 C9399
AxoGuard® Nerve Connector	Peripheral nerve repair	64999	Q4100 C1763
AxoGuard® Nerve Protector	Peripheral nerve repair	64999	Q4100 C1763
Axolotl Ambient™	Soft tissue repair	No specific code	Q4215
Axolotl Cryo™	Soft tissue repair	No specific code	Q4215
Axolotl DualGraft™	Soft tissue repair	15271-15278	Q4210
Axolotl Graft™	Soft tissue repair	15271-15278 C5271-C5278	Q4210
BellaDerm® Acellular Hydrated Dermis	Integumental tissue repair Soft tissue repair	No specific code	Q4100 C9399
BioDfactor™	Wound care Soft tissue repair	15271-15278 C5271-C5278	Q4100 C9399

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
BioDfence™	Surgical wrap/barrier Tendon repair	No specific code	Q4140
BioDfence™ DryFlex	Surgical wrap/barrier Tendon repair	No specific code	Q4138
BioDRestore flowable	Soft tissue repair	No specific code	Q4100 C9399
Biodesign® Dural Graft	Dural repair	No specific code	Q4100 C1763
Biodesign® (Surgisis®) Anal Fistula Plug (AFP™)	Anal and rectal fistula repair	46707	Q4100 C1763
Biodesign® (Surgisis®) Hiatal Hernia Graft	Hernia repair	No specific code	Q4100 C1781
Biodesign® (Surgisis®) Inguinal Hernia Graft	Hernia repair	No Specific Code	Q4100 C1781
Biodesign® Otologic Repair Graft	Otologic repair	No specific code	Q4100 C1763
Biodesign® Fistula Plug Set, previously Biodesign® (Surgisis®) RVP™ Recto-Vaginal Fistula Plug	Recto-vaginal fístula repair	No specific code	Q4100 C1763
Biodesign® Peyronie's Repair Graft	Urological deficits	No specific code	Q4100 C1763
Biodesign Rectopexy Graft	Rectal prolapse/rectal intussusception	No specific code	Q4100 C1763
Biodesign® Sinonasal Repair Graft	Wound care	No specific code	Q4100 C1763
BioFix®	Wound care	15271-15278 C5271-C5278	Q4100 C9399
BioNextPatch	Burn care Wound care	15271-15278 C5271-C5278	Q4100 C9399
CanGaroo™ Protect ECM Envelope	Implantable electronic device pocket	No Specific Code	Q4100 C9399
CardioCel®	Pericardial closure Cardiac and vascular defect repairs	No specific code	Q4100 C9399
CardioGRAFT MC® Decellularized Pulmonary Patch Graft	Repair of right ventricular outflow tract	No specific code	Q4100 C9399
carePATCH	Burn care Wound care	15271-15278 C5271-C5278	Q4236
CellerateRX®	Wound care	No specific code	A6010

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
Clarix 100	Surgical covering/wrap/barrier	No specific code	Q4156
Clarix Cord 1K	Surgical covering/wrap/barrier	No specific code	Q4148
Clarix® Regenerative Matrix	Surgical covering/wrap/barrier	No specific code	Q4100 C9399
Clarix® Flo	Integumental tissue repair	No specific code	Q4155
Cocoon membrane	Wound care	15271-15278 C5271-C5278	Q4264
Coll-e-Derm	Soft tissue repair	15271-15278	Q4193
Cogenex Amniotic Membrane	Burn care Wound care	15271-15278 C5271-C5278	Q4229
Complete™ FT	Wound care	15271-15278 C5271-C5278	Q4271
Complete™ SL	Wound care	15271-15278 C5271-C5278	Q4270
Conexa™	Tendon repair	No specific code	Q4100 C1781
Coretext and Protext	Tissue repair	No specific code	Q4246
CorMatrix® ECM® for Cardiac Tissue Repair	Intracardiac patch	No specific code	Q4100 C9399
CorMatrix® ECM® for Carotid Repair	Carotid artery repair	No specific code	Q4100 C9399
CorMatrix® ECM® for Pericardial Closure	Pericardial repair	No specific code	Q4100 C9399
Creos™ Xenoprotect	Bone and tissue regeneration	No specific code	Q4100 C9399
CryoMatrix®	Connective tissue repair	No specific code	Q4100 C9399
CryoSkin®	Wound care	15271-15278 C5271-C5278	Q4100 C9399
Cygnus®	Wound care Nerve wrap	15271-15278 64999	Q4170
Cytal®	Wound care	15271-15278	Q4166

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
		C5271-C5278	
DermaMatrix Acellular Dermis	Facial soft tissue defects Breast reconstruction	15275-15278 15777	Q4100 C9399
DermaPure™	Wound care	15271-15278	Q4152
DermaSpan™	Wound covering Tendon repair	15271-15278	Q4126
Dual layer impax membrane	Wound care	15271-15278 C5271-C5278	Q4262
Duraform™	Dural repair	No specific code	Q4100 C9399
DuraGen®	Dural repair	No specific code	Q4100 C9399
Dura-Guard	Dural repair	No specific code	Q4100 C1763
DuraMatrix™	Dural repair	No specific code	Q4100 C9399
DuraSeal® Dural Sealant System	Dural repair	No specific code	Q4100 C9399
DuraSeal® Exact Spine Sealant System	Dural repair	No specific code	Q4100 C9399
DuraSorb® Monofilament Mesh/ Polydioxanone Surgical Scaffold™	Soft tissue reinforcement	No specific code	C1718
Durepair Regeneration Matrix®	Dural repair	No specific code	Q4100 C9399
Endoform Dermal Template™	Wound care	15271-15278 C5271-C5278	Q4100 C9399
EpiBurn®	Wound care	15271-15278 C5271-C5278	Q4100 C9399
EpiCord™	Wound care	15271-15278	Q4187
Esano™ A	Wound care	15271-15278	Q4272
Esano™ AAA	Wound care	15271-15278	Q4273
Esano™ AC	Wound care	15271-15278	Q4274
Esano™ ACA	Wound care	15271-15278	Q4275

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
FloGraft™ flowable	Tendonitis Soft tissue trauma	No specific code	Q4100 C9399
Fortaderm™/Puraply™	Wound care	15271-15278	Q4195
Fortiva® Porcine Dermis	Soft tissue reinforcement	No specific code	Q4100 C1763
GalaFLEX® Scaffold	Soft tissue repair	No specific code	Q4100 C9399
GalaFLEX 3DR Scaffold	Soft tissue repair	No specific code	Q4100 C9399
GalaFLEX 3D Scaffold	Solft tissue repair	No specific code	Q4100 C9399
Gentrix®	Soft tissue reinforcement	No specific code	C1763 C1781
GORE® BIO-A® Fistula Plug	Anorectal fistulas	46707	Q4100 C1781
GORE® BIO-A® Tissue Reinforcement	Soft tissue reinforcement	15777 17999	Q4100 C1781
GraftJacket® Xpress	Wound care	No specific code	Q4113
Helicoll™	Wound care	15271-15278	Q4164
HydroFix® Vaso Shield	Vessel guard	No specific code	Q4100 C9399
Integra™ Flowable Wound Matrix	Wound care	No specific code	Q4114
Integra® Reinforcement Matrix	Soft tissue reinforcement	No specific code	Q4100 C1763
InteguPly (TranZgraft))	Tendon repair	15271-15278	Q4126
Kerecis Omega3 Marigen Shield	Wound care	15271-15278 C5271-C5278	A2019
Kerecis® Omega3 Wound	Wound care	15271-15278	Q4158
Lyoplant®	Dural repair	No specific code	Q4100 C1763
MatriStem®	Wound care	15271-15278	Q4118
Matrix HD™	Wound care Tendon repair	15271-15278 C5271-C5278	Q4100 C9399
MemoDerm™	Wound care Tendon repair	15271-15278	Q4126
Miamnion®	Wound care	No specific code	Q4100 C9399

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
Microlyte® Matrix	Wound care	15271-15278	A2005
MiroFlex® (formerly Miromesh®)	Soft tissue reinforcement	No specific code	Q4100 C9399
Miro3D® Wound Matrix	Wound care	15271-15278 C5271-C5278	Q4100 C9399
Myriad Matrix™	Wound care	15271-15278 C5271-C5278	Q4100 C9399
NeoMatriX®	Wound care	15271-15278 C5271-C5278	A2021
NeoStim DL	Wound care	15271-15278 C5271-C5278	Q4267
NeoStim Membrane	Wound care	15271-15278 C5271-C5278	Q4266
NeoStim TL	Wound care	15271-15278 C5271-C5278	Q4265
Neox® 100	Wound care	15271-15278	Q4156
Neox® Cord 1K	Wound care	15271-15278	Q4148
Neox® Flo	Wound care	No specific code	Q4155
Neox® Wound Matrix	Wound care	15271-15278 C5271-C5278	Q4100 C9399
NeuraGen® Nerve Guide	Peripheral nerve repair	64910	C9352
NeuraWrap™ Nerve Protector	Peripheral nerve repair	64999	C9353
NeuroFlex™	Peripheral nerve repair	64999	Q4100 C9399
NeuroMatrix™	Peripheral nerve repair	64999	C9355
NeuroMend™	Peripheral nerve repair	64999	C9361
Novafix® DL	Wound care	15271-15278	Q4254

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
		C5271-C5278	
NuCel™	Tendon repair	No specific code	Q4100 C9399
Nucel Bioactive Amniotic Suspension	Tissue repair	No specific code	Q4100 C9399
NuShield™ Orthopaedics	Tendon repair	No specific code	Q4160
NuShield™ Spine	Dura repair	No specific code	Q4160
Oasis® Burn Matrix	Burn wounds	15271-15278	Q4103
Orcel®	Burn wounds	15271-15278 C5271-C5278	Q4100 C9399
Orion Amniotic Membrane	Wound covering	15271-15278	Q4276
OrthADAPT™ Bioimplant	Soft tissue reinforcement	15777 17999	Q4100 C1781
OrthoNovis Guard Allograft Membrane	Wound care	15275-15278 C5275-C5276	Q4100 C9399
OsseoGuard®	Oral defects	15275-15278 C5275-C5276	Q4100 C9399
Ovation®	Wound healing	15271-15278 C5271-C5278	Q4100 C9399
OviTex®	Soft tissue reinforcement Breast reconstruction	No specific code	C1781
PalinGen® Flow	Soft tissue repair	No specific code	Q4174
PalinGen® Xplus	Soft tissue repair	No specific code	Q4173
Paraderm™ Dermal Matrix	Integumental tissue repair	No specific code	Q4100 C9399
Peri-Guard® Repair Patch	Soft tissue repair Pericardial and intracardiac repair	No specific code	Q4100 C1763
Peri-Strips® Dry	Staple line reinforcement	No specific code	Q4100 C9399
Permacol™	Soft tissue reinforcement/repair	15777 17999	C9364
Phasix Mesh	Soft tissue reinforcement/repair	15271-15278	C1781

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
		C5271-C5278	
Phasix™ Plug and Patch	Soft tissue reinforcement/repair	15271-15278 C5271-C5278	C1781
PhotoFix® Decellularized Bovine Pericardium	Vascular repair	No specific code	Q4100 C1763
Preclude® Dura Substitute	Dural repair	No specific code	Q4100 C9399
Preclude® Pericardial Membrane	Pericardial repair	No specific code	Q4100 C9399
Preclude® Vessel Guard	Vessel covering	No specific code	Q4100 C9399
Pro3™ Amniotic Fluid	Wound care	No specific code	J3590
Pro3™ Membrane	Wound care	15271-15278 C5271-C5278	Q4100 C9399
Proceed® Surgical Mesh	Hernia repair	No specific code	Q4100 C9399
ProgenaMatrix™	Wound care	15271-15278	Q4222
ProLayer Acellular Matrix	Wound care	15271-15278 C5271-C5278	Q4100 C9399
ProLayer Xenograft	Soft tissue repair	No specific code	Q4100 C9399
ProMatriX™	Wound care	No specific code	Q4174
Promote™ Amnio-Frt™	Wound care	15271-15278 C5271-C5278	Q4100 C9399
Promote™ Amnio F™	Wound care	15271-15278 C5271-C5278	Q4100 C9399
Promote AmnioStrip®	Wound care	15271-15278 C5271-C5278	Q4100 C9399
Puracol®	Wound care	15271-15278 C5271-C5278	Q4100 C9399

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
PuraPly® Wound Matrix	Wound care	15271-15278	Q4195
PuraPly® Antimicrobial/PuraPly® AM	Wound care	15271-15278	Q4196
PX50®/PX50® Plus	Damaged or inadequate tissue repair	No specific code	Q4100 C9399
RECELL® Autologous Cell Harvesting Device	Burn Care	15110-15116	C1832
REGENETEN Bioinductive Implant	Tendon repair	No specific code	C1763
Renuva® Allograft Adipose Matrix	Reconstructive surgery Breast reconstruction	No Specific code	J3590
Repliform™	Integumental tissue repair	No specific code	C1762
Restore® Orthobiologic Soft Tissue Implant	Soft tissue reinforcement	17999	Q4100 C1763
Restorigin™ Amniotic Fluid	Wound care	No specific code	Q4192
Revita	Wound care	15271-15278	Q4180
RX Flow	Connective tissue repair	No specific code	Q4100 C9399
Rx Membrane	Soft tissue repair	15777 17999	Q4100 C1781
Seamguard® Staple Line Reinforcement	Staple line reinforcement	No specific code	Q4100 C9399
SERI™ Surgical Scaffold	Soft tissue reinforcement/repair	15777 17999	Q4100 C1781
Simpliderm™	Soft tissue reinforcement/repair Breast reconstruction	No specific code 15777	Q4100 C9399
SJM™ Pericardial Patch with EnCap™ AC Technology	Pericardial repair	No specific code	Q4100 C9399
SomaGen® Meshed Tissue	Wound care	15271-15278 C5271-C5278	Q4100 C9399
SportMesh™	Soft tissue reinforcement	15777 17999	Q4100 C1781
SteriShield™	Soft tissue reinforcement/repair	15777 17999	Q4100 C9399
Strattice™ Reconstructive Tissue Matrix	Soft tissue reinforcement/repair	15777 17999	Q4130
Stravix ™	Integumental tissue repair	No specific code	Q4133

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
SurGraft® FT	Wound care	15271-15278 C5271-C5278	Q4268
SurGraft TL®	Wound care	15271-15278 C5271-C5278	Q4263
SurGraft® XT	Wound care	15271-15278 C5271-C5278	Q4269
SurgiMend®	Breast reconstruction	15777	C9358 C9360
Symbotex™ Composite Mesh	Soft tissue reinforcement	15777 17999	Q4100 C9399
SYNTHECEL™ Dura Repair	Dural repair	No specific code	Q4100 C1781
tarSys™	Eyelid reconstruction	67961-67966	Q4100 C9399
TenoGlide® Tendon Protector Sheet	Tendon repair	No specific code	C9356
TEXAGEN Amniotic Membrane Allograft	Wound care	15271-15278 C5271-C5278	Q4100 C9399
TissueMend	Soft tissue repair Tendon repair	No specific code	C1781 Q4100
Tornier® BioFiber Absorbable Biological Scaffold	Soft tissue reinforcement/repair	15777 17999	Q4100 C1781
Tornier® Collagen Coated BioFiber Scaffold	Soft tissue reinforcement/repair	15777 17999	Q4100 C1781
Tutopatch® Bovine Pericardium	Soft tissue reinforcement/repair	15777 17999	Q4100 C1781
Unite® Biomatrix	Wound care	15271-15278 C5271-C5278	Q4100 C9399
VascuCel®	Vascular patch	No specific code	Q4100 C9399
Vascu-Guard®	Peripheral vascular reconstruction	No specific code	Q4100 C9399
VersaShield™	Wound care Soft tissue covering	15271-15278 C5271-C5278	Q4100 C9399
Veritas Collagen Matrix	Soft tissue reinforcement/repair	15777	Q4100

Not Covered Products	Reason(s) for Request (this list may not be all inclusive)	Application CPT/HCPCS Codes	Product HCPCS Codes
		17999	C9354
Veritas Collagen Matrix Peri-Strips Dry	Staple line reinforcement	No specific code	Q4100 C9399
Viaflow™/Viaflow C	Connective tissue repair	No specific code	Q4100 C1781
VIAGENEX™ Matrix Amnion Allograft	Soft tissue covering Wound covering	15271-15278 C5271-C5278	Q4100 C9399
VIAGENEX™ Max Umbilical Cord Membrane	Soft tissue covering Wound covering	15271-15278 C5271-C5278	Q4100 C9399
WoundEx® Membrane	Wound care	15271-15278	Q4163
WoundEx® Flow	Integumental tissue repair	No specific code	Q4162
Xceed™	Wound care	No specific code	Q4100 C9399
Xcellerate	Burn care Wound care	15271-15278	Q4234
XCelliStem® Wound Powder	Wound care	No specific code	A2004
Xenform®	Soft tissue reinforcement/repair	15777 17999	C1763
XenMatrix™ Surgical Graft	Soft tissue reinforcement/repair	15777 17999	C1781
XenoSure® Biologic Patch	Cardiac reconstruction/repair Vascular reconstruction/repair	No specific code	Q4100 C1781
Zenith™ Amniotic Membrane	Burn care Wound care	15271-15278 C5271-C5278	Q4253

General Background

Skin Substitutes

Biologic skin substitutes can refer to skin that is harvested from a donor site and transplanted into the recipient site. Also called biological tissue, these skin substitutes can be an autograft, allograft, or xenograft. Autograft skin substitutes are harvested from another location of the patient's body. Allografts are harvested from a donor of the same species, and xenografts are derived from a different species such as porcine, bovine or piscine. These biologics may provide temporary coverage of the wound or may be resorbed and become a permanent part of the body. Skin substitutes ideally possess the composition and function of skin or have the potential to allow the body to heal itself (Shahrokhi, 2023).

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 (Wood, 2021; Ahmad et al., 2010; Ge et al., 2010). PureSkin™ is an example of an allograft that is available in fresh configuration or cryopreserved from, meshed and non-meshed. PureSkin is primarily used in burn patients to advance wound healing when autografting is not feasible (Allosource, 2022). Maxxeus is a provider of a cryopreserved allograft for burn care (Maxxeus, 2023).

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 burns (including acute or reconstructive), breast reconstruction and chronic wounds such as venous status ulcers and diabetic foot ulcers unresponsive 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.

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. To date evidence is lacking supporting superiority of one product over another for the treatment of lower extremity wound therapy.

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 under section 361 of the Public Health

Service (PHS) Act for the manufacture human cells, tissues, and cellular and tissue-based products (HCT/Ps). AATB oversees a voluntary accreditation program and the FDA focuses on preventing the transmission of communicable diseases by requiring donor screening and testing. Establishments that manufacture HCT/Ps must register with the FDA and list each cell or tissue produced (FDA, 2021). An example of a banked human tissue product is AlloDerm, an acellular dermal matrix.

In 2021, the FDA issued a safety communication regarding acellular dermal matrix (ADM) products indicating that higher complication rates may be present in certain ADMs used in implant-based breast reconstruction. ADMs are developed from either human (e.g., FlexHD, AlloMax, AlloDerm) or animal skin (e.g., SurgiMend) and have had the cells removed leaving behind the support structure for use. The FDA has not approved any ADMs for the indication of implant-based breast reconstruction. The FDA's safety communication cited a prospective corhort study evaluating safety outcomes (i.e., reoperation, explantation, infection) from implant-based breast reconstruction surgeries after mastectomy in multiple centers in the United States and Canada that showed significantly higher complication rates in patients with FlexHD and AlloMax ADMs two years after surgery compared to a control group that did not receive an ADM. The FDA pointed to a need for additional, high-quality studies evaluating the safety and efficacy of ADMs. As a result of their analysis, the FDA has given the following recommendations for health care providers:

- "Discuss the potential benefits and risks of all relevant treatment options with your patients as part of a shared decision-making process.
- Be aware that the FDA has not approved or cleared any ADM products for use in implant-based breast reconstruction. Data analyzed by the FDA and published literature suggest that some ADMs may have higher risk profiles than others.
- Be aware that the FDA does not recommend reoperation or removal of implanted ADM as a preventive measure.
- Report any patient adverse events to the FDA MedWatch program, using the information in the Reporting Problems with Your Device page" (FDA, 2021).

In June 2021, the FDA updated a July 2020 consumer alert on regenerative medicine therapies. These products require FDA licensure/approval to be marketed to consumers. These unapproved products include stem cells, stromal vascular fraction (fat-derived cells), umbilical cord blood and/or cord blood stem cells, amniotic fluid, Wharton's jelly, ortho-biologics, and exosomes. The warning included the statement that "regenerative medicine therapies have not been approved for the treatment of any orthopedic condition, such as osteoarthritis, tendonitis, disc disease, tennis elbow, back pain, hip pain, knee pain, neck pain, or shoulder pain."

Per the FDA, safety concerns with these products included the following:

- "Blindness;
- Tumor formation;
- Neurological events;
- Bacterial infections including life-threatening blood infections;
- Reactions at the site of collection and administration;
- Unwanted inflammatory or immune response to the cell or therapy;
- Cells moving to another part of the body and turning into an unintended type of tissue or excessively growing in the body (i.e., forming a tumor);
- Failure of the therapy to work as anticipated when approved treatments are available;
- Cross-contamination with bacteria, viruses or mold related to processing (preparation of the product) or the therapy not being tested for infectious diseases such as hepatitis and HIV."

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 (Allergan™, Parsippany, NJ; formerly 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 (Kim, et al., 2012; Jansen and Macadam, 2011; Nguyen, et al., 2011; Chun, et al., 2010; Spear, et al., 2008; Bindingnavele, et al., 2007; Breuing and Colwell, 2007; Zienowicz and Karacaoglu, 2007; Gamboa-Bobadilla, 2006; Salzberg, 2006; Breuing and Warren, 2005; Nahabedian, 2005). Various forms of AlloDerm are available including AlloDerm™ Regenerative Tissue Matrix, AlloDerm Select™ Regenerative Tissue Matrix and AlloDerm Select Restore™ Regenerative Tissue Matrix (AbbVie, 2024).

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) (de Moya, 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: Parotidectomy exposes the postganglionic parasympathetic fibers, which can cause severance and inappropriate regeneration. It is proposed that the syndrome is prevented by putting a barrier between skin and the auriculotemporal nerve to prevent the switched parasympathetic fibers from innervating the sweat glands or skin, thus preventing Frey 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 and the authors 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. (2009) 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. However, studies are primarily in the form of retrospective reviews with small patient populations and the authors reported less that beneficial clinical outcomes were not seen with the addition of AlloDerm (Li, et al., 2005; Taban, et al., 2005).

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 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.

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.

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

AlloPatch® Pliable
AlloPatch® Pliable (Musculoskeletal Transplant Foundation [MTF], Edison, NJ) is an acellular allogenic human dermal graft designed to support host tissue remodeling. AlloPatch Pliable is used as a wound care scaffold for the replacement of damaged or inadequate integumental tissue. Regulated under the FDA Human cells, tissues, and cellular and tissue-based products, the graft is proposed for the treatment of acute traumatic wounds such as burns and penetrating trauma, surgical skin cancer wounds and scar revisions. Indications for the treatment of chronic wounds include: diabetic foot ulcers, venous ulcers, pressure/decubitus ulcers and vascular arterial ulcers. It is a pre-hydrated matrix that comes in four sizes from 1.5 x 1.5 cm to 4 x 8 cm. (MTF, 2024).

Zelen et al. (2017) conducted a multicenter, randomized controlled trial to investigated the effectiveness of AlloPatch Pliable plus standard of care (SOC) (n=20) compared to SOC alone (n=20) in the treatment of nonhealing diabetic foot ulcers (DFUs). The objective of the study was to compare complete wound healing at six weeks and twelve weeks. Selection criteria included: age ≥ 18 years; type 1 or type 2 diabetic, DFU of ≥ 4 weeks duration with failure to treatment; DFU ≥ 1 cm^2; no signs of infection, HBA1C < 12%; adequate circulation within past 60 days; dorsum transcutaneous oxygen test ≥ 30 mmHg; and ABI ≥ 0.7 and ≤ 1.2. Following a two-week screening period in which DFUs were treated with offloading and moist wound care, patients were randomized to SOC alone or AlloPatch plus SOC applied weekly for up to 12 weeks. Patients whose index wound had not healed greater than 20% at two weeks were randomized to the AlloPatch plus SOC or SOC alone group. Wounds were defined as healed if there was complete (100%) re-epithelialization without drainage or need for dressing. For patients in the SOC group, daily dressing changes with a collagen-alginate were performed weekly. Overall, significantly better outcomes were reported in the AlloPatch plus SOC group. At six weeks 65% of patients treated with AlloPatch had healed compared with 5% of DFUs in the SOC alone group. Mean time to heal at six weeks was 28 day vs. 41 days in the SOC group. Ten patients from the SOC group (50%) and one patient from the graft group (5%) exited from the study at six weeks per protocol because their wounds failed to reduce by at least 50%. At 12 weeks 80% of the study group and 20% of the SOC group had healed (p=0.00036). Mean time to healing at 12 weeks was 40 days in the AlloPatch group and 77 days in the SOC group (p=0.00014). The mean number of grafts used to achieve closure was 4.7 per wound. Adverse events in both groups were related to foot infections and none were attributed to the use of the graft. Limitations of the study include the small patient population, short-term follow-up and a larger mean wound area in the AlloPatch group (4.7 cm^2) compared with the SOC group (2.7 cm^2).

AmnioBand® or Guardian

AmnioBand or Guardian (Musculoskeletal Transplant Foundation (MTF), Edison, NJ), is an allograft made of human amnion and chorion and proposed as a covering for internal and external wounds. The product is regulated by the American Association of Tissue Banks (AATB) and the FDA guidelines for banked human tissue. Although marketed under two different names, the products are exactly the same. The membrane is hydrophilic and can be used in a hydrated or dehydrated state. AmnioBand Membrane is used as a wound care scaffold for the replacement of damaged or inadequate integumental tissue such as diabetic foot ulcers, venous leg ulcers, pressure ulcers, or for other homologous use. AmnioBand comes in 13 sizes (MTF, 2024; Centers for Medicare and Medicaid, 2014).

Serena, et al. (2022) conducted a multicenter, randomized control trial to evaluate the safety and efficacy of weekly (n=20) and biweekly (every two weeks) (n=20) applications of AmnioBand plus standard of care compared to standard of care alone (n=20) on chronic venous leg ulcers (VLU). Standard of care included the cleaning and debriding of the study ulcer, application of multilayer compression bandaging, and instructions to keep leg elevated and bandage dry. Inclusion criteria included: age ≥ 18 years; ankle brachial index (ABI) >0.75 or skin perfusion pressure (SPP) >30 mmHg or transcutaneous oximetry measurement (TCOM) >30 mmHg; VLU wound area ≤ 2 cm^2 but < 20 cm^2 of a duration longer than one month that extended through the full thickness of the skin but not down to the muscle, tendon, or bone; study ulcer with a clean, granulating base with minimal adherent slough and treated with compression therapy for a minimum of 14 days prior to randomization. Patients were excluded if the ulcer was infected, suspicious for cancer, caused by a condition other than venous insufficiency, required treated by negative-pressure wound therapy or hyperbaric oxygen therapy or had previously been treated with cellular and/or tissue-based products. Patients were also excluded if they had a history of HIV/AIDS, drug or alcohol abuse, radiation therapy at the ulcer site, ulcers on the dorsum of the foot or with ≥ 50% of the ulcer below the malleolus, pregnant or breastfeeding, diabetes with HbA1c >12.0 within the past 90 days, renal dysfunction with serum creatinine levels ≥ 3.0 mg/dl within the last 90 days, used tobacco within the last 30 days or had a history of liver disease with active cirrhosis. The primary endpoint was the proportion of ulcers achieving complete closure (defined as macroscopic wound closure at 12 weeks) using the Silhouette three-dimensional laser camera system by Aranz Medical (Christchurch, New Zealand). Secondary endpoints included the proportion of ulcers achieving 40 percent area reduction at four weeks and the incidence of adverse events. At 12 weeks, complete healing occurred in 75% (15/20) of the weekly AmnioBand treatment group and in 75% (15/20) of the biweekly AmnioBand treatment group compared to 30% (6/20) of the SOC group (p=0.001). The percentage of ulcers achieving 40 percent area reduction at four weeks, was 65% (13/20) in SOC group, 80% (16/20) in the weekly AmnioBand group, and 70% (14/20) in the biweekly AmnioBand group. Thirty-eight adverse events occurred including nine serious adverse events. The most common types of adverse events were wound-related infections and formation of a new ulcer. None of the events was related to the study allograft or procedure. There were no amputations or deaths. An author noted limitation was the lack of blinding of patients and investigators to the treatment received. The application of AmnioBand (either weekly or biweekly) in conjunction with standard of care improved outcomes in the treatment of venous leg ulcers when compared to standard of care alone.

DiDomenico et al. (2016) conducted a multi-center, randomized controlled trial to compare AmnioBand (n=20) to standard of care (SOC) (n=20) in facilitating wound closure in nonhealing diabetic foot ulcers (DFUs). Included patients were age ≥ 18 years, type 1 or type 2 diabetic, had at least one unhealed neuropathic DFU ≥ 1 cm^2 with no sign of infection, had an HBA1c < 12%, and had failed conservative therapy for at least four weeks. Patients also had adequate circulation to the affected extremity within 60 days of the study, as demonstrated by dorsum transcutaneous oxygen test ≥ 30 mm Hg; or ABI with results of ≥ 0.7 and ≤ 1.2; or Doppler arterial waveforms, which were triphasic or biphasic at the ankle of the affected leg. SOC included: off-loading, appropriate debridement, and moist wound care. During a two-week screening period, patients

were treated with SOC. During the screening period, wounds were assessed and measured weekly and debridement was performed as necessary. If the index wound did not reduce by more than 20% in size at the end of the screening period, the patient was randomized to SOC or AmnioBand + SOC. Following randomization, each patient was treated weekly during the study period until the index wound closed or for 12 weeks. Wounds were defined as healed if complete (100%) epithelialization occurred without drainage and need for dressing, At six weeks, mean time to healing with AmnioBand was 30 days vs. 40 days with SOC (p=0.00073) and 70% (14/20) of the AmnioBand group healed compared with 15% (3/20) of DFUs treated with SOC alone. At six weeks eight SOC patients and one AmnioBand patient were withdrawn from the study because their wounds failed to reduce in area by at least 50%. Two DFU in the SOC group reopened after initial closure. Twelve weeks following treatment, 85% (17/20) of the AmnioBand patients were healed compared with 25% (5/20) in the SOC group. The mean time to heal was 36 days for AmnioBand and 70 days for SOC. The mean number of grafts used at 12 weeks was 3.8 (median 3.0). Four adverse events involved foot infection but were not found to be related to the graft. Limitations of the study include: small patient population, short-term follow-up; and mean wound size at randomization was larger in the SOC group (3.3 vs. 2.0 cm^2).

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 (Organogenesis, 2021; FDA, 2000). The safety and efficacy of more than five applications has not been reported in the published peer-reviewed literature.

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, 2021; 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; Falanga, et al., 1999; Falanga 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 (Smith and Nephew, 2023). 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. 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).

Cortiva®
Cortiva (RTI Surgical, Alachua, FL) is a non-crosslinked, cadaveric human acellular dermal matrix processed by Tutoplast technology using low-dose gamma irradiation. The matrix is FDA regulated as human cell, tissue, and cellular and tissue-based product (361 HCT/P) and proposed for the repair, replacement, reconstruction or augmentation of soft tissue, including supplemental support and reinforcement of soft tissue in breast reconstruction and hernia repair. There are three products: Cortiva, Cortiva 1.0 mm and Cortiva 1 mm tailored allogragft dermis. The matrixes are offered in regular and 1 mm thicknesses and supplied in a range of sizes from 2x4 cm to 16x20 cm (RTI, Inc., 2024; CMS, 2015). Studies investigating the clinical outcomes of Cortiva are primarily in the form of retrospective reviews with short-term follow-ups (Keifer, et al., 2016; CMS, 2015). Cortiva has evolved into an acceptable tissue substitute for breast reconstruction and a randomized controlled trial with short-term follow-up reported that outcomes with Cortiva were not inferior to outcomes using AlloDerm. There is insufficient evidence in the published peer-reviewed literature to support the clinical effectiveness of Cortiva for all other indications.

Parikh, et al. (2018) reported the outcomes of a phase 2 randomized controlled trial that compared outcomes following breast reconstruction surgery using Cortiva 1 mm allograft or AlloDerm Ready to Use (RTU) regenerative tissue matrix. The 16x8 cm graft was used as a sling to support tissue expanders placed in the submuscular location in one study arm, and prepectoral reconstructions with tissue expanders (TEs) or direct-to-implants (DTI) in a second study arm. The interim analysis of the submuscular reconstruction group is reported herein. Breasts reconstructed with AlloDerm RTU (n=17 patients; 28 breasts) or Cortiva 1 mm (n=17 patients; 31 breasts) submuscular TE, completed the interim analysis. During the study a significant shift to prepectoral reconstructions was noted and the prepectoral arm of the study was added to optimize enrollment rates. Patients who underwent prepectoral breast reconstruction with either DTI or TE supported by a 20x16 cm ADM sheet were compared in a separate study arm. The decision to proceed with prepectoral or submuscular reconstruction with either a TE or DTI was determined preoperatively. Female patients, aged 22–70 years old, undergoing immediate prosthetic reconstruction following therapeutic or prophylactic skin- or nipple-sparing mastectomy with a body mass index (BMI) less than 36 kg/m^2 were included. Excluded patients were those who were pregnant or breastfeeding immediately before mastectomy. The primary outcome measure was premature explantation of the TE before exchange, or unintended explantation of a DTI reconstruction during the first three months postoperatively. Secondary outcome measures included other complications (e.g., seroma, cellulitis, wound or ADM dehiscence, skin flap necrosis). Patients undergoing TE placement in either study arm were followed until there was TE exchange with an implant, flap, or both, or there was premature removal of the device. Patients undergoing DTI reconstruction were followed for at least three months following surgery. Patients undergoing reoperation of the surgical site without device exchange or removal were kept in the study. Patients underwent planned exchange of TEs for implants or flaps within 145.6 ± 51.6 days in the AlloDerm group and 167.0 ± 61.5 days in the Cortiva 1 mm group (p=0.27), not statistically significant. Most patient were exchanged with breast implant alone, but 14.3% in the AlloDerm group and 26.6% in the Cortiva group (p=0.25) received an autologous flap, not statistically significant. There was no significant difference between the group in integration of the ADM to the mastectomy flap (p=0.69), in drain removal between the groups or in physical well-

being, or satisfaction with information or plastic surgeon. A significant difference was seen in detectable seroma in the AlloDerm (n=3) vs. the Cortiva group (n=0). Premature explantation was performed in no Alloderm breast vs. one breast with Coriva. The initial size of the TE selected was significantly larger in patients reconstructed with Cortiva 1 mm (p=0.02). The AlloDerm RTU group was comprised of a significantly higher proportion of patients who had never smoked (p=0.009). This interim analysis of of submuscular reconstructions patients revealed no evidence of inferiority of outcomes of AlloDerm vs. Cortiva. Limitations of the study include the small patient population and short-term follow-up.

DermACELL™
DermACELL (LifeNet Health®, Virginia Beach, VA) is an acellular human dermis allograft collagen scaffold proposed for the treatment of soft tissue injury including second and third degree burns, breast reconstruction, chronic non-healing wounds, dehisced wound sites and cosmetic reconstruction after traumatic burn injuries. DermaCELL AWM is proposed for the treatment of chronic wounds including diabetic foot ulcers (DFUs), venous stasis ulcers (VSUs), arterial ulcers, pressure ulcers, dehisced surgical wounds, and traumatic burns. Dermacell AWM can be used over exposed tendon, bone, joint capsule, and muscle. The Matrix in available in 2X2 cm – 4X8 cm unmeshed and 2X2 cm – 8X12 cm meshed. There is also an AWM porous matrix (LifeNet Health, 2024).

LifeNet Health is registered with the FDA as an establishment producing tissue- and cellular-based products. MatrACELL® is a patented process that removes > 97% of donor DNA that renders DermACELL acellular. Terminal sterilization is performed by low dose gamma irradiation. In December 2014, Novadaq Technologies was appointed the exclusive worldwide distributor of DermACELL. The evidence in the published peer-reviewed literature supports DermACELL for the treatment of diabetic foot ulcers. The use of DermACELL for breast reconstruction has evolved into an accepted standard of practice.

DermACELL has been proposed for the treatment of large, complex diabetic foot ulcers (DFUs) that probed to tendon or bone. Studies are primarily in the form of case series with small patient populations (n=47) (Cazzell, et al., 2019). Evidence supporting DermACELL for the treatment of complex DFUs and all other indications is lacking.

Diabetic Foot Ulcer: Evidence in the published peer-reviewed literature support DermACELL for the treatment of partial and full-thickness diabetic foot ulcers. Walters et al. (2016) conducted a multicenter, randomized controlled trial (n=168) to compare the safety and efficacy of DermACELL (n=53) to conventional therapy (n=56) and to Graftjacket (n=23) in a 2:2:1 ratio. The primary endpoint was assessment of complete reepithelialization with no drainage or dressing requirements with confirmation at two consecutive follow-up visits two weeks apart. The healing rate of wounds at 16 weeks and the percentage of reduction in wound size from baseline were also assessed. Patients were included in the study if they met the following: had a single, full-thickness target DFU, Wagner grade 1 or 2, a wound area ≥ 1 cm^2 or ≤ 25 cm^2, wound depth ≤ 9 mm, and adequate circulation to the affected area. Adequate circulation within the past 60 days was defined as transcutaneous oxygen measurement of 30 mm Hg or more at the dorsum of the foot; ankle-brachial index ranging from 0.8 to 1.2; and/or at least biphasic Doppler arterial waveforms at the dorsalis pedis and posterior tibial arteries. At 16 weeks, the DermACELL arm had a statistically significant higher proportion of completely healed ulcers compared to conventional care (p=0.0385) and a nonsignificantly higher proportion than the Graftjacket group (p=0.1149). The DermACELL arm showed a greater average percent reduction in wound area than conventional care (p=0.0791) and Graftjacket (p=0.0762), but the difference was not significant. The use of the second application was at the investigator's discretion. Severe adverse events were similar among the three groups. Limitations of the study included the small patient population, short-term follow-up and the number of patients lost to follow-up (31%).

Breast Reconstruction: Although the evidence supporting DermACELL for breast reconstruction is primarily in the form of case series and retrospective reviews, outcomes reported a significant improvement in time to drainage removal and fewer "red breast" episodes compared to AlloDerm (Pittman, et al., 2016). Zenn et al. (2016) reported that DermACELL was as good as AlloDerm RTU in the occurrence of postoperative infection, implant loss, seroma and hematoma. Other studies have also reported favorable outcomes with DermACELL (Chang and Liu, 2017; Bullocks, et al., 2014; Vashi, 2014). Therefore, DermACELL has evolved into an accepted skin substitute for breast reconstruction.

Dermagraft®
Dermagraft (Organogenesis, Canton, MA) is a cryopreserved dermal substitute made from newborn foreskin tissue and 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 (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, et al., 2003).

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 (Carson, et al., 2003; Munster, 1996).

Epifix®
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 (MiMedx, 2023). Randomized controlled trials support EpiFix for the treatment diabetic foot ulcers and venous status ulcers. Studies reported significantly greater reduction in wound size and faster healing time (Bianchi, et al., 2017; Zelen, et al., 2016; 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.

Evidence for the effectiveness of EpiFix for all other indications and EpiFix Micronized Powder for all indications is lacking.

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. FlexHD 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 (Chhabra and Houser, 2009). Data supporting the safety and efficacy of FlexHD for other indication 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 quasi-experimental time-interrupted series to evaluate the incidence of hernia recurrence in trauma or emergency surgical patients who were implanted with AlloDerm (n=55) or FlexHD (n=35). Patients had a large (> 200 cm^2) complicated symptomatic (pain, discomfort) ventral hernia as result of surgery. The primary outcome was hernia recurrence (true or functional) at one year. By year one, all AlloDerm patients requested and required a second hernia repair. The mean hernia size in the AllloDerm patients was 402 cm^2 and the mean mesh size used to repair the defect was 318 cm^2. Twelve of these patients were found to have intraoperative contamination at their first hernia repair operation and 33 had significant laxity (functional hernia recurrence) by six months postoperatively. A total of 17 patients had developed a functional recurrence by the one-year follow-up and five were diagnosed with a true recurrence confirmed at the time of the second hernia operation. AlloDerm complication ns included five seromas, seven intra-abdominal abscesses and two enterocutaneous fistulas. In the FlexHD group, mean hernia size was 388 cm^2 and the mean size of the mesh used to repair the defect was 389 cm^2. At the one-year follow-up, three patients had a true hernia recurrence (i.e., through the mesh or through the mesh/fascial interface) and eight had significant laxity (functional hernia recurrence). Of the 11 patients, six patients with functional hernia underwent repair. Complications in the FlexHD group included ten wound infections, two enterocutaneous fistulas, three intra-abdominal abscesses and three seromas. The difference in the groups in complications was not significant. All AlloDerm patients required a second hernia operation vs. 31% of FlexHD patients. Three of ten FlexHD patients vs. all AlloDerm patients in the underlay arm group suffered recurrence by one year ($p<0.001$). The lowest recurrence rate was in the FlexHD overlay group (2/23) as compared to Alloderm (13/13) group ($p<0.001$). Overall, recurrence rates were significantly greater in all three AlloDerm technique groups at one year. The authors concluded that FlexHD appeared to have reduced the recurrence and laxity rates while maintaining a similar complication profile when compared with AlloDerm. Limitations of the study include: the variation in surgical techniques within and between the groups, short-term follow-up, small patient population, and the study design having occurred during different time periods.

Geistlich Derma-Gide® Advanced Wound Matrix

Geistlich Derma-gide (Geistlich Pharma AG, Switzerland) is a collagen wound dressing derived from porcine tissue (mostly collagen Type 1) for covering and regenerating soft tissue defects or soft tissue wounds (Geistlich Pharma AG, 2024). Geistlich Derma-Gide received 510(k) FDA (K182838) approval on Nov 8, 2018. It is proposed for use with partial and full thickness wounds, ulcers (pressure, venous, diabetic, chronic vascular), surgical wounds (donor sites/grafts, post Moh's surgery, post laser surgery, podiatric, wound dehiscence) and trauma skin wounds (abrasions, laceration, second degree burns, skin tears). A randomized control trial and pilot study support the safety and efficacy of Geistlich Derma-Gide for the treatment of diabetic foot ulcers (Armstrong et al., 2020; Armstrong, et al., 2022).

Armstrong et al. (2022) conducted a multicenter, randomized control trial to compare the safety and efficacy of Derma-Gide, a purified reconstituted bilayer matrix (PRBM), to standard of care (SOC) (collagen alginate dressing) in the treatment of full-thickness, non-infected, non-ischemic (Wagner grade 1) diabetic foot ulcers (DFUs). Forty patients were included in an intent-to-treat (ITT) and per-protocol (PP) analysis, with 39 completing the study protocol (n=19 PRBM, n=20 SOC). The average age of patients in the PRBM group was 59.3 years and 66.5 years in the SOC group. The majority of patients were Caucasian males. Patients were adults age ≥ 18 years, had an uninfected DFU Wagner Grade1 present for >4 weeks unresponsive to SOC prior to first visit that was sized between ≥1.0 cm^2 and <25 cm^2. Patients were required to have adequate kidney function, adequate circulation to affected foot and offload the affected target ulcer for ≥14 days prior to randomization. Patients were excluded if they had poorly controlled diabetes (HgbA1c >12) cancer, end-stage renal disease, ulcer not caused by diabetes, recent history of osteomyelitis, radiation or investigational drug use. The primary endpoint was comparison of percentage of wounds closed after 12 weeks. Secondary outcomes included assessments of complications, healing time, quality of life, and cost to closure. Patients were evaluated weekly until either complete healing of the index ulcer or for 12 weeks, whichever came first. Patients were followed for an additional two weeks after index ulcer was 100% reepithelialised. Using the ITT approach, after 12 weeks of treatment, complete healing of ulcers occurred in 85% (17/20) of PRBM group compared to 30% (6/20) of SOC group ($p<0.001$). In the PP analysis, wound closure occurred in 94% (16/17) of PRBM and 30% (6/20) of SOC group ($p<0.001$). Wounds healed at a faster rate in PRBM group with complete wound healing at an average of 37 days compared to 67 days in SOC group ($p=0.002$). Healing rate in the PRBM arm at the 6-week mid-study point was 65% compared with 20% in the SOC arm. The mean percent area reduction (PAR) at six and 12 weeks for wounds treated with PRBM was 95% and 96%, respectively, compared with 24% and 9.8% for wounds in the SOC group. Patients reported 47% improvement in quality of life score in the PRBM group and 23% in SOC group. Both groups reported gradual decreasing VAS pain score over time. A mean of 5.2 (median 4; range 1-12) PRBM grafts were applied to achieve wound healing. No adverse events (AEs) directly related to PRBM treatment were reported. Author noted study limitations include small patient population, the inclusion of only full-thickness, noninfected, non-ischaemic wounds; and short term follow-up.

Grafix®
Grafix Cryopreserved Placental Membrane (Osiris Therapeutics, Inc., Columbia, MD is a subsidiary of Smith and Nephew) is a cryopreserved, human placental, extracellular matrix, amnion or chorion collagen rich, that includes growth factors and mesenchymal stem cells (MSC). It is proposed as the only commercially available placental membrane to contain viable endogenous cells (e.g., epithelial cells, fibroblasts, mesenchymal stem cells) which is accomplished using cryopreservation (Gibbons, 2015). The product is proposed for the treatment of acute and chronic wounds including: diabetic foot ulcers, venous leg ulcers, pressure ulcers, deep tunneling wounds, burns, pyoderma gangrenosum, epidermolysis bullosa, surgical incisions, and surgical dehiscence. Grafix is regulated by the FDA as banked human tissue and Osiris is accredited by the American Association of Tissue Banks (AATB). 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. Grafix Core is a chorion matrix and Grafix Prime is an amnion matrix, Available sizes include: 16 mm disc, 1.5X2 cm, 2X3 cm, 3X4 cm, 5x5 cm (Osiris Therapeutics, 2021). GrafixPL Prime and GrafixPl Core are also are other configuration of the Grafix products intended for the same use. Grafix PL Membrane is lyopreserved and stored at room temperature (Smith and Nephew, 2024).

Multicenter randomized controlled trials and technology assessments have reported that Grafix significantly improves overall wound healing and shortens the time to wound healing for partial and full-thickness diabetic foot ulcers and has evolved into an accepted treatment option for a select subgroups of patient (Ananian, et al., 2018; Lavery, et al., 2014). However, there is insufficient evidence to support the effectiveness of Grafix for complex diabetic foot ulcers including exposure of muscle, tendon, fascia, bone and/or joint capsule.

Published clinical trials have reported completed and faster healing of venous leg ulcers (VLUs) when Grafix was used as an adjunctive therapy with standard wound therapy (SWT) compared to SWT alone.

Farivar et al. (2019) conducted a prospective case series to evaluate the effectiveness of Grafix for the treatment of venous leg ulcers (VLU) (n=21 patients; 30 VLUs). Inclusion criteria were: presence of superficial or deep venous reflux confirmed by duplex ultrasound; active chronic VLU that failed standard wound care therapy; no evidence of active or ongoing wound or systemic infections; no evidence of limb ischemia (ankle-brachial index <0.8); and not immunosuppressed (i.e., human immunodeficiency virus infection, organ transplant recipients, receiving chronic steroid therapy). Ten of the patients had diabetes. The primary outcome measure was complete closure of the index wound. Secondary end points were the percentage change in total ulcer area during the follow-up period and reduction in wound area with application of Grafix. Patients who did not heal after 12 weeks of standard wound therapy (SWT) began receiving SWT and one application of Grafix per week for up to 12 weeks. If the percentage take of the graft was <50%, another application to the ulcer site was applied. Ulcer sites with percentage take >50% did not undergo another application on that follow-up visit. No patient received more than 12 applications. After a mean follow-up of 10.9 weeks, mean wound size was significantly reduced with Grafix therapy (p=0.002). Of the VLUs that failed SWT, 53% (16/30) healed completely with the addition of Grafix with a mean treatment time of 10.9 weeks. Of the remaining VLUs that did not achieve complete wound closure, 57% (8/14 limbs) had >50% wound area reduction. On average, 79.2% wound surface area reduction was achieved with Grafix compared with 29.2% SWT only (p<0.001). Patients received a mean 7.2 applications of Grafix and no ulcers recurred during the 12 weeks following healing. Limitations of the study include lack of a comparator and the small patient population.

Additional case series (Reyzelman, et al., 2019) and retrospective reviews have reported 47%–67.6% complete closure within 12 weeks when Grafix therapy was combined with standard wound therapy (Ananian, et al., 2019; D'Costa and Kurtzl., 2018, Smedley, et al., 2016; and Regulski, et al., 2013).

Osiris is proposing Grafix for the treatment of chronic, complex diabetic foot ulcers including exposure of muscle, tendon, fascia, bone and/or joint capsule. There is insufficient evidence to support the effectiveness of Grafix for complex diabetic foot ulcers. In a multicenter, prospective case series (n=31), Frykberg et al. (2016) evaluated the safety and efficacy of viable cryopreserved human placental (vCHPM) (GrafixCore) for the treatment of chronic complex diabetic foot wounds with exposed bone and tendon. Type 1 and type 2 diabetics, age 18–85 years, with a complex diabetic foot wound ≤15 cm in longest diameter were included. The wound extended through the dermis into the subcutaneous tissue with exposed muscle, tendon, fascia, bone and/or joint capsule. Vascular parameters included: ankle-brachial index (ABI) ≥0.5 and

≤1.2 or toe systolic pressure ≥40 mmHg or transcutaneous tissue oxygen tension (tcpO2) >30 mmHg or skin perfusion pressure of >30 mmHg. The patients had significant comorbidities (hypertension, current or former smoker, heart disease and/or partial food amputation). Three patients had end-stage renal disease and were on hemodialysis. The primary endpoint was 100% granulation (i.e., complete coverage of the exposed tendon and/or bone with collagen-rich connective tissue) of the index wound by 16 weeks after the initial application of GrafixCore. Standard wound care (cleansing, debridement, absorptive foam dressings, off-loading devices) was also performed before and after application. Patients were treated with a weekly application of the graft for up to 16 weeks. If 100% granulation was achieved prior to 16 weeks, the patients continued to receive weekly applications until complete wound closure occurred for up to a maximum of 16 applications. By week 16, 96.3% of patients achieved 100% granulation of the index wound. An average of 6–8 applications was required. In addition, 59.3% of patients achieved complete wound closure (100% reepithelialisation*)* with an average of nine applications without the need for further amputation or surgical intervention. No adverse events related to the graft were reported. The authors noted that this was the first prospective study reporting outcomes for viable cryopreserved human placental for the treatment of complex diabetic foot ulcers. The incidence of amputation in this study group was 6.5%. Twenty-seven patients completed the study. Additional studies with larger patient populations are needed to validate the effectiveness of skin substitutes for complex diabetic foot wounds.

GraftJacket NOW™ formerly GraftJacket® Regenerative Tissue Matrix (RTM)
GraftJacket NOW™ formerly GraftJacket Regenerative Tissue Matrix (RTM) (Wright Medical Group N.V., Memphis, TN) is an acellular human dermal collagen template indicated for the repair or replacement of damaged or inadequate integumental tissue. GraftJacket NOW (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 other types of surgery including hand and shoulder surgery (Wright Medical Group N.V., 2020). 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 and Bazarov, 2015; Reyzelman, et al., 2009; Brigido, 2006).

Evidence in the published, peer-reviewed scientific literature supporting the use of Graftjacket for all other indication including breast reconstruction is lacking and its role is unclear. GraftJacket has been proposed for the repair of rotator-cuff reparis, tendon tears, latissimus dorsi tendon transfer, massive irreparable rotator cuff tears, tibialis anterior tendon segment transposition, and lateral meniscal allograft resurfacing. Studies are primarily in the form of case reports and case series with small patient populations and short-term follow-ups (Sharma, et al., 2018; Strauss, et al., 2014). Marks et al. (2017) conducted a randomized controlled trial (n=60) to compare the 12-month postoperative Michigan Hand Outcomes Questionnaire (MHQ) total score between patients with osteoarthritis (OA) at the first carpometacarpal (CMC I) joint who underwent trapeziectomy with suspension-interposition arthroplasty using the flexor carpi radialis (FCR) tendon compared with those receiving Grafix. The authors reported that there was no clinically meaningful differences between the groups.

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), also called Omnigraft Dermal Regeneration Matrix (Omnigraft), 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 (Integra LifeSciences Corp, 2024; FDA, 2002). Subsequently Integra Template was approved for the repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient. In 2016 the Integra Dermal Regeneration Template (IDRT), was FDA PMA approved "for the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient; repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient; and treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care". Because Integra is also offering the IDRT under the product label Integra Omigraft Dermal Regeneration Matrix, Omnigraft was FDA PMA approved "for use in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care" (FDA, 2016). Integra Dermal Regeneration Template (IDRT) is supported by a multicenter (32 sites) randomized controlled trial (Driver, et al., 2015) for the treatment of non-healing diabetic foot ulcers. Significant improvments were reported following applications of IDRT in wound closure, physical functioning, pain and less chance of reoccurence. Most subjects required one application.

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-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree bums, and skin tears) and draining wounds (FDA, 2008).

Case reports, case series, pilot studies and retrospective reviews have reported the application of Integra for the treatment of other conditions including: 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 other 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. Per the manufacturer, 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-Mohs 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).

PriMatrix
PriMatrix (Integra LifeSciences, Princeton, NJ) 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-Mohs surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds-abrasions, lacerations, and skin tears; tunneled/undermined wounds and draining wounds" (FDA, 2008). A randomized control trial, case reports, case series (n=20-55) and retrospective reviews support the safety and efficacy of PriMatrix for the treatment of diabetic foot ulcers and venous stasis ulcers (Lantis, et al., 2021; Kavros, et al., 2014; Hayn, 2013; Lullove, 2012; Strauss, et al., 2012; Karr, 2011).

Lantis et al. (2021) conducted a multicenter randomized control trial to evaluate the safety and efficacy of a fetal bovine acellular dermal matrix (FBADM) (PriMatrix) plus standard of care (SOC) versus SOC alone for treating hard-to-heal diabetic foot ulcers (DFUs). Participants (n=226) were included if they had confirmed diabetes type 1 or type 2 with HgbA1c < 12%, age 18 years or older, foot ulcer duration of at least two weeks, ulcer area between 1-12 cm^2 post-debridement, and adequate vascular perfusion. Exclusion criteria was active infection, including osteomyelitis; exposed capsule, tendon or bone; and reduction of wound ≥30% during the two week run-in period. Eligible patients who consented were treated with SOC for 2 weeks prior to randomization.

SOC consisted of sharp debridement, infection elimination, use of dressings and offloading. The average age was 58.5 (SOC group) and 57.6 years (FBADM group) with 80.6% and 76.9% males. The majority of participants were Caucasian at 71.2% (SOC) and 78.6% (FBADM), with 25% (SOC) and 18.4% (FBADM) being Black/African American. Hispanic/Latino ethnicity was reported in 29.8% (SOC) and 41.7% (FBADM). The primary outcome was complete wound closure at 12 weeks. Secondary outcomes measured were differences in time to wound closure, weekly rate of wound closure over 12 weeks, and the incidence of adverse and serious adverse events. The study was terminated early due to the COVID-19 pandemic with 161 participants completing the study per protocol (FBADM n=79, without n=82). Complete wound closure occurred in 59.5% (47/79) of the FBADM group and 35.4% (29/82) of the SOC group (p=0.002). Of wounds that healed, median time to close was 43 days for FBADM group and 57 days for SOC group. The mean number of FBADM graft applications was 1.4. Adverse events were similar between groups and no product-related serious adverse events occurred. Author noted study limitations include short term follow up, inability to blind investigators or subjects to treatment type, and patient selection bias towards healthier patients.

Suprathel®
Suprathel® (PolyMedics Innovations Inc, Denkendorf, Germany) is a synthetic epithelial substitute made of polylactide, trimethylene carbonate, and s-caprolactone bioresorbable (tri-polymer). Suprathel is FDA 510(k) approved as a "temporary coverage of noninfected skin defects, such as superficial wounds, under sterile conditions". The Dressing is proposed for the management of the following: partial and full thickness wounds, pressure (stage I and IV) wounds, venous ulcers, ulcers caused by mixed vascular etiologies, venous stasis and diabetic ulcers, first- and second-degree bums, partial thickness bums, cuts and abrasions, acute wounds, trauma wounds, surgical wounds, superficial-wounds, grafted wounds and donor sites. Ideally, the graft remains intact until the wound is healed which is proposed to decrease pain associated with multiple dressing changes that may be required with other types of grafts. Sizes range from 5x5 cm to 18x23 cm (Polymedics, 2016; Iqbal, et al., 2017; CMS, 2016; Madry, et al., 2011; FDA, 2009). Suprathel has primarily been investigated for the treatment of superficial and partial-thickness burns. Comparative studies and multiple case series support the use of Suprathel for the treatment of burn wounds (Iqbal, et al., 2017; Highton, et al., 2013; Madry, et al.,2011; Rahmanian-Schwarz, et. al., 2011).

TheraSkin®
TheraSkin (Bioventus, Durham, NC) 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 (Bioventus, 2023). Randomized controlled trials have reported significant improvement following treatment of partial and full-thickness diabetic foot ulcers and venous leg ulcers with TheraSkin (Towler, et al., 2018; 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.

According to the manufacturer, Theraskin is also proposed for the treatment of wounds with exposed muscle, tendon and bone. A retrospective review (Wilson, et al., 2016) evaluated the safety and effectiveness of Theraskin on 15 patients with 15 lower extremity wounds of which eleven wounds had exposed bone, one wound had exposed tendon and three wounds had exposed tendon and bone. Patients had diabetes (73%) with peripheral neuropathy (47%) and osteomyelitis (67%). The graft was applied following standard treatment. Fourteen of the wounds were reported to have healed completely within a mean duration of 19 weeks (range 53–311

days). The mean duration until there was coverage of the bone and/or tendon with granulation tissue was 36.14 days (range 5–117 days). The mean number of grafts applied was two. No serious adverse events were reported. There was one minor amputation. The author's noted that to their knowledge, this was currently the largest study reporting on the utilization of allograft skin as an adjunct therapy for lower extremity wounds with exposed tendon and/or bone. Limitations of the study include the retrospective study design and the small patient population. Prospective studies with large patient populations are needed to support the effectiveness of skin substitutes for the treatment of complex, lower extremeity diabetic wounds.

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 for any indication. 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.

AC5® Advanced Wound System
AC5® Advanced Wound System (Arch Therapeutics, Inc., Framingham, MA) is a topical gel that is made up of synthetic, biocompatible and resorbable peptides. Once reconstituted and applied, the gel self-assembles into a nanofiber network which resembles the construct of the extracellular matrix. AC5 is completely non-animal and non-plant derived, and contains no preservatives (Arch Therapeutics, 2022). It is intended for the management of partial and full-thickness wounds, such as pressure sores, leg ulcers, diabetic ulcers, and surgical wounds. AC5 Topical Gel received FDA 510(k) clearance on December 14, 2018 (K182681) with a subsequent 510(k) issued on March 11, 2020 (K190129) to add an additional manufacturing process and manufacturer (CMS, 2022). AC5 is provided in a vial containing lyophilized peptide, which must be reconstituted using sterile water prior to use. The kit includes: one 3 mL syringe with Luer-Lok tip; one vial of lyophilized peptide; one vial of sterile water for injection; USP two 18-gauge, 1.5 inch needles; one 18-gauge 1.5 inch blunt fill needles; and two alcohol prep pad wipes (CMS, 2022). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of AC5 Advanced Wound System for any indication.

Actigraft®
Actigraft (RedDress®, Ponte Vedra Beach, FL) is a regenerative wound care product that creates in vitro blood clots from a patient's whole blood. It is proposed that applying the blood clot to the site of the wound recreates the natural wound healing environment and promotes the body's own healing process. ActiGraft is topically applied for the management of exuding cutaneous wounds, such as leg ulcers, pressure ulcers, diabetic ulcers, and mechanically or surgically-debrided

wounds (RedDress, 2023). The RD2 system (a peripheral blood processing device for wound management) received 510(k) approval (BK190349) on Nov 8, 2019. The RD2 System is a kit that contains three components for drawing and handling autologous blood and allowing it to clot in a controlled manner in order to form the provisional wound matrix. The system includes: blood withdrawal kit, coagulation initiator component, and a clotting tray containing coagulation accelerator. There is insufficient evidence to support the safety and efficacy of Actigraft for wound management. Studies are in the form of case studies.

Actishield™ and Actishield™CF Amniotic Barrier Membranes
Actishield™ and Actishield™CF Amniotic Barrier Membranes (Wright Medical Group N.V., Memphis, TN) are biologic allografts derived from dehydrated human amniotic tissue. Actishield is a chorion based membrane and Actirshield CF is amnion only. It is proposed for soft and/or hard tissue repair. These products are processed in accordance with FDA requirements for Human Cellular and Tissue based Products (HCT/P) (21 CFR Part 1271), State regulations, and the Standards of the American Association of Tissue Banks (AATB). They are available in two thicknesses in the following sizes: 2cm x 4cm, 4cm x 4cm and 4cm x 8cm (Wright Medical Group N.V., 2020). There is insufficient evidence to support the safety and efficacy Actishield and Actishield CF Amniotic Barrier Membranes for soft and/or hard tissue repair. Studies are in the form of case studies.

ActiveBarrier®/ActiveMatrix®
ActiveBarrier (Skye Biologics, Inc., Redondo Beach, CA) is a dehydrated amniotic membrane proposed as a wound covering for acute, chronic or surgical wounds. The product is available in two thicknesses. ActiveBarrier 45 is a thinner graft from amnion membrane. ActiveBarrier 200 is a thicker, chorion-based product. These two products come in five sizes (2x2cm, 2x4cm, 4x4cm, 4x6cm, 4x8cm). ActiveBarrier 2000 is the thickest form (2000 microns), is suturable and comes in seven sizes. ActiveMatrix is a decellularized allograft derived from human placental connective tissue. It is intended to replace or supplement damaged or inadequate connective tissue. ActiveMatrix is in a flowable form and comes in 0.5 cc, 1.0 cc, 1.5 cc and 2.0 cc size. These products are regulated under the FDA 21 CFR Part 1271, section 361 as HCT/Ps (Human Cells, Tissues, and Cellular or Tissue-Based Products) and an AATB accredited tissue bank. There is a lack of evidence in the published, peer-reviewed literature to support the effectiveness of these products.

Acuseal Cardiovascular Patch
The Acuseal Cardiovascular Patch (Gore Medical, Flagstaff, AZ) is FDA 510(k) (K984526) approved "for use in cardiovascular patching; reduces bleeding through suture holes". The patch is a polytetrafluoroethylene (ePTFE) with an optional additional interpositional layer or layers of a fluoropolymer material. The additional material is proposed to reduce suture hold bleeding (FDA, 1999). The manufacturer proposes that the ePTFE properties are less thrombogenic than bovine collagen coated/sealed Dacron® material and result in a lower rate of restenosis. The Patch is available in three sizes for vascular (1x9 cm, 0.8x7.5 cm, 2.5x15cm) and cardiovascular use (3x6 cm, 5x7.5 cm, 3x3 cam) (Gore, 2002-2024). There is insufficient evidence to support the safety and efficacy of the Patch.

Adherus Dural Sealant®
The Adherus Dural Sealant system (manufactured by HyperBranch Medical Technology, Inc., Durham, NC distributed by Stryker) 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 (Stryker, 2024). There is insufficient evidence to support the safety and efficacy of Aherus dural sealants nor are they FDA approved.

Affinity®
Affinity (Organogenesis, Inc., Birmingham, AL) is an amniotic membrane allograft proposed for wound repair and healing. The device is comprised of the amniotic epithelial layer, amniotic basement membrane, and amniotic stroma. The membrane contains collagen, hyaluronic acid; proteins, growth factors, tissue Inhibitors and multipotential cells. The intended use includes acute and chronic wounds, including neuropathic ulcers, venous stasis ulcers, pressure ulcers, burns, post-traumatic wounds and post-surgical wounds. Affinity is available in 1.5X 1.5cm and 2.5X2.5 cm sizes (Organogenesis, 2021; Centers for Medicare and Medicaid [CMS], 2014). There is insufficient evidence in the peer-reviewed literature to support the safety and effectiveness of Affinity. One study compared the use of Affinity to standard of care in the treatment of 76 patients with diabetic foot ulcers (Serena, et al., 2020).

AlloMend®
AlloMend® Acellular Dermal Matrix (ADM) (Allosource®, Centennial, CO) is decellularized donated human dermal tissue and classified as banked human tissue by the FDA because it is minimally processed and not significantly changed in structure from the natural material. It is proposed to replace or repair integumental soft tissues compromised by disease, injury or surgical procedures (Allosource, 2022). It is available in a variety of square/rectangle sizes and thicknesses. Evidence is lacking in the published peer-reviewed literature to support the clinical effectiveness of AlloMend ADM for any indication.

Allopatch HD™
Allopatch HD (Conmed, Utica, NY) 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 (Conmed, 2023). The graft comes in multiple sizes and thickness. There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of Allopatch HD.

AlloWrap™
AlloWrap DS (double-sided) and Dry (Allosource, Centennial, CO) are wound coverings made of two layers of amniotic membrane processed with a proprietary technology. The implant is derived from scheduled and serological screened cesarean sections and provided by Organ Procurement Organizations. Donated skin is regulated by the American Association of Tissue Banks (AATB) and the FDA guidelines for banked human tissue. The product can be wrapped around tissue or placed as an onlay cover. AlloWrap DS is packaged wet and proposed for surgical application to skin with most wound responding with one application. AlloWrap DS comes in four sizes. AlloWrap Dry is surgically applied, comes in two difference sizes and proposed for a variety of procedures as a wound cover or barrier. AlloWrap DS and AlloWrap Dry are also referred to as AlloWrap Natural Wound Cover (AlloSource, 2022). There is insufficient evidence to support the effectiveness of Alloskin. One study compared the use of Alloskin to petroleum jelly in the treatment of 14 patients with third-degree burns (Moravvej, et al., 2016).

AmnioAMP-MP™
AmnioAMP-MP (CellGenuity, Grapevine, TX) is a decellularized dehydrated human amniotic membrane indicated for the management of partial and full-thickness acute and chronic wounds including burns, diabetic wounds, venous wounds, arterial wounds, pressure wounds and wounds with exposed tendon, muscle, and bone. The AmnioAMP-MP allograft is available in single and dual layers in the following sizes: 2x3 cm, 2x4 cm, 2x6 cm, 3x8 cm, 4x4 cm, 4x6 cm (CMS, 2020).

There is a lack of evidence in the published, peer-reviewed literature to support the effectiveness of this product.

AmnioBand Particulate
AmnioBand Particulate is a lyophilized (freeze-dried) placental matrix in particulate form, aseptically processed to preserve the tissue's natural cytokines and tissue matrix. The Particulate is intended to be used as a wound care scaffold for the replacement of damaged or inadequate integumental tissue, such as diabetic foot ulcers, venous leg ulcers, pressure ulcers, or for other homologous use, particularly irregularly-shaped or crevassing wounds. AmnioBand Particulate is available in a variety of masses, ranging from 40 mg to 160 mg (CMS, 2016). There is insufficient evidence to support the safety and efficacy of the Amnioband products.

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 (Applied Biologics, 2016). Studies are primarily in the form of case reports and case series with small patient populations (n=≤20). 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.

AmnioClear®/AmnioClear LTC
AmnioClear (Liventa Bioscience, formerly AFCell Medical, West Conshohocken, PA) is a placental amnionic membrane consisting of amnion and chorion. The product is proposed for the treatment of difficult to heal wounds or as a protective barrier in surgical procedures. Liventa is partnered with the Musculoskeletal Transplant Foundation (MTF) for allograft procurement and processing. AmnioClear is available in four sizes (2x2 cm, 4x4 cm, 4x6 cm, 1 cm disks). Liventa also offers AmnioClear LCT (loose connective tissue) which is a flowable, injectable amniotic allograft for knee pain and inflammation secondary to osteoarthritis. Its use is intended for supplementing synovial fluid in articulating joints. The product is not FDA approved (CMS, 2015). There is a lack of data in the peer-reviewed literature to support the safety and efficacy of these products.

AmnioCore™
AmnioCore (Stability Biologics®, Nashville, TN; also distributed by Innovasis® Inc., Salt Lake City, UT), is a dual layer amniotic tissue allograft available in multiple formats. The allograft is a non-viable cellular amniotic membrane, particulate or fluid that contains multiple extracellular matrix proteins, growth factors, cytokines and other specialty proteins present in amniotic tissue. AmnioCore is intended for homologous use in the treatment of acute and chronic wounds to reduce scar tissue formation, modulate inflammation, provide a barrier and enhance healing. The Innovasis AmnioCore Product Line is regulated by the FDA under 21 CFR Part 1271 Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps). Innovasis, Inc. is registered with the FDA for tissue storage and distribution. Stability Biologic is registered with the FDA for tissue processing and is accredited by the American Association of Tissue Banks (AATB). AmnioCore membrane sizes include: 16 mm, 2x3 cm, 2x12 cm, 3x4 cm, 3x3 cm, 4x4 cm, 4x6 cm, 4x8 cm,

6x6 cm, 6x9 cm, 6x16 cm, and 9x20 cm. AmnioCore particulate volume sizes include: 20 mg, 40 mg, 100 mg, 160 mg. AmnioCore Flow is available in 0.50 ml, 1.0 ml, 2.0 ml, and 4.0 ml (Stability Biologics, 2024; Centers for Medicare & Medicaid Services (CMS), 2020). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of AmnioCore products for any indication.

AmnioEffect™
AmnioEffect™ (MiMedx, Marietta, GA) is a lyophilized human placental-based allograft membrane that includes amnion, intermediate layer, and chorion. It is proposed to provide a semi-permeable protective barrier that supports the healing cascade and protects the wound bed to aid in the development of granulation tissue (MiMedx. 2023). The product is classified as a human tissue and cell-based product regulated by the American Association of Tissue Banks (AATB) and in compliance with U.S. FDA regulations (21 CFR 1271). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of AmnioEffect for any indication.

Amniocyte™ Flowable Matrix
Amniocyte Amniotic Fluid Allograft Suspension (Stemcellife Corporation, Newport Beach, CA) is an injectable amniotic fluid matrix intended to supplement or replace damaged or inadequate connective tissue. Amniocyte is processed from donated human tissue from full term, c-section deliveries in accordance with the FDA and the American Association of Tissue Banks (AATB) standards and is regulated as a human cell, tissue, or cellular or tissue-based product (HCT/ P) under 21 CFR Part 1271 and Section 361 of the Public Health Service Act. The fluid is proposed to have similar characteristics as the synovial fluid present in the joints and processed to preserve the cytokines, growth factors and proteins in amniotic fluid for homologous use. Proposed treatment indications include: large joints (knee, hip, shoulder & ankle), chronic partial rotator cuff tears, persistent partial tendon tears (tennis elbow), plantar fasciitis/bone spurs, quadriceps and patellar tendon tears, muscular tears, meniscus tears, cartilage tears, intervertebral disc and spinal facet joints, and radicular and sacroiliac nerves. There is insufficient evidence in the published peer-reviewed literature to support the effectiveness of Amniocyte products.

AmnioExCel® and AmnioMTM/AmnioMatrix®
AmnioExCel or BioDExCel™ (Integra LifeSciences Princeton, NJ) is a non-crosslinked, dehydrated, 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 for acute and chronic wounds including diabetic ulcers, venous and arteria ulcers, pressure ulcers, traumatic injuries, burns, surgical wounds), ridge augmentation, soft tissue repair, periodontal defects, boney defects and sinus coverage. AmnioExcel is available in 12mm to 24 mm discs and 2.25-100 total cm squared. AmnioExcel Plus is available in 17 mm disc and 2 cm^2–40 cm^2 sheets. AmnioMTM™ or AmnioMatrix® is the injectable form of the amnion allograft (Integra, 2018). There is insufficient data in the published clinical trials to support the safety and efficacy of AmnioExCel and AmnioMTM.

Snyder et al. (2016) conducted a multicenter, randomized controlled trial to evaluate the safety and efficacy of AmnioExcel plus standard of care (SOC) (DAMA+SOC) (n=15) vs SOC alone (n=14). Patient characteristics included: type 1 or type 2 diabetics; with one or more Wagner grade 1 or superficial 2 foot ulcer, measuring between 1–25 cm^2 in area, presenting for more than one month with no signs of infection/osteomyelitis; ABI > 0.7; HbA1c < 12%; and serum creatinine < 3.0 mg/dL. The primary outcome measure was the proportion of subjects who achieved complete wound closure prior to or on week six after initiation of treatment. Following a two-week screening period, subjects received treatment for six weeks or until complete reepithelialization without drainage or need for dressings (complete wound closure) occurred. SOC

included debridement of necrotic/nonviable tissue and hemostasis, moist wound dressings, offloading where appropriate, infection surveillance, and weekly dressing changes, inspection, and debridement, and in the study group application of DAMA. A nonadhesive dressing and compression bandage were also applied. DAMA application was determined by the investigator based on ulcer appearance and clinical judgment. The study group received a mean 4.3 ± 1.7 pieces of DAMA applied weekly. A total of 33% of DAMA+SOC subjects achieved complete wound closer at or before week six compared to 0% of SOC subjects (p=0.017). DAMA patients achieved significantly faster wound closure compared to SOC alone (p<0.0001). There was no significant difference in adverse events (infection, bleeding, osteomyelitis). The authors noted that although the study suggested that DAMA is safe and effective in the treatment of DFUs, additional research is needed. Limitations include: subjects lost to follow-up (n=4 in each group); small patient population and short-term follow-up.

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. However, the manufacturer must meet specific FDA regulations for the collection, processing, and selling of HCT/Ps. 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, 2023). The Matrix is available in a 16 mm disk sheet, and 2x3 cm, 2x12 cm, 3x3 cm, 4x4 cm, and 4x6 cm sheets. The wrap is available in 2x2 cm, 2x4 cm and 4x6 cm sizes.

AmnioFix injectable which is a powder form is intended for the treatment of tendon and soft tissue injuries, patellar tendon inflammation, tendonitis, tendinosis, plantar fasciitis, tennis elbow, ulcer perimarginal and intramarginal adjuctive use, bursitis, neuritis and capsulitis. AmnioFix Sports Med and AmnioFix Wrap are for nerve and tendon protection (MiMedx, 2016, 2014).

There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of Amniofix products.

Cazzell et al. (2018) conducted a multicenter, randomized controlled trial (n=145) to investigate the safety and effectiveness of a micronized dehydrated human amnion/chorion membrane (dHACM) injection (Amniofix) for the treatment of plantar fasciitis (PF). Inclusion criteria were: age 21 to < 80 years; confirmed diagnosis of PF for 1–18 months; VAS pain sale of ≥ 45 at time of randomization; and had undergone conservative treatment for ≥ 30 days (rest, ice, compression, and elevation [RICE]; stretching exercises; nonsteroidal anti-inflammatory drugs [NSAIDs] and/or orthotics). Patients were excluded if they had trauma or previous surgery to the affected area; bilateral PF; prior use of lower limb injection therapy; diabetes and multiple other comorbidities and contraindications. Patients were randomized to receive one injection of Amniofix (n=73) or sodium chloride placebo (n=72). The primary outcome was the mean change in the visual analog scale (VAS) score between baseline and three months post-injection. Secondary outcome was mean change in Foot Function Index–Revised (FFI-R) score between baseline and three months follow-up. Overall, at the 3-month follow-up, 60 subjects in the treatment group compared to 34 control subjects reported at least a 50% reduction in VAS scores from baseline. VAS scores in the treatment group were 76% lower compared with a 45% reduction in mean VAS scores for controls (p<0.0001). Compared to baseline the FFI-R scores for treatment subjects showed a significant mean reduction (p=0.0004) of 60% compared to a 40% reduction in the control group at the 3-month follow-up. Control group subjects reported a reduction in pain and improved function over time. No serious adverse events were related to the study. Two cases of

post-injection pain at the injection site and one case of post-injection itching were considered normal events. Limitations of the study include the small patient population and short-term follow-up. It is unknown if additional injections would be effective for persistent symptoms. Three Amniofix and two control subjects did not complete the three month follow-up and the last observation data was carried forward to the three-month analysis.

Zelen et al. (2013) conducted a feasibility 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 anti-inflammatory 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 Orthopedic Foot and Ankle Society (AOFAS) Hindfoot scores at one week and at eight weeks follow-up in each group ($p<0.01$, each). The significant difference was greater in the AmnioFix groups vs. control ($p<0.001$). No significant differences in outcomes were noted in those who received 0.5 cc Amniofix vs. 1.25 cc. Overall, at weeks 1–8, AmnioFix subjects demonstrated statistically significantly lower median Wong–Baker FACES pain scores scores compared to the control group ($p<0.001$). No adverse events related to AmnioFix were reported. Limitations of the study include the short-term follow-up and small patient population.

AmnioHeal® Plus
AmnioHeal® Plus (Tides Medical, Lafayette, LA) is a dehydrated amniotic membrane graft proposed to stimulate wound healing and to reduce inflammation and the formation of scar tissue. It is proposed as a covering for chronic wounds (e.g., diabetic, pressure and venous status ulcers; burns) and numerous surgical applications (e.g., podiatric, urological, spinal, plastic/reconstructive, vascular, orthopedic, ophthalmic). AmnioHeal Plus is regulated under the FDA 21 CFR Part 1271, section 361 as HCT/Ps (Human Cells, Tissues, and Cellular or Tissue-Based Products). It is available in eight sizes (Tides Medical, 2022). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of AmnioHeal Plus.

Amnio-Maxx™
Amnio-Maxx™ (Royal Biologics, Hackensack, NJ) is a family of amnion products proposed for numerous indications. Amnio-Maxx is a dual layered, dehydrated, amniotic tissue membrane graft. The allograft is proposed for used as a chronic wound covering or an anatomical (soft tissue) barrier and used for chronic non-healing wounds (e.g., diabetic foot ulcers and venous leg ulcers) (CMS, 2020). The Amnio-Maxx Lite is a single layer version. Amnio-Maxx DL is a dual layer amnion allograft derived from the amnion layer of the placental membrane. Amnio-Maxx UC is a maximum natural thickness allograft derived from the umbilical cord and has the ability to be sutured. Amnio-Maxx is processed in accordance with FDA regulations and AATB standards. Amnio-Maxx DL sizes include: 2x3 cm, 4x4 cm, 4x6 cm, 4x8 cm. Amnio-Maxx UC sizes are 3x6 cm and 3x8 cm (Royal Biologics, 2022). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of Amnio-Maxx for all indications.

AmnioPro Membrane
AmnioPro Membrane (Human Regenerative Technologies [HRT®], LLC, El Segundo, CA) is a human amniotic tissue allograft, consisting of dehydrated and decellularized human amniotic membrane. The Membrane is processed with HRT's proprietary HydraTek® technology. AmnioPro thin membrane is designed as a single layer wound covering for common wounds and AmnioPro thick membrane is designed as a thicker single layer wound covering for deeper wounds where tissue bulk is required. It is intended to be used as a wound covering and is surgically applied to

the skin in the treatment of chronic acute and surgical wounds. HRT® is accredited by the American Association of Tissue Banks® (AATB).Both products are available in the following sizes: 10mm, 12mm, 15mm, 1x1cm, 1.5x2cm, 2x2cm, 2x4cm, 4x4cm, 4x6cm, and 4x8cm. Amniopro flow is the fluid form of the placental matrix (CMS, 2015). Product information on Bioskin, Bioskin Flow, Biorenew, Biorenew Flow, Amniogen-45, Amniogen-200, Amniogen-A and Amniogen-C was not available at the time of the update of this policy. Per CMS (2017) the following products have been discontinued AmnioGen-A, Amnio Gen-C, BioRenew Flow, and AmnioPro Flow.

Amniorepair and AltiPly®
Amniorepair and AltiPly® (Zimmer BioMet Warsaw, IN) are lyophilized placental membrane allografts proposed for use as a biological barrier or wound cover proposed to form a protective cover for acute and chronic wounds. Amniorepair and AltiPly are human cellular and tissue based products per 21 CFR Part 1271 (CMS, 2020). They are supplied in sizes ranging from 2x2 cm to 4x6 cm (Zimmer BioMet, 2024). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of Amniorepair or AltiPly for all indications.

Amnios®/Amnios® RT
Amnios® and Amnios® RT (Sapient Medical, Lewisville, TX) are liquid tissue allografts derived from human amniotic fluid proposed for topical application as a wound covering. These products are processed and prepared by Texas Human Biologics in accordance with FDA requirements for Human Cellular and Tissuebased Products (HCT/P) (21 CFR Part 1271), State regulations, and the Standards of the American Association of Tissue Banks (AATB). The allografts are proposed for use for different types of surgical procedures, independently or in combination with autologous tissue or other forms of allograft tissue. Amnios is a cryopreserved liquid available in 0.5 ml, 1.0 ml, 1.25 ml and 2.0 ml. Amnios RT is an acellular ambient temperature liquid amnion available in 0.5 ml, 1.0 ml, and 2.0 ml (Sapient Medical, 2022). Evidence supporting the safety and clinical effectiveness of Amnios is lacking.

Amniovo™
Amniovo (Reign Medical Irvine, CA) is a composite amniotic tissue membrane processed through the proprietary Purion® Process. It is proposed for use in surgical, soft tissue, tendon, and nerve applications to reduce scar tissue formation, reduce inflammation in the surgical site, enhance healing, and act as a barrier. Amniovo is available in sheet/membrane, particulate, and wrap configurations and in in four different thicknesses: Amniovo Solo, Amniovo Dual, Amniovo Matrix, and Amniovo Max. The sheet/membrane sizes are 2x2 cm, 2x4 cm, 4x4 cm, and 4x6 cm. The particulate is available in 20 mg, 40 mg, 100 mg, and 160 mg preparations (Reign Medical, 2023). There is insufficient evidence in the published peer-review literature to support the safety and clinical effectiveness of Amniovo.

Anu RHEO™
Anu RHEO (Anu Life Sciences, Sunrise, FL), previously Regen Anu Rheo, is an amniotic fluid matrix proposed to supplement or replace damaged or inadequate connective tissue such as synovial fluid in joints and to prevent scarring, adhesion and inflammation The Anu RHEO+ preparation contains Wharton's jelly. Wharton's jelly is a mucous tissue within the umbilical cord that protects and insulates blood cells made from mucopolysaccharides such as hyaluronic acid and chondroitin sulfate. Anu Rhea is minimally manipulated and falls under the FDA 361 status. Rheo Plus™ comes in 1 cc and 2cc vials (HNM Medical, 2017). There is insufficient evidence in the published peer-reviewed literature to support the safety and effectiveness of Anu Rheo.

Artacent™ AC Powder
Artacent AC powder is a dehydrated, micronized particulate processed from human chorioamniotic membrane, submucosa of human placenta. The product contains growth factors proposed to promote wound healing. Once applied, the particulate integrates with the surrounding native

tissues with the purpose of stimulating wound healing. The powder is applied directly onto the wound bed and is supplied in 20 mg, 25 mg, 40 mg, 50 mg, 100 mg, 125 mg, 140 mg and 200 mg vials.

Evidence supporting the safety and efficacy Artacent AC powder is lacking.

Arthrex Amnion™ Matrix and Viscous
Arthrex Amnion Matrix and Viscous (Arthrex, Inc., Naples, FL) are amnion matrices proposed to be rich in growth factors and contain regenerative properties that maintain natural healing properties of amnion. The products are proposed as an anatomical barrier or wrap in the treatment of orthopedic conditions to strengthen repair of the wound and prevent adhesions. The Matrix is available as Amnion Thin in eight sizes (2x2 cm, 2x3 cm, 3x3 cm, 4x4 cm, 4x6 cm, 4x8 cm, 7x7 cm, 2x12 cm) and Amnion Matrix Cord in sizes 2x2cm, 2x3 cm, 3x3 cm, 3x4 cm, 3x6 cm, and 3x8 cm (Arthrex Inc., 2024). The Arthrex Amnion Matrix Flowable in available in 0.5 cc, 1.0 cc, and 2.0 cc vials. Data supporting the safety and efficacy of these products is lacking.

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, Aflex103, Aflex 150, or Aflex200, Aflex201, Aflex301, Aflex400, Aflex 401, Aflex500 (Arthrex, Inc, 2024).

Data in the published peer-reviewed scientific literature supporting the safety and effectiveness of Arthroflex are lacking. Studies are primarily in the form of retrospective reviews, case reports and case series with small patient populations (n=9–30) and one to two years follow-up (Denard, et al., 2018; Pennington, et al., 2018; Hirahara, et al., 2017).

ARTIA™ Reconstructive Tissue Matrix: ARTIA Reconstructive Tissue Matrix, also called ARTIA Tissue Matrix, and ARTIA Tissue Matrix-Perforated (Allergan™, Parsippany, NJ [formerly LifeCell™ Corporation, Branchburg, NJ]) is a surgical mesh derived from porcine skin that is processed and preserved in a patented phosphate buffered aqueous solution containing matrix stabilizers. The Matrix is FDA 510(k) approved "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 which require the use of reinforcing or bridging material to obtain the desired surgical outcome. The implant is intended for reinforcement in plastic and reconstructive surgery" (FDA, 2017). ARTIA was originally developed by LifeCell Corporation and is currently distributed by Allergan. There is insufficient evidence to support the safety and efficacy of ARTIA Reconstructive Tissue Matrix for any indication.

Avance® Nerve Graft
Avance Nerve Graft (AxoGen, Inc., Alachua, FL.) is acellular, processed human peripheral nerve tissue proposed for the surgical repair of severed peripheral nerve discontinuities to support regeneration. The device maintains a 3-dimention scaffold that is proposed to support cell migration and tissue regeneration. Avance is regulated by the FDA Human Cellular and Tissue-based Products and the guidelines of the American Association of Tissue Banks (AATB). The product is available in 16 sizes (Axogen, 2024).

There is insufficient evidence to support the safety and efficacy of the Avance Nerve Graft. Studies are primarily in the form of registry data, case reports, retrospective reviews and case series with small patient populations (Dunn et al., 2021; Leckenby et al., 2020; Safa, et al., 2020).

Herman and Ilyas (2019) conducted a systematic review and meta-analysis to compare safety and effectiveness of direct repair (neurorrhaphy), autograft, allograft, and conduit repair in digital nerve repair. A total of fifteen studies were included: four on neurorrhaphy (three prospective [n=12–81], one retrospective [n=63]); four on allograft repair (three prospective [n=5–72], one retrospective [n=24]); six on autograft repair (five prospective [n=15–31], one retrospective [n=15]) and five on conduit repair (three prospective [n=7–35], two retrospective [n=12–16]). Inclusion criteria were observational cohort studies and randomized control trials on patients undergoing surgery for digital nerve lesions that reported a minimum of two of the following outcome measures: static 2-point discrimination (S2PD), moving 2-point discrimination (M2PD), Semmes-Weinstein monofilament testing (SWMF), and complication rates. Studies were excluded if they included pediatric patients, peripheral nerves other than the hand, or used other surgical repair techniques. The mean length of follow up varied: neurorrhaphy (13.3 months), allograft repair (9.4 months), autograft repair (23.2 months), and conduit repair (21.1 months). Static 2-point discrimination outcomes: neurorrhaphy 15% < 6mm (excellent), 60% 6–15mm (good), 24% > 15mm (poor); allograft 23% < 6mm, 57% 6–15 mm, 20% > 15 mm; autograft 28% < 6mm, 67% 6–15 mm, 5% > 15mm; and conduit 19% < 6mm, 59% 6–15 mm, 22% > 15 mm. The autograft repair was statistically superior to allograft ($p<0.001$), conduit ($p<0.005$), and neurorrhaphy ($p<0.0001$). Moving 2-point discrimination outcomes are as follows: neurorrhaphy 67% < 3mm (excellent), 25% 4–7 mm (good), 8% > 7mm (poor); allograft 2% < 3mm, 88% 4–7 mm, 10% > 7mm; conduit 0% < 3 mm, 67% 4–7 mm, 33% > 7 mm. There was no statistical difference between direct repair and allograft repairs ($p=.60$), however both were statistically superior to conduit repair ($p<0.0001$). SWMF outcomes: neurorrhaphy 17% normal sensation, 41% diminished light touch; allograft 18% normal sensation, 51% diminished light touch; autograft 10% normal sensation, 85% diminished light touch; and conduit 7% normal sensation, 40% diminished light touch. Allograft adverse events included prolonged pain, effusion or wound exudate greater than two weeks. Autograft complications were reported as donor site complications. Conduit repair adverse events included infection and prolonged pain. No adverse events were reported for neurorrhaphy. Limitations of the study include heterogeneity of the studies, inclusion of retrospective study designs, small patient populations and short term follow ups. Well-designed comparative studies with large patient populations and long-term follow-up are needed to determine the safety and efficacy of allografts in digital nerve repair.

Mauch et al. (2019) conducted a systematic review of the literature to compare the safety and efficacy of nerve autografts, processed nerve allografts (PNA) and conduits to primary repair (PR). Four studies were identified using autografts including one comparative study (n=12), two observational studies (n=11, n=15), and one retrospective review (n=14). Four PNS studies included: one observational study (n=14), one pilot study (n=14), one retrospective comparative study (n=24), and one case series (n=5). There were five studies identified on nerve conduit reconstruction including two prospective cohort studies (n=40, n=12), two prospective observational studies (n=9, n=19) and one pilot study (n=14). Seven retrospective reviews (n=15-150) on PR were included. Studies on traumatic digital nerve injuries repaired with PR, nerve autograft, PNA, or nerve conduit were included. Studies were excluded if they were prior to 1990, had follow-ups less than six months, were case reports, or on PNA that were not commercially available. Primary outcomes measured included: static 2-point discrimination (S2PD), the British Medical Research Council Scale (BMRC), or Semmes-Weinstein (SW). Static 2-point discrimination measures the ability to localize two points of pressure on the skin and identify them as discrete sensations. Normal is less than 6 mm, fair 6–10 mm, poor 11–15 mm, protective- one point perceived, anesthetic- no points perceived. The British Medical Research Council Scale is as follows: S0: absence of sensibility in the autonomous area; S1: recovery of deep cutaneous pain sensibility within the autonomous area of the nerve; S2: recovery of some degree of superficial cutaneous pain and tactile sensibility within the autonomous area of the nerve; S3: return of superficial cutaneous pain and tactile sensibility throughout the autonomous area, with disappearance of any previous overresponse; S3+: return of sensibility as in S3; in

addition, there is some recovery of 2-point discrimination within the autonomous area (7–15 mm); S4: complete recovery (2-point discrimination, 2–6 mm). The Semmes Weinstein Monofilaments are a discriminative test used to assess the threshold stimulus necessary for perception of light touch to deep pressure. Follow up ranged from 12–42 months. Results of the S2PD in the autografts studies reported < 15 mm (64–100%) and 0-36% reported > 15 mm. Two studies reported a mean of 5.92 mm and 7.06 mm. All PNA studies reported S2PD < 15 mm. Two studies reported 80% and 83% S2PD < 6 mm. The nerve conduit studies reported 63%–100% of patients with S2PD < 15 mm, the mean ranged from 5.2 mm to 8 mm. A S2PD > 15 mm occurred in 0%–38% of patients. The primary repair group reported 30%–100% S2PD < 15mm with a mean of 8.9 and 10.6 mm. Between 9%–70% reported S2PD > 15 mm. Autograft studies reported 75%–100% regained BMRC S3+ or above. Sensibility of S2 or # occurred in 6%–16%. No return in sensation was reported in 6%–8%. The PNA group reported 84%–100% with S3+ or S4. BMRC S1, S2, or S3 was reported in 16%, S0 0%. In the nerve conduit studies, BMRC of S3+ or S4 was reported in 75%–78%. Complete loss of sensation was reported in 17–22% with 0–8% returning to S2. Primary repair reported 0–2% with no return of sensation, 0–68% between S1–S3, and 30–100% with S3+–S4. The SW results in the autograft group reported 86–100% with normal or diminished light touch and 0–13% with diminished protective sensation. No reports of loss of protective sensation or anesthetic sensation. The PNA group reported 0–78% with normal sensation or light touch, 6–60% diminished protective sensation, and 0–40% with loss of protective sensation. One study reported 17% anesthetic sensation. In the nerve conduit studies, 36–78% reported diminished light touch, 22–54% diminished protective sensation or loss of protective sensation and 0–22% with anesthetic sensation. Only two studies in the PR group reported SW outcomes: 0% and 5% anesthetic sensation, 23% and 37% diminished protective sensation or loss of protective sensation, and 63% and 72% with diminished light touch or normal sensation. Adverse events include infection (two in PNA and one in nerve conduit) and neuromas (four in autograft and two in PR group). The nerve conduit studies reported two amputations, one extrusion, and seven removals. Study limitations include heterogeneity of the studies, inclusion of registry data, retrospective reviews, a case series, small patient populations and short term follow up. Studies with a large patient populations and long-term follow-up are needed to determine the safety and efficacy of allografts in the treatment of digital nerve injuries.

Avive® Soft Tissue Membrane

Avive Soft Tissue Membrane (Axogen, Alachua, FL) is a minimally processed human umbilical cord membrane proposed for use as a homologous, resorbable soft tissue covering to separate tissue layers. It is intended for use during nerve surgeries to separate certain tissues for the purpose of reducing inflammation and scar formation. The membrane is thicker than placental amnionic products due to the thickness of the umbilical cord. It may be sutured or secured or laid across the tissue. Avive Soft Tissue Membrane had been reported to be processed and distributed in accordance with US FDA requirements for Human Cellular and Tissue-based Products (HCT/P) under 21 CFR Part 1271 regulations, US State regulations and the guidelines of the American Association of Tissue Banks (AATB) Axogen suspended the market availability of Avive Soft Tissue Membrane (Avive) effective June 1, 2021 pending ongoing discussions with the FDA regarding the regulatory classification of Avive (Singh, 2021). There is insufficient evidence to support the effectiveness of Avive. Studies have primarily been in the form of case reports.

AxoGuard® Nerve Connector

AxoGuard Nerve Connector is a surgically implanted porcine submucosa extracellular matrix (ECM) proposed for the protection and isolation of injured nerves to prevent soft tissue attachment. It is proposed for reinforcement during nerve reconstruction and as a wrap for a partially severed or compressed nerve. The product is manufactured at Cook Biotech (West Lafayette, IN) and sold by Axogen Inc. (Alachua, FL). AxoGuard is FDA 510(k) approved as Surgisis® Nerve Cuff produced by Cook Biotech, Inc. The FDA intended use is "for the repair of peripheral nerve discontinuities where gap closure can be achieved by flexion of the extremity". The Nerve Connector is proposed

as an alternate to suturing and the Nerve Protector is proposed for wrapping and protecting injured peripheral nerves. Both products come in numerous sizes (Axogen Inc., 2024; Cook Biotech, 2024; FDA, 2003). There is insufficient evidence to support the safety and efficacy of AxoGuard. Studies are primarily in the form of case reports and retrospective reviews with small patient populations (Salomon, et al., 2016; Papatheodorou, et al., 2015).

AxoGuard® Nerve Protector
AxoGuard Nerve Protector (AxoGen, Inc., Alachua, FL) is a porcine submucosa extracellular (ECM) matrix which is surgically implanted to protect injured nerves and to reinforce the nerve reconstruction while preventing soft tissue attachments. Per the manufacturer, the nerve protector separates and protects the nerve from surrounding tissue during the healing process. The patient's cells incorporate into the matrix to remodel and form new tissue. It is proposed for injured nerves up to 40 mm. AxoGuard Nerve Protector was FDA 510(k) approved as a nerve cuff (Cook Biotech, Inc. West Lafayette, IN) "indicated for the repair of peripheral nerve injuries in which there is no gap or where a gap closure is achieved by flexion of the extremity (Axogen, 2024; FDA, 2014). There is insufficient evidence to support the safety and effectiveness of AxoGuard Nerve Protector. Studies are primarily in the form of retrospective reviews, case reports and case series with small patient populations (n=12) investigating the use of Axoguard in lingual nerve surgery and cubital tunnel syndrome (Wilson, et al., 2017; Theberge and Ziccardi, 2016; Papatheodorou, et al., 2015).

Axolotl Products
Axolotl Ambient™ (Axoloti Biologics, Inc., Phoenix, AZ) is a liquid allograft derived from the amniotic components of the placenta. The product is proposed for soft tissue repair and reconstruction. It contains growth factors and cytokines such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), transforming growth factor – beta (TGF-ß), and Interleukin-10 (IL-10). Axolotl Ambient is currently being investigated as a Investigational New Drug product by the FDA (Axoloti Biologics, 2024). Proposed indications by the manufacturer include the treatment of tendinitis, bursitis, plantar fasciitis, ruptured achilles tendon, osteo-chondral defects, labral tears of the shoulder and hip, flexor tendon repair, and osteoarthritis, Axolotl Ambient is also proposed for pain management associated with hip abductor/adductor tears, knee injections, rotator cuff lesions, epicondylitis (tennis elbow), hamstring strains/tears, chronic non-healing wounds, and ankle sprain (CMS, May 2019).

Axolotl Graft™ is a dehydrated human amnion membrane allograft (dhAM) also derived from the amniotic components of the placenta and proposed for soft tissue repair and reconstruction. It is classified as minimally manipulated under FDA regulation 21 CFR Part 1271 and section 361 of the PHS. The Biologix proprietary BioSym™ process is used to manufacture the graft. The product is proposed to create a natural 3-D extracellular matrix scaffold for cellular attachment to promote cell migration and proliferation. Axolotl Graft is available in a 4x4 cm size. The Axolotl DualGraft is a bi-layered form of the product and is available in 1x2 cm, 2x2 cm, 2x4 cm, 4x4 cm, 4x6 cm, and 4x8 cm sizes (Axoloti Biologics, 2024).

There is insufficient evidence in the peer-reviewed literature to support the clinical effectiveness of the Axolotl products.

BellaDerm® Acellular Hydrated Dermis
BellaDerm Acellular Hydrated Dermis (Musculoskeletal Transplant Foundation, Edison, NJ) is a human allograft minimally processed to remove epidermal and dermal cells. The process used to prepare the dermis is intended to preserve the extracellular matrix resulting in an allograft that serves as a framework to support cellular repopulation and vascularization at the surgical site. The production of the Dermis is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. BellaDerm is proposed for the replacement of damaged or

inadequate integumental tissue or for the repair, reinforcement or supplemental support of soft tissue defects. Per the manufacturer, BellaDerm is specifically for cosmetic use and sized for use in lower eyelid retraction repair; rhinoplasty and other cosmetic facial procedures; breast augmentation revision procedures, including correction of symmastia, capsular contracture, bottoming out and malposition; and ultra thick grafts for male urological procedures. BellaDerm is available in sizes ranging from 1x2 cm to 10x20 cm and in thin and thick preparations.

There is insufficient evidence to support the safety and efficacy of BellaDerm Acellular Hydrated Dermis. Studies have primarily been in the form of animal studies, retrospective reviews, and case series with small patient populations and short-term follow-ups for lower eyelid retraction (Scruggs, et al., 2015) and phalloplasty for penis girth augmentation (Solomon, et al., 2013).

BioDfactor™/BioDfence™/BioDfence™ DryFlex/BioDRestore™
Amedico Corporation (Salt Lake City, UT) provides products that are 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, 2x6 cm and 4x4 cm. BioDfence DryFlex comes in sheets 2x3 cm, 2x6 cm, 4x4 cm and 4x8 cm. BioDRestore Elemental Tissue Matrix is an amniotic flowable tissue allograft proposed for soft tissue repair to reduce pain and inflammation. It is proposed for use with soft tissue injuries, tendonitis, plantar fasciitis, inflamed nerves, muscle tears and repetitive motion injuries. This product is offered 0.5 cc, 1.0 cc and 2.0 cc sizes. BioDFence G3 is a multilayer amnion and chorion allograft that is available in multiple sizes (Integra LifeSciences, 2024).

There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of these products.

Biodesign® Dural Graft
Biodesign® Dural Graft (Cook® Biotech, Inc., West Lafayette, IN) is a porcine, small intestinal submucosa (SIS), bioabsorbable, extracellular collagen matrix. It is FDA 510(k) approved for use as a dura substitute for the repair of dura mater (K131015). The FDA approval was based on predicate devices and an animal study. The matrix is available in four sizes (2x3 cm, 4x7 cm, 7x10cm, 7x20 cm) (Cook Biotech, 2024; FDA. 2013). There is insufficient evidence to support the safety and efficacy of Biodesign Dural Graft for a dural repair.

Biodesign® (Surgisis®) Anal Fistula Plug (AFP™)
The Biodesign (Surgisis) Anal Fistula Plug AFP (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., 2024). The Surgisis AFP (i.e., SIS Fistula Plug) received 510(k) approval (K050337) 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 (Schwandner, et al. 2009; Zubaidi and Al-Obeed, 2009; Garg, 2008; Ky, et al., 2008; Schwandner, et al., 2008; Thekkinkattil, et al., 2008). 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%.

Jayne et al. (2021) conducted a multicenter randomized controlled trial comparing safety, efficacy, and cost-effectiveness of the Surgisis anal fistula plug with other surgical treatments (surgeon's preference) for the treatment of transsphincteric anal fistula. Participants (n=304) were randomized to either the fistula plug (n=152) or surgeon's preference (n=152) (advancement flap, cutting seton, fistulotomy, Ligation of the Intersphincteric Fistula Tract procedure). Participant median age was 45.1 years with 55% being males. No difference in co-morbidity between the groups. At the 12 month follow up, there were no significant differences in faecal incontinence quality of life (FIQoL) scores between the two groups and clinical fistula healing was similar between the two groups: 54% fistula plug and 55% surgeon's preference. No significant difference in fecal incontinence rates (p=0.48). Infective complication rate was 50% in fistula plug group versus 38% in the surgeon's preference group at 12 months. Author noted study limitations include the small patient population and short-term follow-up.

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.

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 (Cook Biotech, 2024). 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 Graft (SIS Hernia Repair Device, Surgisis Gold Hernia Repair Graft) (Cook® Biotech, Inc., West Lafayette, IN) is a porcine derived device (Cook Biotech, 2024). 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® Fistula Plug Set, previously 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 (Cook Biotech, 2024). 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 or anorectal fistulas." (FDA, 2006). The predicate device is the original SIS Fistula Plug 510(k) (K050337), cleared for marketing by the Food and Drug Administration on March 9, 2005. 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).

Biodesign® Otologic Repair Graft

Biodesign® Otologic Repair Graft (Cook® Biotech, Inc., West Lafayette, IN) is a porous biomaterial composed of laminated extracellular collagen matrix derived from porcine small intestinal submucosa (SIS) (Cook Biotech, 2024). It is FDA 510(k) approved "for use as an implant material to aid in surgical repairs and as an adjunct to aid in the natural healing process in various otologic procedures, including but not limited to myringoplasty and tympanoplasty." Biodesign is available in 4 mm, 6 mm and 9 mm diameter discs, and 2.5x2.5 cm and 5x5 cm square sheets (Cook Biotech, 2024; FDA 2015). Data supporting the safety and effectiveness of the Biodesign Otologic Repair Graft is lacking. A single retrospective review was identified with a small patient population (n=55) and short-term follow-up (four weeks) (Wang and Isaacson, 2020).

Biodesign® Peyronie's Repair Graft
Biodesign Peyronie's Repair Graft (Cook® Biotech, Inc., West Lafayette, IN) is FDA 510(k) approved for implantation to reinforce soft tissue. Per the manufacturer the Graft is intended for use in urological anatomy including repair of tunica albuginea defects and Peyronie's disease. The Graft is proposed to provide strength and flexibility for reinforcement and correction of penile curvature and once sutured in place the body completely remodels Biodesign into vascularized tissue. Biodesign is derived from a porcine source and is available in 4x10 cm and 7x10 cm sizes (Cook Biotech, 2024; FDA, 2016). Data supporting the safety and effectiveness of the Biodesign Peyronie's Repair Graft is lacking. Studies are primarily in the form of retrospective reviews and case series with small patient populations and short-term follow-ups. There are conflicting outcomes regarding the clinical effectiveness of these grafts in the treatment of Peyronie's disease and tunica albuginea defects (Cosentino, et al., 2016; Knoll, 2007; Santucci and Barber, 2005).

Biodesign Rectopexy Graft
Biodesign Rectopexy Graft (Cook® Biotech, Inc., West Lafayette, IN) is a porcine derived, non-cross linked, dried multi-layered small intestinal submucosa (SIS) sheet. Biodesign Rectopexy Graft is proposed to reinforce soft tissue where weakness exists in the gastroenterological anatomy including transabdominal repair of colon and rectal prolapse (Cook Biotech, 2024). The product received FDA 510(K) approval on May 6, 2016 as Biodesign Sling, Biodesign Plastic Surgery Matrix, Biodesign Anal Fistula Plug (K161221). The three devices were bundled under the same 510(k) submission because the devices share many of the same technological characteristics: composed of porcine small intestinal submucosa (SIS), packaged in a Tyvek/PE pouch, labeled with a shelf-life of 18 months, and sterilized using ethylene oxide. The only differences between the three devices are the indications (and associated labeling) and the dimensional specifications (specific to the indication and anatomic requirement for each device) (CMS, 2016). The Biodesign Sling FDA indication for use: for implantation to reinforce soft tissues where weakness exists in the urological, gynecological and gasteroenterological anatomy including but not limited to the following procedures: transvaginal repair of stress urinary incontinence, such as pubourethral support and bladder support, and transabdominal repair of apical vaginal prolapse, colon and rectal prolapse, and sacrocolposuspension. Per the manufacturer, the rectopexy graft and sling are the same product, just renamed. There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Biodesign Rectopexy Graft. Studies have primarily been in the form of retrospective reviews (Brunner, et al., 2018; Albayati, et al., 2017; Evans, et al., 2015; Ogilvie, et al., 2014).

Biodesign® Sinonasal Repair Graft
Biodesign Sinonasal Repair Graft (Cook® Biotech Inc., West Lafayette, Indiana) is a bioabsorbable, small intestinal submucosa (SIS), extracellular collagen membrane matrix derived from a porcine source (Cook Biotech, 2024). The Graft is FDA 510(k) approved "to separate tissue or structures compromised by surgical trauma, help control minimal bleeding, and act as an adjunct to aid in the natural healing process. The device is indicated for use where an open wound dressing material is required in the nasal and/or sinus cavities following nasal and/or sinus surgery where separation of tissues or structures is desired". Biodesign Sinonasal Repair Graft is available in 1x2

cm, 2x3 cm, 4x7 cm and 7x10 cm sizes (Cook Biotech, 2024). Data supporting the safety and efficacy of Biodesign Sinonasal Repair Graft are lacking. The clinical utility of this Graft has not been established. Studies are primarily in the form of retrospective reviews or small case series (n=10-11) (Membreno et al., 2021; Ambro et al., 2003).

BioFix® Amniotic Membrane Allograft
BioFix Amniotic Membrane Allograft (Integra LifeSciences Corp., Plainsboro, NJ) represents a group of three products: BioFix, BioFix Plus and BioFix Flow. BioFix and BioFix Plus are derived from human placental tissue. The tissue is dehydrated and decellularized using a proprietary HydraTek® Technology. The products are proposed for the treatment of ulcers, burns, chronic wounds, dermal lesions, surgical wounds, voids and tissue defects. BioFix and BioFix Plus are available in four sizes (2x4 cm, 4x4 cm, 4x6 cm, 4x8 cm). BioFix Flow is a placental tissue matrix allograft and is available in 0.5 cc, 1.0 cc and 2.0 cc sizes. It is intended for use as a connective tissue matrix. There is insufficient evidence to support the effectiveness of the BioFix products.

BioNextPATCH
BioNextPATCH (BioNext Solutions LLC, Philadelphia, PA) is a dehydrated amniotic membrane allograft used for the treatment of non-healing wounds and burn injuries. BioNextPATCH amniotic membrane allograft is available in the following sizes: 2x2 cm, 2x4 cm, 4x4 cm, 5x5 cm, 4x6 cm, 4x8 cm (CMS, 2020). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of BioNextPATCH for all indications. Per CMS (2021), "BioNextPATCH is no longer manufactured or used."

CanGaroo® Envelope
CanGaroo® Envelope (Aziyo Biologics, Roswell, GA rebranded to Elutia Inc., Silver Spring, MD) was FDA 510(k) Class II (K140306) approved to be used to securely hold an implantable electronic device to create a stable environment when implanted in the body. The devices that may be used with the Envelope include pacemaker pulse generators, defibrillators, or other cardiac implantable electronic devices. The pouch is made with two sheets of decellularized, non-crosslinked ECM from porcine small intestinal submucosa and was tested in a rabbit (FDA, 2014). It is provided in four different sizes (FDA clears CormatrixCanGaroo ECM Envelope, 2014). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of CanGaroo® Envelope.

CardioCel®
CardioCel (LeMaitre Vasular Inc., Burlington, MA; developed by Admedus Innovative Health Solutions, Minneapolis, MN acquired by Anteris Technology, Eagan, MN) is an acellular, collagen cardiovascular patch prepared from glutaraldehyde-crosslinked bovine pericardium using a patented ADAPT® process. The rights to CardioCel were sold to Genpharm in 2019 while Anteris retained the propriety ADAPT technology. The product is FDA 510(k) approved for "use as a patch in pericardial closure and the repair of cardiac and vascular defects including intracardiac defects; septal defects, valve and annulus repair; great vessel reconstruction, peripheral vascular reconstruction and suture line buttressing" (LeMaitre Vascular, Inc., 2024). It is supplied in three sizes: 4x4 cm, *5*x8 cm and 14x7 cm (FDA, 2014).

To date, studies are primarily in the form of animal studies, case series with small patient populations and retrospective reviews (van Beynum, et al., 2021; Bell, et al., 2019; Neethling, et al., 2013). One case series (n=30) (Neethling, et al., 2013) evaluated pediatric patients who underwent surgery utilizing CardioCel for a wide range of congenital heart deformities. Follow-ups were reported for 12 months with 19 patients followed for 36 months. At 36 months there was no evidence of device calcification, infection, thromboembolic events or device failure on echocardiographic data. According to the authors, it is evident from the literature that the ideal prosthetic material for congenital heart deformity repair has not been established. Additional

studies with larger, heterogeneous patient populations and long-term follow-ups are needed to support the safety and efficacy of CardioCel.

CardioGRAFT MC® Decellularized Pulmonary Patch Graft (previously known as MatrACELL™ Decellularized CardioGRAFT)
The CardioGRAFT-MC® Decellularized Pulmonary Patch Graft (LifeNet Health, Virginia Beach, VA) is composed of human, cryopreserved, decellularized, pulmonary artery tissue. It is FDA 510(k) approved for repair of the right ventricular outflow tract (FDA, 2008). The patch is available as a thin or thick graft, 2.5–5.0 cm in width and 3.0–8.0 cm in length, or as a hemi pulmonary artery in sizes that vary by donor (LifeNet Health, 2024). There is insufficient evidence in the published peer-reviewed literature to support the safety and effectiveness of the MatrACELL Patch. Studies are primarily in the form of retrospective reviews (Hopkins, et al., 2014; Lofland et al., 2012).

carePATCH
carePATCH (Extremity Care LLC, Conshohocken, PA) is a dehydrated amniotic membrane allograft proposed for the treatment of non-healing wounds and burn injuries. The dosage for carePATCH amniotic membrane allograft is per square centimeter and available in absorbable and non-absorbable suture material and/or tissue adhesives. The allograft is supplied in 2x2 cm, 2x4 cm, 4x4 cm, 4x6 cm, 5x5 cm, 4x8 cm sizes (CMS, 2020). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of carePATCH for all indications.

CellerateRX® Surgical Powder
CellerateRX® Surgical Powder (Sanara MedTech, Fort Worth, TX) is a medical hydrolysate of Type I bovine collagen. It is proposed for the management of surgical wounds, traumatic wounds, partial- and full-thickness wounds, and first- and second-degree burns (Sanara MedTech, 2024). It is supplied in 1 gm and 5 gm size. There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of CellerateRX Surgical Powder for any indication.

Clarix® Surgical Matrix
Clarix Surgical Matrix (BioTissue, Inc., Miami, FL) is an amniotic membrane/umbilical cord product 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 (five sizes) and Clarix 100 (three sizes) (BioTissue, Inc., 2024). An additional product is Clarix Cord RT (CMS, 2017). 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.

Clarix™ Flo
Clarix Flo (Amniox Medical, Inc., Marietta, GA) is the particulate form of Clarix. It is also comprised of amniotic member and umbilical cord products. Clarix is proposed as a replacement or supplement for damaged or inadequate integumental tissue. The product comes in 25 mg, 50 mg and 100 mg sizes. The data supporting the clinical utility of Clarix Flo is lacking.

Coll-e-Derm
Coll-e-Derm (Parametrics Medical, Leander, TX) is a human-derived dermal allograft comprised of collagen, elastin and proteoglycans which are proposed to allow cellular regeneration upon implantation. The product is placed over a wound and may be sutured when necessary. Per CMS the use of Coll-e-Derm is restricted to the "replacement of damaged or inadequate homologous tissue" and the repair of soft tissue defects in those with "chronic, non-infected, full-or partial

thickness diabetic or venous insufficiency ulcers". Use is also proposed for second or third degree burns. There are three patches: Coll-e-Derm patch, thin (0.05 – 1 mm thickness); Coll-e-Derm patch, medium (1-2 mm thickness); and Coll-e-Derm patch, thick (≥ 2 mm thickness). All are available in 5x4 cm, 7x5 cm, 10x5 cm, 16x8 cm and 20x8 cm sizes. The Coll-E-Derm patch, thick, SCR (2.75 – 3.25 mm thickness) comes in 5x4 cm and 7x5 cm. Parametrics is accredited by the American Association of Tissue Banks (AATB) and complies with the AATB Standards for Tissue Banking (Parametrics Medical, 2023; CMS, 2018). Data supporting the safety and effectiveness of Coll-e-Derm is lacking.

Cogenex
Cogenex amniotic membrane (Stimlabs LLC., Roswell, GA) is a minimally manipulated amniotic membrane allograft that offers protection from surrounding environment in reparative and reconstructive procedures. These procedures include but are not limited to chronic wound repair, urologic and gynecological surgeries, and burn wound reconstruction. The product is regulated under section 361 of the Public Health Service Act. Cogenex Amniotic Membrane is available wet or dry in various sizes (Stimlabs LLC, 2023; CMS, 2020). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of Cogenex amniotic membrane for all indications.

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. 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). According to the National Institute of Health's U.S. National Library of Medicine Access GUDID, Conexa Reconstructive Tissue Matrix ended commercial distribution on July 31, 2018.

Cocoon Membranes
Cocoon Membranes (Pinnacle Transplant Technologies) is a human-derived amnion allograft that is a minimally manipulated placental membrane used as a wound covering and barrier. It is intended to serve as a covering and barrier for full and partial-thickness, chronic, and acute wounds. The product is classified as a human tissue and cell-based product regulated by the American Association of Tissue Banks (AATB) and in compliance with U.S. FDA regulations (21 CFR 1271). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of Cocoon Membranes for all indications.

Complete FT/ Complete SL
Complete™ SL is a single layer amnion derived allograft and Complete™ FT is a full thickness amnion-chorion derived allograft. Each product is intended to serve as a barrier and provide protective coverage from the surrounding environment to acute and chronic wounds. Complete™ SL and Complete™ FT are applied directly to the wound, adheres to the wound bed without fixation, is fully resorbable and does not have to be removed from the wound bed. The products are classified as a human tissue and cell-based product regulated by the American Association of

Tissue Banks (AATB) and in compliance with U.S. FDA regulations (21 CFR 1271). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of Complete SL and Complete FT for all indications.

Coretext™ and Protext™
Coretext™ and Protext™ (Regenative Labs, Gulf Breeze, FL) are both Wharton's jelly products or human umbilical cord product. The products are proposed to reduce scarring, fibrosis and adhesions in surgical and wound sites, specifically for muscle and cartilage tears and to aid in the repair of damaged tissue. The products are applied directly to the defect using a syringe. The cell sorter used in the preparation of Protext is 300 um mesh and 200 um for CoreText. CoreText and ProText are regulated by the FDA as a human tissue product subject to Section 361 of the Public Service Act and 21 CFR 1271 (Regenative Labs, 2024). Coretext is available as Coretext 1000 or Coretext 2000 (CMS, 2020). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of Coretext or Protext for all indications.

CorMatrix®
CorMatrix ECM® products (CorMatrix, Inc. Roswell, Georgia) are porcine, small intestinal submucosa (SIS) extracellular matrix (ECM). 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). According to the manufacturer, Proxicor (Aziyo Biologics, Silver Springs, MD) is the same product as CorMatrix Patch for Cardiac Tissue Repair.

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. Outcomes have been conflicting regarding the clinical effectivenss and complications following implantation of Cormatrix.

Mosala et al. (2016) conducted a systematic review to evaluate CorMatrix for cardiovascular surgeries. A total of 47 articles were included. Twenty studies were animal studies. Two human studies investigated CorMatrix for pericardial reconstruction and vascular repair at different sites. Eleven studies used CorMatrix at intracardiac sites for various indications. Several case reports for various conditions were also included. CorMatrix has been used in congenital cardiac and vascular surgery, pericardial reconstruction, valve reconstruction in adults and children, endocarditis, acquired vascular defects at different sites and for repair of damaged myocardium after infarction. Overall, patient populations have been small (n=2–57) with short-term follow-ups. There are few reports of complications when used in the low pressure conditions, usually extracardiac environment (i.e. veins). However when used at higher pressure intracardiac sites such as the aortic valve or in semilunar valves, more complications have been reported. Data also suggested that CorMatrix may cause significant inflammatory reactions. Due to the heterogeneity of the studies, retrospective study designs and lack of a comparator the safety and effectiveness of CorMatrix has not been established.

Creos™ Xenoprotect
Creos Xenoprotect (Nobel Biocare®, Zurich, Switzerland) is a resorbable, non-chemically cross-linked porcine collagen. It is proposed for guided bone regeneration (GBR) and guided tissue

regeneration (GTR) dental procedures. The membrane was FDA 510(k) approved in 2013 as Matricel Dental Barrier Membrane (Matricl GmbH, Germany) for "use during the process of guided bone regeneration and guided tissue regeneration" for multiple condtions. Creos is proposed to add stability and protection to grafted dental sites. Creos comes in three sizes: 5x20 mm, 25x30 mm and 30x40 mm (Nobel Biocare, 2024). There is insufficient evidence to support the safety and effectiveness of Creos. The limited number of studies have investigated Creo for immobilizing bone augmentation material during horizontal guided bone regeneration (GBR) procedures and guided bone regeneration at dehisced implant sites involving small patient populations and short-term follow-ups. Studies comparing collagen membrane to no membrane are lacking (Wessing, et al., 2017; Wessing, et al., 2016).

CryoMatrix®
CryoMatrix (Skye® Biologics, Inc., Redondo Beach, CA) is a cryopreserved, placental connective tissue matrix, proposed for surgical use to supplement or replace damaged or inadequate connective tissue. The tissues are collected, processed, stored and distributed in compliance with FDA regulations governing Human Cells, Tissues, and Cellular or Tissue-Based Products. The matrix is a flowable graft supplied in 0.5 cc, 1.0 cc, 1.5 cc and 2.0 cc vials. There is insufficient evidence in the published peer-reviewed literature to support the safety and effectiveness of CryoMatrix.

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. 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.

Cygnus®
Cygnus products (Vivex® Biologics, Miami, FL) are amniotic tissue matrixes obtained from umbilical cord and are proposed to support healing without adhesion or scar formation. The products are proposed for use as an adhesion barrier, wrap, patch, protection bandage, nerve wrap, and reconstruction patch for various applications (e.g. neurosurgery, burn care, urology, dermatology). Cygnus products include Cygnus Solo™, Cygnus Max™, and Cygnus Max XL. Cygnus Solo is a single layer amnion that is proposed for use as a soft tissue barrier and wound covering. Cygnus Max is the maximum thickness graft (eight times thicker than traditional amnion) with a high concentration of growth factors. The Max can be sutured. Cygnus Max XL is fenestrated. The products are processed in accordance with the FDA regulations for tissues and biologics and the American Association of Tissue Banks (AATB) standards and come in multiple sizes from 2x2 cm to 7x7 cm and three thicknesses (Vivex Biologics, 2024; CMS, 2023). Evidence in published peer-review literature supporting the safety and efficacy of Cygnus products is lacking.

Cytal®
Cytal Wound Matrix (Integra, Columbia, MD) is a porcine extracellular matrix (urinary bladder matrix) proposed for wound care. 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-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds". Cytal is available as 1-layer, 2-layer (meshed), 3-layer and 6-layer sheets in a 10x15 cm size. Cytal Wound Matrix 1-Layer and

2-Layer are also marketed as MatriStem® Wound Matrix and Multilayer Wound Matrix. There is also a product labeled Cytal Burn Matrix available in 5x5 cm, 7x10 cm, and 10x15 cm sizes (Integra, 2024; CMS, 2016; FDA, 2015). There is insufficient evidence to support the safety and efficacy of Cytal for all indications.

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. Per the manufacturer, as of June 2014, DermaMatrix is no longer available for distribution.

DermaPure™
DermaPure (Tissue Regenix Group [TRG], San Antonio, TX) is a decellularized, human dermis allograft donated from human tissue intended for transplant. The dermis is produced using dCELL® proprietary technology, removes all cells and DNA and acts as a scaffold for cell growth. The implant becomes integrated into the host tissue. DermaPure is proposed as a covering for difficult or hard to heal, acute and chronic wounds. Donated tissue is processed in accordance to the standards of the American Association of Tissue Banks. DermaPure comes in three sizes (2x3 cm, 3x4 cm, 4x6 cm) (TRG, 2024). There is insufficient evidence to support the clinical utility of DermaPure for the treatment of wounds. Published studies are primarily in the form of a pilot study with a small patient population (n=20) who had 70% venous ulcers (Greaves, et al., 2013).

DermaSpan™
DermaSpan (Zimmer Biomet, 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 (Zimmer BioMet, 2024). There is insufficient evidence to support the safety and efficacy of DermaSpan.

Dual Layer Impax Membrane
Dual Layer Impax Membrane (Legacy Medical Consultants, Fort Worth, TX) is a sterile dehydrated dual layered human amniotic membrane allograft. It is intended to serve as a barrier or cover for acute and chronic wounds and for use as a barrier to protect wounds from the surrounding environment. The product is classified as a human tissue and cell-based product regulated by the American Association of Tissue Banks (AATB) and in compliance with U.S. FDA regulations (21 CFR 1271). There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of Dual Layer Impax™ Membrane for any indication.

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" (Integra LifeSciences, 2024; 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 (Baxter, Deerfield, IL) is prepared from a bovine pericardium cross-linked with glutaraldehyde. It is a membranous 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 (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™ (Stryker, Portage, MI) 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 (Integra Lifesciences, Princeton, NJ) 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 fascia; vascularized 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® Exact Spine Sealant System
DuraSeal™ Spine Sealant System (Integra Lifesciences, Princeton, NJ) 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.

DuraSorb® Monofilament Mesh/ Polydioxanone Surgical Scaffold™
DuraSorb® Monofilament Mesh/ Polydioxanone Surgical Scaffold™ (Surgical Innovation Associates, Inc [SIA]; Philadelphia, PA) is a resorbable, colorless, monofilament knit surgical mesh made entirely of uncolored and undyed polydioxanone (PDO) thread. Polydioxanone Surgical Scaffold is proposed for use in reinforcement of soft tissue where weakness exists. On August 1, 2018, 510(k) approval (K181094) was given to Polydioxanone Surgical Scaffold™. It is manufactured in two rectangular shapes: 6x16 cm and 10x25 cm. According to the manufacturer's Instructions for Use, DuraSorb has not been studied for use in the repair of direct inguinal hernias, intraperitoneal use, contaminated and/or infected wounds or in breast reconstructive surgeries (Surgical Innovation Associates, 2024). Evidence is lacking in the published peer-reviewed literature to support the clinical effectiveness of DuraSorb Monofilament Mesh/Polydioxanone Surgical Scaffold for any indication.

Durepair® Regeneration Matrix
Durepair Regeneration Matrix (Medtronic, 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 (Aroa Biosurgery Limited, San Diego, CA) 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-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree bums; and skin tears) and draining wounds" (FDA, 2010). Endoform is prepared from propira submucosa of ovine forestomach tissue. The dressing contains 90% natural collagen and 10% extracellular matrix. The template is a temporary matrix that is completely replaced by the patient's own tissue over time and is porposed to be effective for up to seven days. There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Endoform. Studies are primarily in the form of retrospective reviews with small patient populations and heterogeneitity of wound types (e.g., diabetic foot ulcers, venous leg ulces, heel pressure ulcers) (Ferreras, et al., 2017; Lullove, 2017; Bohn and Gass, 2014).

EpiBurn®
EpiBurn (MiMedx, Marietta, GA) is a bioactive, dehydrated human amnion/chorion membrane (dHACM) proposed for the treatment of wounds to promote healing, act as a barrier membrane, reduce scar tissue and prevent inflammation. The Membrane has multiple layers including a layer of epithelial cells, a basement membrane, and an avascular connective tissue. EpiBurn is proposed for the treatment of partial and full-thickness burns, surgical debridement and donor sites. EpiBurn is processed from human tissue according to the Food and Drug Administration (FDA) regulations and the American Association of Tissue Banks (AATB) standards, and is regulated as a human cell, tissue, or cellular or tissue-based product (HCT/P) under Section 361 of the Public Health Service Act. The Membrane is available in 6x6 cm, 9x7 cm and 7x15 cm sizes (LifeHealthcare, 2024). Evidence supporting the use of EpiBurn for any indication is lacking.

EpiCord™
EpiCord (MiMedx Group, Kennesaw, GA) is a minimally manipulated, dehydrated, human umbilical cord allograft for homologous use. It is comprised of the protective elements of the umbilical cord with a thin amnion layer and a thicker Wharton Jelly mucopolysaccharide component. It is proposed for the treatment and management of chronic and acute wounds, burns and as a natural biological barrier to protect tendons. EpiCord™ is processed from human tissue according to the American Association of Tissue Banks (AATB) standards, and is regulated as a human cell, tissue, or cellular or tissue-based product (HCT/P) under Section 361 of the Public Health Service Act. It is available in various sizes (Mimedex, 2023; CMS, 2016). Evidence supporting the safety and effectiveness for Epicord for all indications is lacking.

Tettelbach et al. (2018) conducted a multicenter, randomized controlled trial to investigate the safety and efficacy of EpiCord (n=101) compared to an alginate wound dressing (control group) (n=54) for the treatment of diabetic foot ulcers (DFU). Inclusion criteria were a confirmed diagnosis of Type 1 or Type 2 diabetes and a 1–15 cm^2 ulcer located below the ankle for at least 30 days that had undergone debridement. The control group had an alginate dressing applied (excluding silver and collagen), covered by a non-adherent silicone dressing and an absorbent hydropolymer secondary dressing. The 18-week study period included a two-week run-in phase in which the DFU was treated with moist dressings and offloading. If the DFU did not reduce by at least 30% from baseline, subjects were randomized 2:1 into the EpiCord or control group, respectively. The run-in period was followed by a 12-week treatment phase and final follow-up at week 16. EpiCord was applied weekly following debridement. The primary outcome measure was the percentage of subjects in the intention to treat (ITT) population with complete wound closure

of the study ulcer within 12 weeks of treatment. Secondary outcomes included 12-week healing rates in subjects who completed the study per protocol and wounds that were determined to have received consistent, adequate debridement. Complete healing was defined as 100% epithelialization of the wound. Data were analyzed in an intent-to-treat (ITT) population. Analysis was also conducted on subjects (n=134) who completed the study per protocol (PP) (EpiCord, n=86; alginate, n=48) and subjects who received adequate debridement (EpiCord, n=67, alginate, n=40). 12-week outcomes included the following:

- ITT analysis showed that significantly more DFUs treated with EpiCord (71/101; 70%) healed compared to subjects treated with alginate dressings (26/54; 48%) (p=0.0089).
- Healing rates at 12 weeks for subjects treated PP showed significantly better healing rates with EpiCord (70/86; 81%) than alginate-treated subjects (26/48; 54%) (p=0.0013).
- Significantly more EpiCord-treated subjects who received adequate debridement (64/67; 96%) completely healed compared to the control group (26/40; 65%) (p<0.001).
- In the ITT population, DFUs that received adequate debridement healed completely with EpiCord (64/67; 96%) compared with the control group (26/40; 65%) (p<0.0001).

At the 16-week follow-up significantly more ulcers treated with EpiCord were healed compared with control group in the ITT population (p=0.0199). For subjects completing the study per protocol more EpiCord-treated ulcers (73/86; 85%) were healed compared to the control group (29/48; 60%). The median number of EpiCord allografts applied per healed wound was seven (range 2-12). There were no reported adverse events related to EpiCord or alginate dressings. Limitations of the study include the small patient population, short-term follow-up and 2:1 randomization. The authors noted that this is the first randomized controlled trial to examine the safety and efficacy of an allograft derived from umbilical cord as a treatment for chronic DFUs. Additional studies are indicated to support the clinical effectivenss of EpiCord.

Esano™ A, Esano™ AAA, Esano™ AC, Esano™ ACA
Esano™ (Evolution Biologyx™, LLC., Center Valley, PA) family of products are comprised of decellularized, dehydrated human amniotic membrane allografts (Evolution Biologyx, 2024). Esano A is a single layer sheet, Esano AAA is a tr-layer with a preserved natural epithelial basement membrane and an intact extracellular matrix structure, Esano AC is a dual-layer, and Esano ACA is a triple layer amnion/chorion/amnion allograft. The products are proposed for use as a cover or barrier for acute and chronic wounds and to provide protective coverage from the surrounding environment for acute and chronic wounds. Esano products are applied directly to the wound, adheres without fixation, and are available in various sizes. The products meet the criteria for FDA regulation solely under section 361 of the Public Health Service (PHS) Act and the regulations in 21 CFR part 1271 (CMS, 2023). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of these products.

FloGraft™
See the AmnioCare®, AmnioMatrix®, and FloGraft™ information above.

Fortaderm™/Puraply™: See Puraply

Fortiva® Porcine Dermis
Fortiva porcine dermis (also known as Tutoplast porcine dermis) (RTI Surgical, Inc., Alachua, FL) is a non-crosslinked acellular porcine dermal matrix. Fortiva is intended for use as a soft tissue patch to reinforce soft tissue where weakness exists and for the surgical repair of damaged or ruptured soft tissue membranes. The implant is indicated for use in repairing hernias and/or body wall defects that require the use of reinforcing or bridging material to obtain the desired surgical outcome. Fortiva porcine dermis (also known as Tutoplast porcine dermis) received FDA 510(k) clearance (K142070) Oct 27, 2014 (FDA, 2014). The product is available in a range of sizes up to 35cm x 35cm (RTI Surgical, Inc., 2024). There is insufficient evidence to support the safety and efficacy of Fortiva porcine dermis for soft tissue reinforcement.

GalaFlex® Scaffold/GalaFLEX Mesh: GalaFlex (Tepha, Inc., Lexington, MA) is a sterile, knitted, resorbable mesh, constructed of non-dyed monofilament fibers made from poly-4-hydroxylbutyrate (P4HB). P4HB, a proprietary product, is produced from a naturally occurring monomer (small molecule that reacts with a similar molecule to form a larger molecule) and is processed into monofilament fibers and knitted into a surgical fold. It is provided in single sheets of varying widths, lengths and shapes, and may also be cut to the shape or size desired for a specific application (Galatea Surgical, 2024). According to the FDA 510(k) approval, GalaFLEX Mesh is indicated for use as a transitory scaffold for soft tissue support and to repair, elevate and reinforce deficiencies where weakness or voids exist that require the addition of material to obtain the desired surgical outcome including reinforcement of soft tissue in plastic and reconstructive surgery, and general soft tissue reconstruction (Williams, et al., 2016; FDA, 2014). There is insufficient evidence to support the safety and efficacy of GalaFLEX for any indication. The published literature is primarily in the form of retrospective reviews and case series with small patient populations (n=11-62) and short-term follow-ups (12 months). Studies have investigated GalaFLEX for high-risk ventral and incisional hernia repair, mastopexy and reduction mammoplasty (Adams, et al., 2018; Nair et al., 2018; Adams, et al., 2016).

GalaFLEX 3DR Scaffold, GalaFLEX 3D Scaffold: GalaFORM 3D Scaffold (Tepha, Inc., Lexington, MA) is a bioresorbable surgical mesh made from the biologically derived poly-4-hydroxybutyrate (P4HB) used in plastic and reconstructive surgery. After implantation, the scaffold slowly bioresorbs while tissue grows into the scaffold. According to the FDA 510(k) approval, GalaFORM 3D scaffold is indicated for use "as a bioresorbable scaffold for soft tissue support and to repair, elevate and reinforce deficiencies where weakness or voids exist that require the addition of material to obtain the desired surgical outcome. This includes reinforcement of soft tissue in plastic and reconstructive surgery, and general soft tissue reconstruction. GalaFORM 3D scaffold is also indicated for the repair of fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result". GalaSHAPE 3D is approved for the same indications and now known as GalaFLEX 3D (Galatea Surgical, 2024; FDA, 2017; FDA, 2016; FDA 2014). The Galatea products are available in various sizes in oval, rectangular, triangular, circular shapes and can be custom made. There is insufficient evidence to support the safety and efficacy of Galatea products.

Gentrix®

Gentrix Surgical Matrix products (Integra LifeSciences, Princeton, NJ Acell, Inc., Columbia, MD) are engineered using Integra's proprietary MatriStem UBM (Urinary Bladder Matrix) technology (Integra LifeSciences, 2024). Gentrix was previously marketed as Matristem. In 2017 Acell announced that all products previously marketed under Matristem were being rebranded to Gentrix Surgical Matrix to differentiate Acell's surgical products from their wound management products. In 2021, ACell was acquired by Integra LifeSciences. Gentrix Surgical Matrix 2-layer, 3-layer, 6-layer, and 8-layer are FDA 510(k) approved for "implantation to reinforce soft tissue where weakness exists in patients requiring gastroenterological or plastic & reconstructive surgery. Reinforcement of soft tissue within gastroenterological and plastic & reconstructive surgery includes, but is not limited to, the following procedures: hernia and body wall repair, colon and rectal prolapse repair, tissue repair, and esophageal repair". The Gentrix™ Surgical Matrix Thick and Gentrix Surgical™ Matrix Extend are also FDA 510(k) approved for the same indications. Per the manufacturer's website the surgical products include Gentrix Surgical Matrix Thin, Gentrix Surgical Matrix, Gentrix Surgical Matrix Plus, Gentrix® Surgical Matrix Thick (Integra LifeSciences, 2024). There is insufficient evidence to support Gentrix for any indication. Studies are primarily in the form of retrospective reviews.

GORE® BIO-A® Fistula Plug

The GORE BIO-A Fistula Plug (Gore Medical, Flagstaff, AZ) 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. It is a surgical mesh supplied in a preformed three-dimensional shape (disk with attached tubes) and comprised of a porous structure of synthetic bioabsorbable PGAP:TMC copolymier fiber, degraded via a combination of hydrolytic and enzymatic pathways. 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. Studies are primarily in the form of case reports, retrospective reviews and case series with small patient populations and short-term follow-up. According to the manufacturer's website, the product has been discontinued (Gore Medical Products, 2024).

Narang et al. (2016) conducted a systematic review of the literature to evaluate the safety and efficacy of GoreBio-A synthetic plug for the treatment of anal fistula. Six studies (n=221) met inclusion criteria and were included in the analysis, data extraction (n=187) and data synthesis. Studies of adult patients undergoing treatment for simple or complex fistulas with the Gore fistula plug regardless of etiology or pathological anatomy were included. Most fistulas were cryptoglandular and others were due to surgical trauma, Crohn's disease or HIV infection. Three studies were prospective in design and three were retrospective. No randomized controlled trials were found. Subject ages ranged from 19–82 years. Follow-ups ranged from 2–19 months. Thirteen patients (5.9%) were lost to follow-up and 21 (9.5%) underwent alternative treatment. Fistula healing rates ranged from 15.8%–72.7%. Early or delayed plug extrusion occurred in 16/187 patients (8.5%). Limitations of the studies included: small patient population, lack of randomized or comparative study design, and heterogeneity of etiologies and follow-up protocols. Due to the low quality of evidence, conclusions regarding the effectiveness of the Gore Bio-A fistula plug and improved clinical outcomes could not be made.

GORE® BIO-A® Tissue Reinforcement
GORE BIO-A Tissue Reinforcement (Gore Medical, Flagstaff, AZ) is a synthetic bioabsorbable copolymer fiber (polyglycolic acid:trimethylene carbonate [PGA:TMC]), gradually absorbed by the body and proposed for soft tissue reinforcement. The product is FDA 510(k), Class II, approved for use in the reinforcement of soft tissue including hernia repair, muscle flap reinforcement, perforated tissue repair and general tissue reconstruction. Six sizes are available (7x10 cm, 8x8 cm, 9x15 cm, 10x30 cm, 20x20 cm, 20x30 cm) (Gore Medical, 2024; FDA, 2012). The safety and efficacy of this product has not been established. Studies are primarily in the form of retrospective reviews, case reports and case series with small patient populations and short-term follow-up (Smith and Slater, 2021).

Rosen et al. (2017) conducted a multicenter prospective observational study (n=104) to evaluate the use and performance of Gore Bio-A Tissue Reinforcement. Adult patients with incisional hernias of ≥ 9 cm^2, undergoing a planned single-staged repair of a ventral/incisional hernia with an operation classified by Centers for Disease Control (CDC) wound criteria as a clean-contaminated or contaminated wound were eligible for study enrollment. The CDC wound classification showed 77% of wounds were contaminated and 23% were clean-contaminated. Patients were enrolled if a single unit of the Mesh could adequately reinforce the midline fascial closure with at least four centimeters of lateral overlap. The biosynthetic mesh was placed as a sublay in either the intraperitoneal or retrorectus position, based on the discretion of the surgeon, to reinforce midline fascial closure. The primary outcome measure was the rate of hernia recurrence based on physical examination at the two-year follow-up. Hernia recurrence was defined as a new hernia within seven centimeters of the repair, and categorized as midline, at the stoma site, or both. Secondary outcomes included incidence of wound events and quality-of-life assessments. Recurrent herniation occurred in 16 patients (17%) at the 2-year follow-up. The recurrence rate was significantly higher in patients with mesh placement in the intraperitoneal

position (40%; 4/10) versus placement in the retrorectus position (13%; 12/94) (p=0.0451). Time to recurrence was shorter in patients with postoperative infection (p=0.0098) than those without and those with parastomal compared with midline hernia recurrences (p<0.0001). Overall patients reported significant sustained improvement in physical health of the two-year follow-up period (p<0.05). There were nine superficial surgical site infections that resolved with oral or intravenous antibiotics. Of the ten deep surgical site infections, six required percutaneous drainage alone, three underwent minor operative debridement and one underwent wide wound debridement with partial mesh excision. Additional wound events included development of a postoperative seroma (n=6). Three required percutaneous drainage and eventually resolved. Two postoperative bowel obstructions occurred in patients with mesh placed in the retrorectus position. Author-noted limitations of the study included: the selected study format of a longitudinal observational study potentially limited the ability to apply the results; lack of a control group and randomization; short-term follow-up; diversity of hernia sizes; heterogeneity of the patient population and surgical procedures performed; inherent limitations of outcomes researched (e.g., quality-of-life indices) in patients with complex ventral hernia repair; lack of post-operative computerized tomogram; and lack of generalizability. Additional studies are needed to establish the clinical effectiveness and safety of Gore Bio-A Tissue Reinforcement.

GraftJacket® Xpress
GraftJacket Xpress (Wright Medical Group N.V., Memphis, 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).

Helicoll™
HeliColl (EnColl Corporation, Fremont, CA) is a semi-occlusive, self-adhering, acellular, Type- 1 collagen graft proposed for wound care. It is derived from a bovine or ovine source. The product is FDA 510(k) approved for topical wound management including: partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence). It was approved as a predicate device to existing similar products. According to Encoll healing occurs within 1–4 applications. HeliColl comes in 18 sizes ranging from 2x2 cm to 16x16 cm (Wound Source, 2023; Dhanraj, 2015; FDA, 2004). Data supporting the safety and efficacy of HeliColl is lacking.

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 a granulated, acellular bovine tendon collagen and glycosaminoglycan device that is 510(k) FDA (K072113)

approved for the treatment of advanced wound care. The granulates are reconstituted with saline to form a gel-like substance. The Matrix 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-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds" (Integra LifeSciences, 2024; 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.

Campitiello et al. (2017) conducted a randomized, placebo-controlled trial to evaluate the efficacy of Integra Flowable Wound Matrix (n=23) compared with a wet dressing (n=23) for the treatment of diabetic foot ulcers (DFUs) with irregular geometries (tunneling or cavity lesions). Inclusion criteria were diabetic patients, age > 18 years, who had Grade 3 Wagner classification DFUs with an ankle-brachial index (ABI) of ≥ 0.5. Antibiotic therapy was started 7–10 days prior to surgery and continued until the wound had healed. The primary objective of the study was to determine the percentage of patients with wound closure (100% re-epithelialization). Secondary outcome measures included the time to healing and safety (number of major amputations and hospitalizations). Wounds were cleaned and necrotic tissue was removed until normal healthy tissues appeared. After mixing the dry granular collagen with saline solution, the matrix was applied to the lesion, until completely filled. The edge of the wound was sutured. Wounds in the control group were covered with a sterile saline-moistened gauze before the dressing was applied. Compression dressings and offloading devices were used by both groups. Patients were followed until complete wound healing had occurred or for up to six weeks. Healing was determined by clinical examination and complete healing was defined as 100% re-epithelialization in the absence of discharge. At six weeks, complete healing had occurred in significantly more Integra patients (n=20; 86.95%) than control group patients (n=12; 52.17%) (p=0.001). Healing time was significantly shorter in the study group, where the surgical breach was closed by primary intention compared to the control group, where the surgical breach healed by secondary intention. The biomaterial allowed closure of wound by primary intention, reducing the healing time. Minor amputations were performed in nine study group subjects and eight control group subjects. Major amputations (p=0.0019) and re-hospitalization rates (p=0.028) were significantly less in the Integra group. Limitations of the study include the small patient population and short-term follow-up. The authors concluded that additional studies are needed with large patient populations and long-term follow-up to validate these findings.

Integra® Reinforcement Matrix
Integra Reinforcement Matrix (Integra LifeSciences Corp., Plainsboro, NJ) is an acellular porcine dermal matrix proposed for use in the reconstruction of soft tissue deficiencies. Per Lifesciences, the matrix is "intended for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue, including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Integra Reinforcement Matrix is not intended to replace normal body structure or provide the full mechanical strength. 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 Integra Reinforcement Matrix is available in 4x7 cm and 5x10 cm. There is insufficient evidence in the published peer-reviewed literature to support the safety and effectiveness of this matrix.

InteguPly (TranZgraft)
Integuply, previously known as TranZgraft, (AZIYO® Biologics, Silver Springs, MD) is a dual-sided, human acellular collagen matrix proposed for the treatment of sports related injuries, including tendons and ligaments. The epidermis and all viable cellular components are removed from the

collagen matrix during processing. The dermal side is proposed to host tissue vascularization and cellular incorporation. The tissue preparation is compliant with the FDA, AATB and state regulatory requirements (OsseoDent, 2024). There is insufficient evidence published in the peer-reviewed literature to support the safety and effectiveness of TranZgraft.

Kerecis® Omega3 MariGen™
Kerecis Omega3 MariGen wound dressing (Kerecis Ltd., Reykjavik, Iceland), also known as Kerecis MariGen or Kerecis Omega3 Wound, is a processed, fish (piscine) dermal matrix composed of fish collagen. Variations of Kerecis MariGen include Kerecis MariGen Micro and MariGen Expanse. MariGen Micro consists of small units of fragmented fish skin intended to cover uneven and irregular wound spaces. MariGen Expanse is designed to cover large wounds of 100 cm^2 or larger. Kerecis Omega3 Wound (formerly Marigen Wound) is FDA 510(k) (K132343) approved for the treatment of partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, draining wounds and trauma and surgical wounds. MariGen Wound Extra is FDA 510(k) (K190528) approved for the same indications. It is supplied as a meshed sheet ranging in sizes up to 20 x 30 cm. Kerecis SecureMesh is FDA 510(k) (K153364) approved for use as a prosthesis when staple line reinforcement is needed in surgical repair of soft tissue deficiencies using surgical staplers. It can be used for reinforcement of staple lines during lung, bariatric, gastric, colorectal and other surgeries. Kerecis Gingiva Graft is FDA 510(k) (K192612) approved for localized gingival augmentation to increased keratinized tissue around teeth or implants. Kerecis Reconstruct (also known as Kerecis Omega3 SurgiBind) is FDA 510(k) (K202430) approved for use for implantation to reinforce soft tissue where weakness exists, in patients requiring soft tissue repair, or reinforcement in plastic or reconstructive surgery. Kerecis® Omega3 Marigen® Shield received FDA 510(k) clearance (K213231) on June 29, 2022. MariGen Shield is a bilayer of processed resorbable acellular fish dermal matrix skin substitute adhered to a thin, transparent, porous, soft silicone layer. The silicone layer is a transparent polyurethane film single-coated with soft, medical grade silicone that is attached to the scaly side of the fish dermal matrix. The silicone layer is porous, soft and conformable to the wound surface which can be peeled off as the fish dermal matrix is resorbed. It is indicated for the management of wounds. As part of the processing of Kerecis products, cells and antigenic materials are extracted. The fish skin is derived from cod farmed in the North Atlantic Ocean. Kerecis Omega3 serves as a scaffold for revascularization and repopulation by the patient's cells and is converted into living tissue. In comparison to human skin substitutes, Kerecis Omega3 contains omega3 polyunsaturated fatty acids. In comparison to porcine grafts, fish skin is proposed to have lower risk of disease. Kerecis Ltd distributes additional products which are available in various countries and may have different names. These other products include: Kerecis® SurgiClose™, Kerecis® SurgiClose Micro™, Kerecis GraftGuide™, GraftGuide™ Micro, and GraftGuide™ Mano. The various products are indicated for use as a wound covering for burns, chronic wounds, surgical repairs, and traumatic wounds. Additional products under development include: Kerecis Omega3 Dura for reconstruction of dura mater, Kerecis Omega3 Hernia for abdominal repair, and Kerecis Omega3 Pectus for breast reconstruction. These additional products are not FDA approved and are in various stages of development (Kerecis, 2024; FDA, 2021, 2020, 2019, 2016, 2013).

There is insufficient evidence in the published peer-reviewed literature to support the clinical utility of MariGen/Kerecis Omega3 Wound product. Studies are primarily in the form of small randomized control trials, case series, retrospective reviews and case reports with small patient populations (n=5–85) with short-term follow-up (28 days to 12 weeks) (Kim, et al., 2021; Lullove, et al., 2021; Badois, et al., 2019; Kirsner, et al., 2019; Michael, et al., 2019; Woodrow, et al., 2019; Dorweiler, et al., 2018; Yang, et al., 2016; Baldursson, et al., 2015; FDA. 2013).

Lullove et al (2021) conducted a randomized control trial to evaluate the safety and efficacy of Kerecis Omega3 in the treatment of diabetic foot ulcers. Included in the study (n=49) were adults ≥18 years or older with diabetic foot ulcers (DFUs) for a minimum of four weeks who

demonstrated adequate renal function and perfusion to affected extremity. The DFU could be through the dermis but not into tendon, muscle, or bone with the index ulcer size of ≥1cm² and ≤25cm². Patients were excluded if they were being treated with systemic antibiotics at time of randomization; had an ulcer on heel; were on any investigational drug or therapeutic device within 30 days preceding study visit; had received a biomedical or topical growth factor for wound within the previous 30 days; were pregnant or breastfeeding; had a HbAic >12.0; or end-stage renal disease as evidenced by a serum creatinine ≥3.0 mg/dL within the previous six months. No significant difference was noted between the study groups in terms of demographics, renal function, or blood glucose. All patients were first treated with standard of care (SOC) (offloading, appropriate debridement, and moist wound care) for a 2–week screening period then randomized to SOC plus fish skin graft (n=25) applied weekly for up to 12 weeks or SOC using collagen alginate dressing (n=24) applied weekly by investigator and three times weekly by patient/caregiver. Primary outcome was the percentage of wounds closed at 12 weeks. Secondary outcome measures included time to heal (for DFUs that healed) and wound area reduction by percentage at 12 weeks. Percentage of wounds healed at 12 weeks was 67% (16/24) for fish skin group and 32% (8/25) in SOC group. Time to closure was six weeks for both groups. Percentage of area reduction at six weeks was 72.8% for fish skin and 41.2% for SOC. Percentage of area reduction at 12 weeks was 97.3% fish skin and 76.8% SOC. Adverse events included mild erythema and irritation which was experienced by both groups. Study limitations included small patient population.

Lyoplant®
LyoPlant (Aesculap® Inc., Center Valley, PA) is a pure collagen implant that is produced from bovine pericardium and proposed for substitution and enlargement of connective tissue structures in neurosurgery (e.g., covering for cerebral and cerebellar dura defects; cerebral decompression surgery; covering spinal dura defects; spinal compression surgery). Lyoplant is FDA approved for neurological procedures for soft tissue reconstruction of damaged, impaired or missing tissue (Aesculap, Inc. 2023; FDA, 1997). Lyoplant Onlay is FDA 510(k) approved as a dura substitute for the repair of the dura mater and is a biological, collagen-based absorbable dura substitution consisting of a bilayer membrane. The onlay is proposed to help prevent cerebrospinal fluid (CSF) leakage. It can be sutured in place as needed and is gradually broken down and replaced by the body's connective tissue. The Onlay comes in five sizes ranging from 1x1 cm to 4x5 cm (Aesculap, Inc. 2023; FDA, 2013). Data supporting the safety and efficacy of LyoPlant are lacking.

MatriStem® (Gentrix®)
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-Mohs 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 Matrix; MatriStem Multilayer Wound Matrix (meshed sheets); MatriStem Pelvic Floor Matrix (surgical sheets); MatriStem Plastic Surgery Matrix; MatriStem Surgical Matrix RS, PSM, PSMX, & Thick (surgical sheets; MatriStem Burn Matrix; and MatriStem Hernia Matrix. The MatriStem MicroMatrix® consists of micronized particles that are sprinkled onto the wound and covered with a moist dressing. MatriStem Wound Matrix and Multilayer Wound Matrix are also marketed as Cytal Wound Matrix 1-Layer and 2-Layer (Integra LifeSciences, 2024). In 2017 Acell announced that all products previously marketed under Matristem were being rebranded to Gentrix Surgical Matrix for soft tissue repair to differentiate Acell's surgical products from their wound management products Cytal and MicroMatrix (Integra LifeSciences, 2024).

Matristem has been proposed for the treatment of diabetic foot ulcers, pilonidal wounds, anal fistulas, burns, septal ulceration and perforation, esophagojejunal anastomotic leaks after total gastrectomy for malignancy and venous status and decubitus ulers. Studies investigating Matristem for these conditions are primarily in the form of retrospecitive review with small patient populations (Geiger, et al., 2016; Kraemer, et al., 2016). There is insufficient evidence to support Matristem for these conditions.

Frykberg et al. (2016) conducted a multicenter randomized controlled trial (n=56) to compare the treatment of non-healing DFUs with both MatriStem MicroMatrix (MSMM) and MatriStem Wound Matrix (MSWM) (porcine-derived) (n=27) to ulcers treated with Dermagraft (DG) (n=29) (living skin substitute). Prior to study initiation, patients participated in a four-week screening phase during which they received physician-selected standard of care (e.g., debridement, saline irrigation, primary dressing, offloading boot). Following the screening phase, patients with DFUs that decreased in size by ≤ 30% or increased by ≤ 50% and met other inclusion criteria were enrolled in the study. Other inclusion criteria included: ulcer present for ≥ 4 weeks and extended through the dermis and into the subcutaneous tissue without muscle, tendon, bone or joint capsule exposure; HbA1c <12%; wound free of necrotic debris following debridement and appeared to have healthy vascularized tissues; and Doppler measured ankle-bronchial index (ABI) of ≥ 0.7 after 10 minutes rest. Once granulation began to occur on the wound bed, only MSWM was applied. The matrix was applied weekly until wound closure (complete re-epithelialization with no drainage, no dressing required) or until the patient had received one application per week without wound closure, whichever came first, up to a maximum of eight applications. Following complete wound closure, patients returned for a six-month follow-up visit to assess for ulcer recurrence. There were no statistically significant differences between the two groups in the following: complete wound closure at day 56 (p=0.244), change in wound size over eight week treatment period (p=0.762); complete wound closure at day 70 (p=0.768); or mean time to closure (p=0.523). At the end of treatment the MS group reported statistically significant improvement in quality of life compared to the DG group (p=0.004 to 0.049). There was no statistically significant difference in wound recurrence at the six month follow-up (n=10). One MS-treated patient and two DG treated patients had ulcer recurrence. There was no significant difference in adverse events between the two groups. Limitations of the study include the small patient population and the manual nature of the data collection tracing the wounds to a Visitrak system.

Matrix™ HD
Matrix HD (RTI Surgical, 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 Surgical, 2024). Evidence supporting the safety and efficacy of Matrix D from published clinical trials is lacking.

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. There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of Memoderm.

Miamnion®

Miamnion® (Vivex Biologics, Atlanta, GA) is an amnion tissue allograft that is processed in accordance with FDA regulations and AATB standards. It is proposed for use as a soft tissue barrier and wound covering in the following clinical applications: spine and neurosurgery, foot and ankle, wound care, burn care, and dermatology (Vivex Biologics, 2024). The sizes available vary in thickness. Evidence is lacking in the published peer-reviewed literature to support the clinical effectiveness of Miamnion for any indication.

Microlyte® Matrix
Microlyte® Matrix (Imbed Biosciences, Inc., Madison, WI) is a synthetic, bioresorbable wound matrix composed of a resorbable polymer–polyvinyl alcohol (PVA) and contains bacteria-killing antimicrobial silver (Imbed Biosciences, 2023). It is proposed for the management of: wounds, partial and full thickness wounds including pressure ulcers, venous stasis ulcers, diabetic ulcers, first and second degree burns, abrasions and lacerations, donor sites and surgical wounds, and may be used over debrided and grafted partial thickness wounds. Microlyte Matrix received FDA 510(k) (K153756) approval in 2016 (FDA, 2022). Microlyte Matrix is available in the following sizes: 2x2 in and 4x4 in. Evidence in the published peer-reviewed literature consists of a prospective pilot study (Manning, et al., 2020) and case reports on the manufacturer's website and is insufficient to support the clinical effectiveness of Microlyte Matrix for any indication.

MiroFlex® (formerly Miromesh®)
MiroFlex (formerly known as Miromesh®) (Reprise Biomedical, Plymouth, MN; Miromatrix Medical, Inc., Eden Prairie, MN) is a non-crosslinked, acellular surgical mesh derived from whole, compressed porcine livers for the reinforcement of soft tissue. Proposed indications include hernia repairs, and reinforcement in plastic and reconstructive surgery. MiroFlex uses a perfusion decellularization as opposed to an immersion decellularization technology to remove cells from the mesh. Miromesh sales and manufacturing will be managed by Reprise Biomedical (Reprise Biomedical, 2023; FDA, 2014). The mesh is available in various sizes. Studies investigating the safety and effectiveness of Miromesh include a retrospective review for patients who underwent hernia repair and a case series for repair of esophageal hernia (Rosen, et al., 2019)

Rosen et al. (2019) conducted a multicenter prospective single arm study (n=41) evaluating the outcomes of MiroMesh when used for repair of a symptomatic paresophageal hernia. Inclusion criteria were: adults age 18–80 years; candidate for elective laparoscopic paraesophageal hernia repair; > 5 cm hiatal hernia in axial/vertical dimension; evidence of Type II or III paraesophageal hernia; and committment to not smoking for at least four weeks prior to procedure. Subjects were excluded if they had undergone prior esophageal or gastric surgery; had a sensitivity to porcine material; were immunocompromised (i.e., HIV, post-organ transplant, on chemotherapy); required emergent surgery for acute gastric volvulous or strangulation; had a BMI ≥ 40; life expectancy < 2 years; and/or had an associated GI disease that required extensive medical or surgical intervention (e.g., Crohn's Disease) that might interfere with quality of life assessment. The primary endpoint of the study was hernia recurrence that required surgical re-intervention at two years postoperate due to symptoms or adverse events. The secondary endpoints included: radiologic recurrence, symptomatic improvement, quality of life, adverse events and perioperative outcomes. All patients underwent a laparoscopic transabdominal approach with no conversions to an open procedure. Twenty-seven patients completed the two-year follow-up. Radiologic evaluation demonstrated hiatal hernia recurrences in three patients who did not require surgical reintervention. GERD HRQL scores were significantly improved from baseline to two years follow up (19.3 to 3.8) ($p<0.0001$). At the two-year follow-up 89% of patients reported satisfaction with their condition vs. 17.9% preoperatively. Results of the SF-36 questionnaire showed that quality of life was significantly improved at all time points with overall quality of life improvement seen at 24 months compared to baseline. There were no major intraoperative complications reported. Eighteen postoperative adverse events included four serious events that were not related to the mesh. Limitations of the study include the lack of a comparator, small patient population, number

of patients lost to follow-up and the short-term follow-up. Randomized controlled trials with large patient populations and long-term follow-up are needed to validate the results of this study.

Miro3D® Wound Matrix
Miro3D® Wound Matrix (Reprise Biomedical, Inc; Plymouth, MN) is a three-dimensional biologic matrix that is manufactured from decellularized porcine liver. The Miro3D Wound Matrix received FDA 510(k) approval on August 18, 2022 (K221520). FDA indications for use: partial and full thickness wounds; pressure ulcers; venous ulcers; chronic vascular ulcers; diabetic ulcers; tunneled, undermined wounds; trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds; and surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of Miro3D Wound Matrix for any indication.

Myriad Matrix™
Myriad Matrix™ (Aroa Biosurgery, Auckland, New Zealand) is a soft tissue bioscaffold engineered extracellular matrix (ECM) derived from ovine (sheep) forestomach tissue. It is proposed for use in the management of the following wounds: partial and full-thickness wounds, ulcers (pressure, venous, diabetic, chronic vascular), 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, and skin tears), and draining wounds (Aroa Biosurgery, 2024). Aroa received FDA 510(k) clearance (K171231) for Myriad Matrix in June 2017. It is available in 5x5cm, 7x10 cm, 10x10cm, 10x20cm, and 20x20 cm sizes. Evidence in the published peer-reviewed literature consists of case series (Chaffin, et al., 2021; Desvigne, et al., 2021; Bohn and Chaffin, 2020) and is insufficient to support the clinical effectiveness of Myriad Matrix for any indication.

NeoMatriX® Wound Matrix
NeoMatriX® Wound Matrix (NeXtGen™ Biologics, Alachua, FL) is a wound covering derived from the dermal extracellular matrix of axolotl (salamander). It is proposed to support in the healing of chronic and hard-to-heal wounds. In 2018, NeoMatriX Wound Matrix received FDA 510(k) approval (K181330) 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, trauma wounds, and draining wounds. The product was modified and received an additional FDA 510(k) approval in 2021 (K210024) due to changes in the manufacturing process. There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of NeoMatriX for any indication.

NeoStim Membrane/NeoStim DL/NeoStim TL
NeoStim (BioNTech, Mainz, Germany) are a family of dehydrated amnion membrane allografts derived from donated human amniotic membrane. NeoStim Membrane is a single layer, NeoStim DL is a double layer, and NeoStim TL is a triple layer dehydrated amnion membrane allograft. The products are proposed to serve as a barrier or provide a protective coverage from the surrounding environment for acute and chronic wounds such as: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds and trauma wounds. The product is applied directly to the wound, adheres to the wound bed without fixation and it is fully resorbable. The products are classified as a human tissue and cell-based product regulated by the American Association of Tissue Banks (AATB) and in compliance with U.S. FDA regulations (21 CFR 1271). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of NeoStim products for all indications.

Neox™ Wound Matrix/Neox Cord 1k/Neox 100

Neox Wound Matrix, previously Neox 1K, (BioTissue, Inc., Miami, FL) is an amniotic membrane and umbilical cord 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 Cord RT is an amniotic and umbilical cord product, one mm thick, available in four sizes. Neox 100 amniotic product quick peal is available in three sizes (BioTissue, 2024). A third product is the Neox Cord 1K (CMS, 2017). The safety and efficacy of these products has not been established in randomized controlled trials. Studies are primarily in the form of case reports and retrospective reviews with small patient populations (Caputo, et al., 2016; Raphael, 2016).

Neox® Flo
Neox Flo (Amniox Medical™, Marietta, GA) is the particulate form of Neox 100 and is also made from human placental tissue including amniotic membrane and umbilical cord tissues. The product is proposed for managing complex wounds and tunneling anatomies. It contains growth factors, cytokines and proteins and is FDA-regulated as a Human Cell, Tissue, and Cellular and Tissue-Based Product. Neox Flo is available in three sizes (i.e. 25 mg. 50 mg, 100 mg) (WoundReference, 2024). There is insufficient data to support the clinical utility of Neox Flo.

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, 2024). 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.

Neuroflex™, NueroMatrix™, NeuroMend™
Neuroflex (Collagen Matrix, Inc. Oakland, NJ) is a flexible, resorbable, type 1 collagen nerve cuff that is proposed to provide an encasement for peripheral nerve injuries and protection of the neural environment. It allows repair without tension of peripheral nerve discontinuities of less than three centimeters. Nerve gaps may occur in crushing injuries; penetrating injuries such as lacerations, stabbings, fractures; failed primary repairs; and oncology related excisions. When hydrated the cuff becomes a flexible collagen conduit with a proposed kink-resistant property. It is designed to be an interface between the nerve and surrounding tissue to prevent ingrowth of scar tissue. The cuff may be placed at the terminal end of a nerve in an effort to prevent formation of a neuroma. Neuroflex is FDA 510(k) approved as a nerve cuff used "for the management of peripheral nerve injuries in discontinuities where gap closure can be achieved by flexion of the extremity (e.g., to prevent ingrowth of scar tissue) or at the end of the nerve in the foot to reduce the formation of symptomatic or painful neuroma". It is proposed for severed inuires where there is a gap across the joint. The product comes in six 2.5 cm lengths with an inner diameter of 2.0 mm to 6.0 mm (Stryker, 2024; FDA, 2014 [K131541]).

NeuroMatrix (Collagen Matrix, Inc. Franklin Lakes, NJ) is a standard type 1 collagen matrix designed for peripheral nerve repair through encasement and protection of the neural environment. The matrix is semi-permeable and is proposed to allow diffusion of nutrients and

neurotrophic factors into the conduit and to provide a barrier to large, scar-forming cells. The FDA 510(k) approval for NeuroMatrix is for "use in repair of peripheral nerve discontinuities where gap closure can be achieved by flexion of the extremity". NeuroMatrix is sutured in place and expected to completely resorb within 3–6 months following implantation. It is recommended for straight gap locations. NeuroMatrix is available in 2.5 cm length in 2.0 mm to 6.0 mm inner diameter (Stryker, 2024; FDA 2001 [K012814]).

NeuroMend (Collagen Matrix, Inc. Franklin Lakes, NJ) is a semipermeable type I collagen nerve wrap matrix proposed to be completely resorbed. It has a self-curling design to allow for 25% of the conduit to wrap over itself and eliminate the need for a running suture. It is proposed for use on nerves 2.0 mm to 12.0 mm in diameter. NeuroMend is FDA 510(k) approved "for the management of peripheral nerve injuries in which there has been no substantial loss of nerve tissue and where gap closure can be achieved by flexion of the extremity". Per the manufacturer, Neuromend is ideal for crush or compression injuries and partially severed nerves. Neuromend is available in 4.0 mm, 6.0 mm, and 12.0 mm maxium inner diameters in 2.5 cm and 5.0 cm lengths. The size used depends on the diameter of the injured nerve (Stryker, 2024; FDA, 2006).

These Matrixes are marketed as a peripheral nerve portfolio by Stryker Orthopedics (Mahwah, NJ). Data investigating the safety and effectiveness of these collagen nerve matrixes are lacking. Studies are primarily in the form of animal studies, case reports and retrospective reviews with small patient population used in a variety of different procedures.

Novafix® DL
Novafix DL (Triad Life Sciences®, Inc., Memphis, TN) is a dehydrated human amnion chorion membrane allograft indicated for wound management including partial and full thickness wounds, pressure sores/ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor site/grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, wound dehiscence), trauma wounds, (e.g., abrasions, lacerations, partial thickness burns, skin tears), and draining wounds (CMS, 2020). It is available in the following sizes: 2x2 cm, 4x4 cm, 4x6 cm, 4x8 cm. There is a lack of evidence in the published, peer-reviewed literature to support the effectiveness of this product.

NuCel™/Nucel Bioactive Amniotic Suspension/NuShield™ Spine/NuShield™ Orthopaedics/
NuShield Spine (Nutech Medical, Birmingham, AL; acquired by Organogensis; Canton, MA) 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 (Organogenesis, 2021). 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. 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. Nucel Bioactive Amniotic Suspension (HCT/P) is an allograft derived from human amnion and amniotic fluid. It is proposed for use in tissue repair. Nucel suspension is available in small, medium, large and extra-large sizes.

Due to the lack of evidence in published clinical trials, the safety and efficacy of NuCel products have not been established. Studies are primarily in the form of case series with small patient population (Anderson, et al., 2014).

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 (H990013) 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.

Orion Amniotic Membrane
Orion Amniotic Membrane (Legacy Medical Consultant, LLC., Fort Worth, TX) is a sterile dehydrated dual layered human amniotic membrane allograft (Legacy Medical Consultant, 2023). It is proposed for use as a barrier or cover for acute and chronic wounds and for use as a barrier to protect wounds from the surrounding environment. The product meets the criteria for FDA regulation solely under section 361 of the Public Health Service (PHS) Act and the regulations in 21 CFR part 1271 (CMS, 2023). Orion Amniotic Membrane is available in multiple sizes. There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of this product for any indication.

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).

OrthoNovis Guard Allograft Membrane

OrthoNovis Guard Allograft Membrane (OrthoNovis, Inc., Palm Coast, FL) is a dehydrated amniotic membrane sheet produced using minimal manipulation. It is proposed for use is as a protective covering and in wound management. OrthoNovis products are processed and registered in compliance with all current Good Tissue Practices as mandated by the FDA and AATB and regulated under Section 361 of the Public Health Service Act. There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of OrthoNovis Guard allograft membrane products for any indication.

OsseoGuard®
The OsseoGuard Membrane (ZimVie formerly 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 OsseoGuard 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 (ZimVie, 2024). Biomet also provides OsseoGuard Flex™ Membrane which is proposed for defects in which more drapability is indicated. Data are primarily in the form of case series with small patient populations and case reports and insufficient to establish the safety and efficacy of these products.

Ovation®
Ovation (Osiris Therapeutics, Inc. Columbia, MD), 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.

OviTex®
OviTex® (TELA Bio®, Inc., Malvern, PA) is a reinforced tissue matrix composed of interwoven biologic material derived from ovine rumen and polymer reinforcement. The polymer fiber is available in resorbable or permanent variations. It is proposed for use as a surgical mesh to reinforce and/or repair soft tissue where weakness exists. Indications for use include the repair of hernias and/or abdominal wall defects that require the use of reinforcing or bridging material to obtain the desired surgical outcome. The OviTex portfolio of products includes: OviTex, a four layer device not intended for intraperitoneal placement; OviTex 1S, a six layer device with smooth external layers suitable for intraperitoneal placement; OviTex 2S, an eight layer device with two smooth external layers suitable for intraperitoneal placement; OviTex LPR, a four layer device with a smooth side suitable for laparoscopic and robitic-assisted intraperitoneal placement; and OviTex PRS, a two or three layer device available in four shapes for plastic and reconstructive surgery. In order to achieve better fluid management, tissue integration, and directional flexibility, OviTex PRS was designed with micropores, macropores, and stents to address soft tissue repair in plastic and reconstructive surgery. OviTex received FDA 510(k) (K141053) as Ovine Tissue Matrix (OTM) in 2014 (FDA, 2022). It is available in various sizes. Evidence in the published peer-reviewed literature consists of an observational study (DeNoto, et al., 2021) and case series (Parker, et al., 2020; Sawyer, 2018) and is insufficient to support the clinical effectiveness of OviTex for any indication.

PalinGen®
There are three PalinGen products (Amnio ReGen Solutions, LLC., Las Vegas, NV), PaliGen Flow, PaliGen Xplus and PalinGen Xplus HydroMembrane. The products are made from placental amniotic tissue and proposed for use as a wound covering following various procedures (e.g.,

orthopedic surgeries and injuries, nerve wrapping, spinal surgery, general surgery, burns and wounds). The tissue is designated for human homologous allograft use under FDA regulations and processed, cleansed, and packaged at an AATB accredited tissue bank. PalinGen Flow is available in 0.25 ml, 0.50 ml, 1.00 ml, and 2.00 ml sizes. A wet form of PalinGen, the Xplus Hydro Membrane, is also available. The Membranes come in ten sizes and can be customized (BioPro, 2022). There is insufficient evidence in the published studies to support the effectiveness of these products for their proposed use.

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 (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 Peri-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, rectocele repair, Frey's syndrome, nasal septal perforation, fecal incontinence, 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; complex abdominal wall repair; perianal fistulas; various urological, gynecological and plastic surgery indications and urodynamic stress incontinence (Dirani, et al., 2021; Vollebregt, et al., 2021; Sileri, et al., 2012; Wahed, et al., 2012; Bachman and Ramshaw, 2008; Hammond, et al., 2008;

Hsu, et al., 2008; Papadogeorgakis, et al., 2008; Teicher, et al., 2008; Hammond, et 2008, Papadogeorgakis, et al., 2008; Shaikh, et al., 2007). Case series, case reports and retrospective reviews with small patient populations (n=15-86) and short-term follow-ups lack the data needed to support the efficacy of Permacol in the treatment of these conditions.

Gossetti et al. (2021) conducted a prospective multicenter study to evaluate the safety and efficacy of the biologic surgical implant, Permacol, in the surgical treatment of complex abdominal wall reconstruction (CAWR) in adult patients (n=114) through 36 months postoperatively. Patients had a mean age of 60.8 ± 12.2 (29–87) years, 58.8% male, with a mean BMI of 31.2 ± 6.0 (18.7–45.4) kg/m^2. At 24 months, the cumulative hernia recurrence rate was 18.7% (17/91) and 22.4% (19/85) at 36 months. Reoperation for hernia repair within 36 months occurred in 12 (14.1%) patients. Patients reported improvement in the Carolina comfort scale (CSS) measures of severity of pain, sensation of mesh, and movement limitations between 6- and 36- months post-surgery. Adverse events included 13 (11.3%) dehiscences, 11 (9.6%) wound infections, 11 (9.6%) seromas, four (3.5%) hematomas and one stoma site pain. Study limitations include small patient population, short term follow up, and lack of a comparator.

Maeda et al. (2013) 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.

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.

Phasix Mesh™ and Phasix™ Plug and Patch
Phasix™ Mesh (Davol, Inc., Warwick, RI) is a knitted monofilament mesh scaffold using Poly-4-hydroxybutyrate (P4HB), a biologically derived, fully resorbable material. The Mesh is FDA 510(k) approved and "indicated to reinforce soft tissue where weakness exists in patients undergoing plastic and reconstructive surgery, or for use in procedures involving soft tissue repair, such as the repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result" (FDA, 2016, FDA, 2015).

Phasix™ Plug and Patch (Bard Davol [BD], Inc., Warwick, RI) is a fully resorbable monofilament knitted mesh constructed of monofilament Poly-4-Hydroxybutyrate (P4HB) which is pre-formed into a three-dimensional (cone shape) configuration constructed of a fluted outer layer and multiple inner layers (petals) of mesh attached at the tip. The Phasix™ Plug and Patch is FDA 510(k) approved for reinforcement of soft tissue where weakness exists, in procedures involving soft tissue repair, such as groin hernia defects. The device is proposed to support host tissue formation at the repair site and gradually degrade via hydrolysis within 12 to 18 months or until fully resorbed. Phasix Plug and Patch come in four sizes: 2.5x3.6 cm, 3.3x4.1 cm, 4.1X4.8 cm, 3.8x5.1 cm (Bard Davol, 2024; FDA, 2012).

There is insufficient evidence in the published peer-reviewed literature to support the safety and effectiveness of the Phasix products. Studies report conflicting results with small patient

populations (n=15-215) and short term follow-ups (48 days to 36 months) and have primarily been in the form of prospective observational and retrospective reviews (Aiolfi, et al., 2021; Charleux-Muller, et al., 2021; Christopher, et al., June, 2021; Christopher, et al., Aug 2021; Christopher, et al., Dec 2021; Claessen, et al., 2021; Faulkner, et al., 2021; Levy, et al., 2021; van Driel, et al., 2021; van Rooijen, et al., 2021; Vauclair, et al., 2021; Abdelmoaty, et al., 2020; Aldohayan, et al., 2020; Panici Tonucci, et al., 2020; Rognoni, et al., 2020; Roth, et al., 2020; van Rooijen, et al., 2020; Yu, et al., 2019).

PhotoFix® Decellularized Bovine Pericardium
PhotoFix Decellularized Bovine Pericardium (Artivion, Inc. formerly CryoLife®, Kennesaw, GA) is a cardiovascular patch prepared from bovine pericardium which is stabilized using a dye-mediated photooxidation process, using ethylene oxide and sterilized using aseptic processing techniques. The photooxidation process creates crosslinks in the bovine tissue. No aldehyde chemistry is used during any phase of manufacturing including the tissue fixation or sterilization processes (Artivion, 2024; FDA, 2017). It is proposed for intracardiac repair, great vessel repair, suture line buttressing, pericardial closure and vascular repair and reconstruction of the carotid, iliac, femoral, tibial blood vessels and arteriovenous access revisions. PhotoFix Decellularized Bovine Pericardium received FDA 510K approval on March 9, 2017 (K162506). It is supplied in the following sizes: 1cm x 1cm, 4cm x 4cm, 6cm x 8cm, 8cm x 14cm, 10cm x 16cm, 14cm x 16cm (FDA, 2017). There is insufficient evidence in the peer-reviewed literature to support Photofix bovine pericardium patch for any indication. Studies are primarily in the form of retrospective reviews (Baird et al, 2017; Majeed et al, 2016).

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. According to the manufacturer's website, GORE PRECLUDE MVP and PDX Dura Substitutes have been discontinued (Gore, 2024).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 three sizes and lengths (Gore, 2024). 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.

Preclude® Vessel Guard
Preclude Vessel Guard (Gore Medical, Flagstaff, AZ) is an FDA 510(k), Class II approved device which was submitted to the FDA as a proposal for a new indication for the Gore Acuseal Cardiovascular Patch. The new indication is marketed under the name of Gore Preclude Vessel Guard. The Vessel guard is FDA approved "as a cover for vessels following anterior vertebral surgery to reduce the risk of potential vessel damage during a revision surgery by providing a plane of dissection". The device is made of polytetrafluoroethylene (fluoropolymer (ePTFE and

fluoroelastomer)The Guard is proposed to reduce the risk of potential vessel damage during reoperations and revision surgeries by allowing a clear plane of dissection and facilitating retraction of a vessel to minimize tissue attachment. Preclude is proposed for the following surgical indications: lumbar interbody fusion, adjacent level disc treatment, total disc replacement, hardware removal, instrumented scoliosis reconstruction, corpectomy for tumor or trauma, open vascular treatment, and also staged procedures or reoperations for any of these procedures. Two sizes are available (5x6 cm, 6x10 cm). There is insufficient evidence in the published clinical studies to support the safety and efficacy of the Preclude Vessel Guard.

Paraderm® Dermal Matrix
Paraderm Dermal Matrix (Paragon® 28, Englewood, CO) is a patent pending, minimally manipulated human collagen matrix that is proposed to promote cellular infiltration and proliferation as an integumentary augmentation. The product is obtained through the University of Miami Tissue Bank. Paragon 28 is a company established for the orthopedic foot and ankle market. The Matrix is provided in 4x4 cm and 4x8 cm sizes (Paragan 28, 2023). There is insufficient evidence to support the safety and effectiveness of this matrix.

Pro3™
The Pro3™ products (Paragon 28, Inc., Englewood, CO) include the Pro3™-F (frozen) and Pro3™-FA (ambient) liquid matrix allografts derived from amniotic fluid. Pro3 amniotic fluid is proposed for use in joint capsules to provide shock absorption, lubrication, and joint stability. Pro3-Placenta Amniotic Placental Membrane and Pro3-Cord Amniotic Umbilical Cord Membrane are tissue matrixes proposed for use as therapeutic grafts for multiple indications including: wound care; burn care; oral surgery; urological wrap; and spinal and neurosurgery adhesion barrier, wrap and patch. The Placental Membrane is a thin graft available in 2x3 cm, 4x4 cm, 4x8 cm, 7x7 cm, and 2x12 cm sizes. The Cord Membrane is eight times thicker than the Membrane and available in 2x3 cm and 3x6 cm sizes. There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of the Pro3 products.

Proceed® Surgical Mesh
Proceed® Surgical Mesh (Ethicon Inc., Somerville, NJ) is a laminate mesh designed for the repair of hernias and other fascial deficiencies. The mesh is comprised of an oxidized regenerated cellulose (ORC) fabric, and Propolene™ Soft Mesh, a nonabsorbable polypropylene mesh, which is encapsulated by a polydioxanone polymer. The polypropylene mesh side allows for tissue ingrowth and the ORC side is proposed to provide a bioresorbable layer to physically separate the polypropylene mesh from underlying tissue and organ surfaces to minimize tissue attachment to the mesh during healing. Proceed is FDA 510(k) approved "for the repair of hernias and other fascial deficiencies that require the addition of a reinforcing or bridging material to obtain the desired surgical result. The mesh is available in 5x10 cm, 7.5x15 cm, 10x20 cm, 20x30 cm, 25x35.5 cm rectangular shapes, 15x15 cm and 30.5x30.5 squares, and 10x15 cm, 15x20 cm, 20x25 cm and 26x34 cm oval shape (Ethicon Inc., 2024; FDA, 2016).

There is insufficient evidence in the published peer-reviewed literature to support Proceed Surgical Mess for any indication. The evidence is primarily in the form of animal studies, retrospective reviews, feasibility studies and small case series (n=22-36) with short-term follow-up (1–36 months) (Bhanot, et al., 2013; Eltayeb, et al., 2013; Rosenberg, et al., 2008).

ProgenaMatrix™
ProgenaMatrix (CellConstructs LLC, Woodstock, GA) is a hydrated keratin wound matrix manufactured from human keratin and other proteins extracted from human hair. ProgenaMatrix is FDA 510(k) approved as a dressing for the treatment of "dry and exuding partial and full thickness wounds such as: pressure (stage I-IV) and venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, donor sites and grafts, first and second degree burns,

superficial injuries, cuts, abrasions and surgical wounds". It is not intended to be used for the treatment of third degree burns. The Matrix is applied directly to the wound bed following debridement. It is available in 2x2 cm, 4x4 cm, 6x6 cm, 10x10 cm, and 12x12 cm sizes (CMS, 2019; FDA, 2019). There is insufficient evidence in the peer-reviewed literature to support the safety and effectiveness of ProgenaMatrix.

ProLayer®
ProLayer Acellular Dermal Matrix (manufactured by AlloSource, Centennial, CO; distributed by Stryker Corp., Mahwah, NJ) is a human allograft with a three-dimensional collagen elastin matrix proposed to allow cells to infiltrate and repopulate for revascularization and remodeling of wounds. ProLayer is proposed for use for a variety of clinical applications including wound coverage, tendon augmentation, and surgical closure. The matrix is available in 13 sizes ranging from 2x4 cm to 6x12 cm in 1.0- 3.3 mm thickness. ProLayer Xenograft is an acellular porcine dermal matrix proposed for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue. Per the manufacturer, ProLayer is indicated for reinforcement 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 xenograft is available in 2x5 cm, 4x4 cm, 4x7 cm and 5x10 cm sizes that are 1.1 ± 0.5 mm thick (Stryker, 2024). There is insufficient evidence to support the safety and efficacy of Prolayer and ProLayer Xenograft. Available data are primarily from animal studies.

ProMatriX™
ProMatriX ACF (BioPro Inc., Port Huron, MI) is a human liquid allograft comprised of amnion and amniotic fluid and proposed for the repair and healing of wounds. The product contains growth factors, cytokines, amino acids, carbohydrates, hyaluronic acid, and extracellular matrix (ECM) proteins. ProMatrX™ ACF is manufactured and regulated for human homologous allograft use under 21 CFR Part 1271 and Section 361 of the Public Health Service Act. It is processed and packaged at an FDA registered and American Association of Tissue Banks (AATB) accredited facility. ProMatrX may be applied topically or implanted for wound care and may be diluted to any ratio (1:1 recommended). The prescribed dosage varies by the size of the wound. Typical doses range from 0.25 cc to 4.0 cc, depending on the size, depth and type of wound. The product is supplied in liquid form in vials containing 0.25 cc, 0.5 cc, 1 cc, 2 cc, and 4 cc (CMS 2016). There is insufficient evidence in the published peer reviewed literature to support the safety and efficacy of ProMatrX.

Promote™ Amnio-Frt™ or Promote™ Amnio F™
Amnio FRT (AllianceSpine™, San Antonio, TX) is a flowable tissue allograft derived from human amniotic fluid. Amnio F is a cryopreserved allograft derived from human amniotic fluid. The products are proposed for use as a topical application over wounds. Collection of the donor placental tissue is performed and processed in accordance with the standards and guidelines established by the American Association of Tissue Banks (AATB). Both Amnio F (2.0 mL) and Amnio FRT (0.5 mL, 1 mL, 2 mL) come in liquid format. There is insufficient evidence to support the safety and efficacy of Promote Amnio-Frt or Promote Amnio F for wound healing.

Promote AmnioStrip®
Promote AmnioStrip (AllianceSpine™, San Antonio, TX) is a placental tissue product supplied as a dual layer amnion patch for wound managment. It is proposed to reduce scarring of dermal and subcutaneous wounds, reduce dural and nerve root adhesions, prevent adhesions to implanted hardware and in tendon grafts. Promote Amnio Strip is processed in accordance with the safety guidelines provided by the U.S. Food and Drug Administration (FDA) Human Cellular and Tissue-based Products (HCT/P) (21 CFR Part 1271) and the standards from the American Association of Tissue Banks (AATB). The product is available in the following sizes: 3cm x 3cm, 4cm x 4cm, 4cm

x 6cm (AllianceSpine, 2024). There is insufficient evidence to support the safety and efficacy of Promote AmnioStrip for wound management.

Puracol®
Puracol, Puracol Plus and Puracol Plus Ag (Medline Industries, Inc., Mundelien, IL.) are type I bovine 100% collagen wound dressings. The dressings are proposed for the treatment of partial- and full-thickness wounds, pressure ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, first- and second-degree burns, donor sites and other bleeding surface wounds, abrasions, trauma wounds, dehisced wounds, and/or surgical wounds. Puracol is a primary wound dressing proposed for all drainage types. Puracol Plus is proposed for chronic or stalled wounds. Puracol Plus Ag with silver chloride is proposed for stalled wounds when the antimicrobial properties of silver are desired. Puracol Plus Ag is FDA 510(k) approved for the management of wounds. These products are offered in 2x2 cm, 4x4 cm and 8x8 cm sizes and as a 1x8 cm rope. The rope configuration is proposed for tunneling wounds. Puracol Ultra Powder is a filler that absorbs the wound's fluids to form a gel-like barrier to protect the wound bed. The powder is proposed for the treatment of irregular shaped wounds and is available in a 1G pouch (Medine, 2024; FDA, 2008). There is insufficient evidence to support the Puracol products for the treatment of wounds. Studies are primarily in the form of case reports and small case series (n=5).

Puraply™ (previously Fortaderm™)
Fortaderm Wound Dressing (PuraPly) and Fortaderm Antimicrobial Wound Dressing (PuraPly Antimicrobial Wound Matrix) (Organogenesis, Inc., Canton, MA) were FDA 510(k) approved in 2001 and 2005, respectively. Fortaderm Wound Dressing (PuraPly wound matrix) is a single-layer fenestrated porcine allograft. The FortaDerm Antimicrobial Polyhexamethylene Biguanide Hydrochloride (PHMB) is FDA approved for the management of wounds and as an effective barrier to resist microbial colonization within the dressing and reduce microbes penetrating through the dressing. Both FortaDerm products are proposed for the management of: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds and draining wounds. Per the FDA, Puraply is the proprietary name for FortaDerm (Organogenesis, 2022; CMS, 2014; FDA, 2005; FDA 2001).

Puraply AM is a five layer fenestrated and cross-linked sheet of porcine collagen, coated with polyhexamethylene biguanide hydrochloride (PHMB) which is proposed to resist microbial colonization and reduce microbial penetration within the matrix. The product is supplied in sheet form (Organogenesis, 2022; CMS, 2018). There is insufficient evidence in the peer-reviewed literature to support the clinical utility of the PuraPly products.

PX50®/PX50® Plus
PX50/PX50 Plus (Skye Biologics, Inc., Redondo Beach, CA) are products made from human tissue allografts derived from decellularized particulate placental, connective tissue matrix. The matrix includes extracellular components, growth factors and collagen scaffolds. PX50 andPX50 Plus are proposed for the treatment of sports medicine and other painful conditions including acute or chronic tendon or muscular injuries such as, posterior tibial tendonitis, peroneal tendonitis, anterior tibial tendonitis, extensor muscles of the foot, plantar musculature of the foot excluding the plantar fascia, and Achilles tendonitis. Per the manufacturer, injection of the matrix is a minimally invasive, in-office procedure. PX50 is a ready-to-use flowable matrix and PX50 Plus is a cryopreserved form that must be kept frozen until used. Both preparations come in a 0.5 cc size. Sky Biologics also offers additional products in larger sizes for more complex injuries. DX100 (1.0cc), DX150 (1.5cc) and DX200 (2.0cc) are flowable forms. The cryopreserved larger preparations are the DX100P (1.0cc), DX150P (1.5cc) and DX200P (2.0cc) (Lullove, 2015). There

is insufficient evidence in the peer-reviewed literature to support the effectiveness of this product. Studies are primarily in the form of small (n=10) retrospective reviews (Lullove, 2015).

RECELL® Autologous Cell Harvesting Device
The RECELL® Autologous Cell Harvesting Device (Avita Medical, Valencia, CA) is a sterile, single use, stand-alone, battery powered cell separation device operated by an appropriately-licensed healthcare professional at the patient's point of care to prepare autologous Regenerative Epidermal Suspension (RES®) for direct application to acute partial-thickness thermal burn wounds in patients 18 years of age and older or application in combination with meshed autografting for acute full-thickness thermal burn wounds in pediatric and adult patients. The device enables the processing of a small, thin split-thickness skin sample 0.006-0.008 inch (0.15-0.20 mm) in depth to prepare a cell population in suspension for immediate delivery onto a prepared wound surface. The user can enzymatically and mechanically process a small skin sample to produce RES. Processing tools provided with the device include off-the-shelf syringes, scalpels, and fill needles. The device also includes nozzles that attach to syringes and can be used to aerosolize the cell suspension onto the wound. The proprietary RECELL Enzyme is reconstituted with sterile water (included) and used to facilitate disaggregation of cells from the harvested donor skin. A buffer solution is also provided to suspend the disaggregated cells for delivery to the prepared wound site. No cell culturing processes are involved in the procedure. The resulting suspension of cells comprises a mixed population predominantly of keratinocytes and fibroblasts. The presence of viable melanocytes has also been demonstrated. The RECELL Autologous Cell Harvesting Device received FDA Premarket Approval (PMA) on 09/20/2018 for treatment of acute thermal burns in adults and the indication was expanded in 2021 for use in combination with meshed autografting for acute full- thickness thermal burn wounds in pediatric and adult patients (PMA Number: BP170122) (FDA, 2022). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of the RECELL Autologous Cell Harvesting Device for the treatment of burns. Studies have primarily been in the form of case reports and one small randomized control trial (Holmes, et al., 2019)

Bairagi et al. (2021) conducted a systematic review and meta-analysis of randomized control trials to evaluate the efficacy of autologous skin cell suspensions (ASCS) on the re-epithelialization of partial thickness burn injuries and skin graft donor site wounds (DSW). Five studies (n=347) were located: two studies on adults (n=183) and one study on children with burn wounds (n=13), and two studies on adults with donor site wounds (n=151). Studies were included if they were on humans with partial thickness burn injuries and split-thickness skin graft donor site wounds. The intervention was autologous skin cell suspension prepared with the RECELL autologous cell harvesting device. The non-cultured mixture of epithelial cells was used in suspension format as a spray or droplet application in the wound management for treatment of burn wounds or split-thickness skin graft donor sites. Comparators included standard of care dressings/treatment with or without a skin graft. Primary outcome measured was wound time to re-epithelialization (TTRE). Secondary outcomes measured included pain, scar sensitivity (itch, tightness), scar characteristics (pigmentation, thickness), scar specific health related quality of life, infection and need for additional surgery. Length of follow up ranged from 12–52 weeks. Two studies reported on the use of ACSC in adult burn wound re-epithelialization compared to control group and had different methods of reporting the results. One study reported ASC had a reduced percentage of re-epithelialization (standardized mean difference [SMD] -0.27, [95% CI: -0.57, 0.03]). The second study reported ASCS increased the TTRE (SMD 0.50, [95% CI: 0.06, 0.94]). However, the time to re-epithelialization was decreased (SMD -1.75, [95%CI: -3.45, -0.05]) in pediatric BW, when ASCS was compared to control group. In adults DSW, ASCS significantly reduced time to re-epithelialization compared to the control group (SMD -5.71, [95% CI: -10.61, -0.81]). Pain was reported using the Visual Analogue Scale (0-100 VAS) in adults and age appropriate scales for the children, either the Children and Infant's Post-operative Pain Scale (CHIPPS, 0-23 months), Face, Legs, Activity, Cry and Consolability Scale (FLACC, 2-7 years), or the Revised Faces Pain Scale

(FPS-R, older children). Adult BW pain was reduced when treated with ASCS (SMD -0.62, [95%CI: -0.90, -0.35]). One study on adult DSW reported reduced pain when treated with ASCS (SMD -6.80, [95%CI: -7.30, -6.30]) and a second study reported low pain scores in both ASCS (median 1.7, IQR 1.3-2.1) and control (median 1.6, IQR 1.3-2.3) groups and not significantly different (p< 0.444). Pain in children with BW was reduced (SMD -0.24 [95%CI: -1.56, 1.08]) when treated with ASCS. Itch was reported in two studies. Adult BW reported no difference in incidence of itch between ASCS and control groups. Adult DSW reported no difference in itch intensity between ACSC and control. When compared to the control group, adult BW treated with ACSC (OR 1.52 [95% CI: 0.25, 9.27]) had 52% higher odds for surgical wound infection when compared to control. Conversely, adult DSW had 81% lower odds of cellulitis when treated with ASCS (OR 0.19, 95%CI: 0.01 to 4.11). Pediatric BW treated with ASCS had higher odds of sepsis and surgical wound infection (OR 3.00 [95%CI: 0.09, 95.17]) compared to control. Need for further surgery increased for BW patients treated with ASCS by 38% (OR 1.38 [95%CI: 0.46, 4.18]). Pediatric BW patients had 96% lower (OR 0.04 [95%CI: 0.00, 1.25) odds of needing another surgery when treated with ASCS compared to control. The authors reported the certainty of evidence was very low. Author noted study limitations included small number of studies, small sample size of studies, varied measurement of outcomes, and most studies were completed on adults which cannot be directly applied to children. Due to the low certainty of evidence no conclusions can be drawn about the role of ASCS in partial thickness burn injury management.

A search of UpToDate and medical textbooks located several references describing the use of RECELL autologous cell harvesting procedure as a spray to cover a burn wound; however no references were located to indicate that RECELL autologous cell harvesting procedure/device has become a generally accepted/standard of care (SOC) procedure in the management of thermal burns.

REGENETEN Bioinductive Implant

REGENETEN Bioinductive Implant (Smith & Nephew, Inc., Largo, FL) is a resorbable type I collagen matrix derived from highly purified bovine Achilles tendon. The REGENETEN Bioinductive Implant System (Smith & Nephew) is the new marketed name of the Rotation Medical Rotator Cuff System (Rotation Medical which was acquired by Smith & Nephew in October 2017). Rotation Medical Inc received FDA 510(k) approval (K140300) on March 24, 2014 for marketing the device with trade name: Collagen Tendon Sheet, common name: Tendon Protector, under the surgical mesh classification, class II device. A subsequent FDA 510(k) (K222501) was approved on May 11, 2023 for the Regeneten Bioinductive Implant for the same indication/intended use (FDA, 2023). The implant is proposed for the management and protection of tendon injuries in which there has been no substantial loss of tendon tissue (FDA, 2023; FDA, 2014). There is a nsufficient evidence in the peer reviewed published literature regarding the long-term outcomes, safety, and efficacy of Regeneten Bioinductive Implant in tendon repair to support the effectiveness of this product.

Ruiz Ibán et al. (2023) conducted a randomized controlled trial (RCT) (n=124) to evaluate the healing rate of the addition of a bioinductive collagen implant (BCI) compared to no implant in rotator cuff repair. Patients were randomized to either arthroscopic posterosuperior rotator cuff tear transosseous equivalent (TOE) repair performed alone (Control group – n=62) or with BCI applied over the TOE repair (BCI group – n=60). The primary outcome was the retear rate (defined as Sugaya 4-5) determined by MRI at 12 months of follow-up (n=122). Study results demonstrated a reduced retear rate (8.3% [5/60] in the BCI group vs 25.8% [16/62] in the Control group, (p=0.010); relative risk of retear of 0.32 [95% confidence interval 0.13-0.83]). Sugaya grade was also better in the BCI group (p=0.030). There were complications in 10 subjects, five having major complications. A total of two subjects (one from each group,1.6% of total) had postoperative deep infections requiring surgical debridement (the BCI implant was left in place in the BCI case), and prolonged antibiotic treatment. At 12-months there were no

differences between groups other clinical outcomes or in complication rates. Additional well-designed RCTs are needed to establish the role of this bioinductive collagen implant (i.e., Regeneten) in the treatment of rotator cuff repair.

Renuva® Allograft Adipose Matrix
Renuva® Allograft Adipose Matrix (MTF Biologics, Edison, NJ) is an injectable allograft adipose matrix processed from human adipose tissue. According to the manufacturer's Instructions for Use, it is proposed for the replacement of damaged or inadequate integumental adipose tissue matrix in areas of the body where native fat would exist and for the reinforcement or supplemental support in underlying adipose tissue matrix as the result of damage or naturally occurring defects (MTF Biologics, 2024). Renuva Allograft Adipose Matrix is regulated by the FDA under 21 CFR Part 1271 Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps). It is available in 1.5cc and 3cc. Evidence in the published peer-reviewed literature consists of an observational study (Gold, et al., 2020) and is insufficient to support the clinical effectiveness of Renuva Allograft Adipose Matrix for any indication.

Repliform ™
Repliform Tissue Regeneration Matrix (Boston Scientific, Marlborough, MA) is a non-crosslinked acellular human dermal allograft. Repliform Matrix is regulated by the US Food and Drug Administration (FDA) as human tissue for transplantation. All tissue is processed and provided in accordance with the FDA's requirements for banked human tissue (21 CFR Part 1271) and Standards for Tissue Banking of the American Association of Tissue Banks (AATB). Repliform is proposed for the repair or replacement of damaged or inadequate integumental tissue as in the treatment of urinary incontinence, to repair enteroceles, rectoceles and/or cystoceles and for pelvic floor reinforcement or other conditions resulting from inadequate or damaged integumental tissue. The graft is available in seven sizes ranging from 2x4 cm to 6x12 cm. There is insufficient evidence to support the clinical effectiveness of Repliform. Studies are primarily in the form of retrospective reviews and case series with short-term follow-ups investigating Repliform for rectocele repair and transvaginal slings for stress urinary incontinence (Marinkovic, et al., 2016; Crivellaro, et al., 2004). Randomized controlled trials comparing Repliform to standard therapy used in these procedures are needed to further evaluate the safety, efficacy, long-term outcomes and complications of this matrix.

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. One randomized controlled trial (Bryant et al., 2016) concluded that it is unlikely that the use of SIS with a standard rotator cuff repair offers better outcomes for patient with a moderate to large rotator cuff tear than surgery without SIS.

Bryant et al. (2016) conducted a pilot randomized controlled trial (n=62) to compare the effectiveness of rotator cuff repair with (n=34) and without (n=28) the use of a porcine small intestine submucosa (SIS) for patients with moderate to large rotator cuff tears. For patients randomized to receive the SIS, a Restore Orthobiologic Implant was extended over the repaired rotator cuff tendon and the tuberosity to which the tendon was attached and then sutured in place. The primary outcome was whether or not the patient had failed the procedure. Patients underwent standardized magnetic resonance arthrography (MRA) of the rotator cuff one year

postoperatively to determine whether the defect had healed and, if it had not healed completely, whether the remaining full-thickness defect had increased by > 5 mm in any dimension from the immediate postoperative appearance. If such a defect was detected, the repair was classified as having failed. Secondary outcomes included pain, range of motion and quality of life. At the one-year follow-up the overall rate of failure was just under 60%. There was no significant difference in the absolute risk of failure between the two groups (p=0.33) or for any of the patient-reported outcomes at one year. Differences between groups in self-reported outcomes were consistently in favor of the control group, but the difference was small. There was no statistically significant difference (p=0.50) between groups in the number of days to being narcotic and pain free. From the SIS group, one patient experienced a deep infection six weeks postoperatively that required surgical washout and one patient experienced a rupture of the biceps tendon 12 months postoperatively that required surgical repair. Two patients experienced transient slight fever and warmth around the wound at week six. In the control group, one patient required a revision at 18 months; one required a manipulation of the shoulder joint at 3 and 12 months postoperatively and one patient had a superficial wound infection. Limitations of the study include: small patient population; number of patients lost to follow-up (n=7), six patients did not undergo preoperative MRI; six patients did not undergo postoperative MRA; variety of tear sizes, muscle atrophy, fatty infiltration, and reparability (i.e., medialization or remaining defect); and the short-term follow-up. Additional data with large populations and long-term follow-ups are needed to establish the clinical utility of Restore Orthobiologic Implant for this indication. The authors concluded that it is unlikely that the use of SIS with a standard rotator cuff repair will offer superior outcomes to patient with a moderate to large rotator cuff tear.

Restorigin™
Restorigin Amniotic Fluid Therapy (AFT) (Parametrics Medical, Leander, TX) is processed in accordance with the United States Food and Drug Administration (FDA) and the American Association of Tissue Banks (AATB) standards. Restorigin Amniotic Fluid is a multipurpose, frozen allograft derived from amniotic fluid and contains growth factors and cytokines. The amniotic fluid is proposed to enhance healing when injected at the site of injury. The allograft is comprised of amnion and chorion layers and is proposed to provide wound protection and reduce inflammation and scarring. Restorigin Amniotic Fluid Therapy (AFT) is applied directly at the site of injury, inflammation and pain. Available sizes include 0.25 ml, 0.5 ml, 1.0 ml and 2.0 ml. There is insufficient evidence in the published peer-reviewed literature to support the safety and effectiveness of the Restorigin products.

Revita
Revita (StimLabs, LLC., Roswell, GA) is a human placental membrane allograft containing hyaluronic acid, collagen, growth factors, glycosaminoglycans and proteoglycans. The Clearify™ processing method is used to preserves all three layers of the amniotic membrane. Clinical applications are proposed for wound care, orthopedic and spinal conditions, urology, plastic and general surgery, OB/GYN, ophthalmology and dental conditions. The product is freeze dried and comes in seven sizes from 2x2 cm to 6x8 cm (StimLabs, 2023; CMS, 2017). Data supporting the safety and effectiveness of Revita are lacking.

RX Flow and RX Membrane
RX Membrane (Skye® Biologics, Inc., Redondo Beach, CA) is a sterile human tissue allograft proposed for surgical use to cover and protect a tissue. The membrane adheres to the patient's tissue and does not require suturing. RX membrane is dehydrated using the Sky Biologics' HydraTek® Process. The tissues are collected, processed, stored and distributed in compliance with FDA regulations governing Human Cells, Tissues, and Cellular or Tissue-Based Products. Five sizes are available from 2x2 cm to 4x8 mm. Rx Membrane 45 is a thinner graft with a thickness of 45 microns and RX 200 is the thicker graft of 200 microns.

RX Flow is a flowable graft of placental connective tissue matrix indicated for surgical use to supplement or replace damaged or inadequate connective tissue. The graft is available at room temperature and cryopreserved preparations in 0.5 cc, 1.0 cc, 1.5 cc and 2.0 cc vials.

There is insufficient evidence in the published peer-reviewed literature to support the safety and effectiveness of RX Membrane and RX Flow.

Seamguard® Staple Line Reinforcement Material
Seamguard Staple Line Reinforcement Material (Gore Medical, 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 Medical, 2024; 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.

SERI™ Surgical Scaffold
SERI Surgical Scaffold (Sofregen Medical Inc., Medford, MA; formerly, Allergan, Medford, MA) is a knitted, multi-filament, bioengineered, long-term bioresorbable scaffold derived from silk that has been BIOSILK™ purified to yield ultra-pure fibroin (Sofregen, 2022). The device is described as a mechanically strong and biocompatible bioprotein. The 510 (k) FDA indications for use state, "SERI Surgical Scaffold is indicated for use as a transitory scaffold for soft tissue support and repair to reinforce deficiencies where weakness or voids exist that require the addition of material to obtain the desired surgical outcome, including, reinforcement of soft tissue in plastic and reconstructive surgery and general soft tissue reconstruction" (Jewell, et al., 2015; FDA, 2013). There is insufficient evidence in the published peer-reviewed scientific literature supporting the efficacy of SERI Surgical Scaffold for any indication. Studies are primarily in the form of retrospective reviews. Per the manufacturer, "As of December 31, 2021, SERI Surgical Scaffold is no longer commercially available" (Sofregen, 2022).

SimpliDerm™
SimpliDerm™ (Elutia formerly Aziyo Biologics, Silver Spring, MD) is a pre-hydrated human acellular dermal matrix minimally processed to remove epidermal and dermal cells and then preserved in an irradiation protection solution. The process utilizes a proprietary and patented technology to preserve the remaining bioactive components and extracellular matrix of the dermis. It is proposed for the repair or replacement of damaged or insufficient integumental tissue and for the repair, reinforcement, or supplemental support of soft tissue defects or any other homologous use of human integument (Elutia, 2024). The product is classified as a human tissue and cell-based product regulated by the American Association of Tissue Banks (AATB) and in compliance with U.S. FDA regulations (21 CFR 1271). It is available in both Ellipse™ and rectangular sizes. There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of Simpliderm (Hydrated Acellular Dermal Matrix) for any indication.

SJM™ Pericardial Patch with EnCap™ AC Technology

SJM is a glutaraldehyde bovine pericardial patch (Glycar, Inc., Dallas, TX) with anti-calcification treatment that is proposed to enhance tissue healing and long-term tissue stability. The product was FDA approved under the trade name "glycar pericardial patch" as a 510(k) Class III device. The intended uses includes: pericardial closure, peripheral vascular reconstruction and repair, and cardiac and great vessel reconstruction and repair. Cardiac and vascular repairs may include annular reconstruction, endocarditis leaflet repairs, septal defect repairs, and aortic root enlargement. The patch is provided in four sizes (2x5 cm, 4x5 cm, 5x10 cm, 9x14 cm). Per the manufacturer, "there is no clinical data currently available that evaluates the long-term impact of anticalcification tissue treatment in humans" (St. Jude Medical, 2024; FDA 1997). Published clinical trials supporting the safety and effectiveness of SJM are lacking.

SomaGen® Meshed Tissue
SomaGen® Meshed Tissue (MTF Biologics, Edison, NJ) is an acellular human reticular dermal allograft that is processed in accordance with FDA regulations and AATB standards. It is proposed to be used as a wound care scaffold for the replacement of damaged or inadequate integumental tissue for a variety of large and complex wounds such as diabetic foot ulcers, venous leg ulcers, pressure ulcers, or for other homologous use. The product is available in the following sizes: 8cm x 9cm, 10.5cm x 13.5cm, 13cm x 17cm, and 17cm x 28cm (MTF Biologics, 2024). Evidence is lacking in the published peer-reviewed literature to support the clinical effectiveness of SomaGen Meshed Tissue for any indication.

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 (DJO, LLC, Lewisville, 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 (Allergan™, Parsippany, NJ [formerly LifeCell™ Corporation, Branchburg, NJ]), a surgical mesh, 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" (Allergan, 2022; FDA, 2007). The Matrix is also available in a

perforated form. There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Strattice for any indication.

Breast reconstruction: Life Cell Corporation has proposed Strattice for use during postmastectomy breast reconstruction to support medial repair for breast pocket size and position. In June 2015 the FDA issued a warning letter to LifeCell Corporation stating that the FDA approval for Strattice did not include the use of Strattice for breast reconstruction. Per the FDA, this indication falls outside of the intended use "because surgical mesh has not been cleared or approved for use in breast reconstructive surgery applications". The FDA requested that Life Cell "immediately cease activities that result in the misbranding or adulteration of the Strattice Reconstructive Tissue Matrix" for breast reconstruction.

Abdominal Wall Defect: Zerbib et al. (2015) conducted a prospective study (n=18) to evaluate the long-term outcomes of Strattice when used as a reinforcement for infected, abdominal wall defects. Subjects had an abdominal wall defect with enterocutaneous fistula or infected prosthetic mesh, considered to be grade IV. The primary outcome measure was the hernia recurrence rate. Follow-ups ranged from 3–22 months (median, 13 months). Length of hospitalizations ranged from 4–56 days (median, 13 days). Fourteen patients were evaluated. Postoperative complications included skin dehiscence (n=3), wound infection (n=2), skin necrosis (n=1), and seroma (n=2). At the last follow-up, six patients (43 %) experienced abdominal wall defect recurrence, three mesh infections and three enterocutaneous fistula patients. After 13 months of follow-up, 57% of patients had a clean and solid abdominal wall. No mesh exposition was observed and no Strattice removals were performed. Limitations of the study include the small patient population, short-term follow-ups, patients lost to follow-up and lack of a comparator.

Abdominal Wall Ostomy: 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).

Hernia Repair: Bellows et al. (2014) conducted a randomized controlled trial to evaluate the safety and efficacy of Strattice (n=84) vs. UltraPro (Ethicon, Semerville, NJ) (n=88) when used in a Lichtenstein's tension-free hernioplasty. Ultrapor is a lightweight, partially abosorbable, polypropylene mesh. Subjects were adult males, age ≥ 18 years, with a primary, unilateral, non-emergent inguinal hernia. The hernia types were indirect (54 %), direct (31 %), pantaloon (14 %), and other (1 %). Data reported herein are the three months follow-up results of an ongoing 24-month study. The primary endpoint is resumption of activities of daily living (ADL) at the one-year follow-up. Secondary outcome measures include long-term pain (persistent groin pain or discomfort affecting ADLs for more than three months postoperatively), postoperative complications, and incidence of recurrence. The average mesh size was significantly larger in the Ultrapro group (p=0.002). The mean surgical time was significantly less in the Ultrapro group (p=0.02). There were no significant differences between the two groups in duration of hospitalization. Six patients in the UltraPro group vs. three in the Strattice group had an overnight stay. At the three-month follow–up, there were no statistically significant differences in the occurrence or type of wound complications (p=0.069), restrictions of ADL, postoperative groin

pain (p=0.25), and C-reactive protein level. There was significantly less pain reported in the first three postoperative days in the Strattice group (p<0.05) and no hernia recurrences. However after the first three days there was no reported advantage of Strattice in terms of chronic pain. There was no advantage to using Strattice over the synthetic mesh. Limitations of the study include the short-term follow-up, heterogeneity of hernia types and absence of female patients.

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.

Stravix™
Stravix (Osiris Therapeutics, Inc., Columbia, MD, a subsidiary of Smith and Nephew, Andover, MA) is a cryopreserved human placental tissue comprised of umbilical amnion and Wharton's jelly, a gelatinous substance within the umbilical cord. Stravix retains the extracellular matrix, growth factors, and endogenous neonatal mesenchymal stem cells, fibroblasts, and epithelial cells. The product is proposed as a surgical covering or wrap for damaged or inadequate integumental tissue. The matrix is available in 2x4 cm and 3x6 cm sizes (Smith and Nephew, 2024). There is insufficient evidence to support the safety and effectiveness of Stravix.

SurGraft® FT/SurGraft® TL/ SurGraft® XT
SurGraft (Surgenex®, LLC, Scottsdale AZ) Allograft Membranes are dehydrated, terminally irradiated amnion derived membranes that are available in multiple configuarations and sizes. SurGraft is a single layer, SurGRaft XT is a dual layer, and Surgraft TL is a triple layer amnion derived allograft (Surgenex, 2023). SurGraft FT is a full thickness dehydrated amniotic and chorionic tissue allograft derived from donated human amniotic and chorionic membrane. Each product is proposed for the treatment of non-healing wounds and burn injuries. SurGraft Allograft Membranes are proposed for use in patients with acute or chronic wounds, including chronic, non-infected, diabetic foot ulcers; chronic, non-infected, partial or full-thickness diabetic foot skin ulcers (due to venous insufficiency); pressure ulcers; and surgical wounds and burns which have not adequately responded to conventional therapy." Data supporting the clinical effectiveness of SurGraft Allograft Membranes are lacking.

SurgiMend®
SurgiMend or SurgiMend Collagen Matrix (TEI Biosciences Inc. Boston, MA; acquired by LifeSciences Corp., Plainsboro, NJ) 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 Collagen Matrix is available in 1.0, 2.0, 3.0 4.0 mm thicknesses and multiple sizes up to 25x40 cm. SurgiMend-e is a collagen matrix specifically designed for application in ventral hernia repair and is available in 3 mm and 4 mm thicknesses and one size, 10x25X3 mm. SurgiMend PRS, a pure collagen product, is designed for plastic and reconstructive surgery and is available in multiple shapes, sizes and thicknesses (Integra LifeSciences Corp, 2023; Butterfield, et al., 2013, Gaster, et al., 2013, Ohkuma, et al., 2013; Endress, et al., 2012; Craft, et al., 2011; Cromwell, et al., 2009).

Historically, TEI has marketed SurgiMend for breast reconstruction. In May 2015, the FDA issued TEI a warning letter stating that TEI did not have FDA clearance or approval to market SurgiMend for breast reconstruction. Per the FDA, this indication falls outside of the intended use "because surgical mesh has not been cleared or approved for use in breast reconstructive surgery applications". The FDA requested that TEI "immediately cease activities that result in the misbranding or adulteration of SurgiMend" for breast reconstruction (FDA, 2015).

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). Althought not FDA approved for breast reconstruction, some studies have evaluated SurgiMend for this indication (Wazir, 2022). There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of SurgiMend for all indications.

Symbotex™ Composite Mesh
Symbotex Composite Mesh (Medtronic Inc., Minneapolis, MN; formerly Covidien LLC.) is made out of a three-dimensional monofilament polyester textile covered with a hydrophilic film on one side. The film is composed of a porcine collagen and glucerol. The FDA 510(k) approval is for use of the product as soft tissue reinforcement where weakness exists such as repair of the primary abdominal wall and incisional hernias. Symbotex is available in multiple sizes (Medtronic, 2024; FDA, 2013). There is insufficient evidence to support the safety and efficacy of Symbotex.

SYNTHECEL™ Dura Repair
SYNTHECEL Dura Repair (DePuy Synthes, West Chester, PA) SYNTHECEL™ Dura Repair is composed of biosynthesized cellulose and water and constructed of non-woven, interconnected cellulose fibers. It is proposed to function as a mechanical layer which protects and repairs the dural defect while preventing further CSF leakage. It is non-resorbable. SYNTHECEL Dura Repair is intended for use as a dura replacement for the repair of dura mater in adults. SYNTHECEL Dura Repair received FDA 510(k) approval on Dec 16, 2013 (K131792). It is available in the following sizes: 1in x 1in (2.5cm x 2.5cm), 1in x 3in (2.5cm x 7.5cm), 2in x 2in (5.0cm x 5.0cm), 3in x 3in (7.5cm x 7.5cm), 4in x 5in (10.0cm x 12.0cm) (DePuy Synthes, 2024; FDA, 2013). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of this product.

tarSys™
tarSys (IOP Inc., Costa Mesa CA), also called Surgisis Ocular Graft, is a porcine small intestinal submucosa (SIS). The graft is FDA 510(k) approved for "implantation to reinforce and support the reconstruction of the soft tissue of the eyelid Studies are primarily in the form of case reports and retrospective reviews of 2-37 patients (Liao and Wei, 2013; FDA, 2005). There is insufficient evidence to support tarSys for eyelid reconstruction.

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 (Integra LifeSciences, 2024). 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". There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of Tenoglide.

TEXAGEN™ Amniotic Membrane Allograft
TEXAGEN™ Amniotic Membrane Allograft (Sanara MedTech Inc., Fort Worth, TX) is a semi-transparent, collagenous membrane derived from the amnion and chorion layers of the amniotic sac. It is proposed for use as a soft tissue barrier and wound covering. The product is classified as a human tissue and cell-based product regulated by the American Association of Tissue Banks (AATB) and in compliance with U.S. FDA regulations (21 CFR 1271) (Sanara MedTech, 2024. There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of TEXAGEN Amniotic Membrane Allograft for any indication.

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 (Tornier, 2024). 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 (FDA, 2012). There is insufficient evidence supporting the safety and efficacy of the Tornier BioFiber Scaffolds.

Tutopatch® Bovine Pericardium
Tutopatch Bovine Pericardium (RTI Surgical, Inc., Alachua, FL) is a solvent-dehydrated gamma irradiated bovine pericardium mesh consisting of collagenous connective tissue with multidirectional fibers (RTI Surgical Inc., 2024). The product is FDA 510(k) approved as a Class II surgical mesh indicated for the reinforcement of tissue during general and plastic surgery repair. It is intended for use "to reinforce soft tissue where weakness exists in general and plastic surgery applications and is indicated for pericardial structures and for use as a prosthesis for the surgical repair of soft tissue deficiencies which includes: gastric banding, muscle flap reinforcement, repair of rectal prolapse using an abdominal approach (excluding rectocele), reconstruction of the pelvic floor using an abdominal approach (excluding transvaginal repair of pelvic organ prolapse), and hernias (including diaphragmatic, femoral, incisional, inguinal, lumbar, paracolostomy, ventral, scrotal, and umbilical)". The mesh is available in 6x8 cm, 6x18 cm, 8x11 cm, 8x14 cm, 8x16 cm, 8x18 cm, 10x12.5 cm, 10x16 cm, 12x12 cm, 12x16 cm, and 14x20 cm. sizes. The product is also

available in an oval fenestrated mesh design, Tutomesh® Fenestrated Bovine Pericardium available in 10x16 cm and 13x22 cm. (FDA, 2012). There is insufficient evidence in the published peer-reviewed literature supporting the safety and effectiveness of Tutoplast and Tutomesh.

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.

VascuCel®
VascuCel® (LeMaitre Vascular, Inc., Burlington, MA) is a bovine pericardial patch prepared from glutaraldehyde-crosslinked bovine pericardium using the ADAPT® TEP technology. VascuCel is proposed for use as a patch in great vessel repair, peripheral vascular reconstruction and suture line buttressing. VascuCel received FDA 510(k) (K162579) approval on Oct 14, 2016. The predicate device in CardioCel. There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of VascuCel for any indication. Articles are in the form of animal studies, case series and retrospective reviews for the predicate device.

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. In September 2016, the FDA notified health care providers that the Vascu-Guard patch may not be performing as intended. Based on reported adverse events, the FDA stated that intraoperative or postoperative bleeding and hematomas, some of which required additional clinical intervention, and three patient deaths may have been related to use of the matrix. The events occurred shortly after carotid endarterectomy (CEA) surgery (FDA, 2016).

Vascu-Guard may be sutured, clipped, or stapled to the edge of the host tissue or vessel. The patches come in four different sizes. 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.

VersaShield™
VersaShield (Orthofix® International, Lewisville, TX) is a human placental amniotic membrane proposed for the treatment of interior or exterior wounds (including covering surgical sites) or as a soft tissue covering or a protective barrier. The dehydrated allograft contains an amnion and chorion layer, as well as four different extracellular matrix proteins and numerous growth factors. VeraShield is regulated by the FDA as a Human Cellular and Tissue Product and processed by the Musculoskeletal Transplant Foundation (MTF). The membrane is available in five sizes (2x2 cm, 4x4 cm, 4x6 cm, 3x4 cm, 3x8 cm) (Orthofix, 2024). There is insufficient evidence in the published clinical trials to support the efficacy of VeraShield for any indication.

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. According to Stamou et al. (2011) PSD is a nonabsorbable 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.

ViaFlow™/ViaFlow™ C
ViaFlow Placental Tissue Matrix and ViaFlow C Flowable Placental Tissue Matrix (Wright® Medical Group, Memphis, TN) are premixed, flowable, tissue matrix allografts made from human placental tissues. Vialfow is proposed for homologous use to supplement or replace damaged or inadequate connective tissues. The matrix is injected into the target using a 23G needle. The two available configurations are ambient temperature (ViaFlow) and cryopreserved (ViaFlow C). A third prodcuts is the ViaFlow Flowable Placental Tissue Matrix which is available in 1.0 cc and 2.0 cc and ViaFlow C is available in 1.0 cc. All tissues are collected, processed, stored, and distributed in compliance with FDA regulations governing HCT/Ps (Wright Medical Group N.V., 2020). There is insufficient evidence available to make informed decisions regarding either safety or clinical effectiveness of ViaFlow and ViaFlow C.

VIAGENEX™ Max Umbilical Cord Membrane and VIAGENEX™ Matrix Amnion Allograft
VIAGENEX™ Max Umbilical Cord Membrane and VIAGENEX™ Matrix Amnion Allograft (Vivex Biologics, Atlanta, GA) are a family of amniotic allografts. The products are proposed for use as a soft tissue barrier and wound covering. The products are processed in accordance with the FDA regulations for tissues and biologics and the American Association of Tissue Banks (AATB) standards (Vivex Biologics, 2024). VIAGENEX products are available in multiple sizes. There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of VIAGENEX products for any indication.

WoundEx® Membrane and WoundEx® Flow
WoundEx Membrane (Skye Biologics, Inc. Redondo Beach, CA) is a dehydrated amniotic membrane proposed as a wound covering for chronic and acute wounds. It can be applied dry or pre-moistened and does not require sutures or fixation. The product is regulated by the FDA under the Human Cells, Tissues, and Cellular or Tissue-Based Products regulations and is obtained from a AATB accredited tissue bank. WoundEx is available in four sizes (1x1 cm, 2x2 cm, 2x4 cm, 4x4 cm, 4x6 cm) (Sky Biologics, 2024). WoundEx Flow is a placental connective tissue matrix in flowable form proposed to replace or supplement damaged or inadequate integumental tissue. The liquid contains the complete placental tissue matrix with growth factors and collagen scaffold. The flowable product is available in 0.5 cc and 1.0 cc sizes. Published studies supporting the safety and effectiveness of these products are primarily in the form of retrospective reviews with small patient populations (n=20) (Lullove ET, 2017).

Xceed™
Xceed Purified Amniotic Fluid (Alaris Biologic Technologies, Inc. formerly AmnioLife Corporation, Gainesville, FL) is described as a non-structural acellular purified amniotic fluid intended for use in covering defects in soft tissue or bone. The product is processed using a propriety purification technology which removes all cells but retains cytokines and growth factors. Xceed is proposed for use for the treatment of tendonitis, gingival defects, reduction of scarring, chronic wound covering, soft tissue or bone trauma and treatment of localized inflammation Product sizes include 0.5 ml, 1.0 ml and 2.0 ml vials. Alaris Biologic Technologies, Inc. is currently inactive. There is a lack of evidence in the published peer reviewed literature to support the use of Xceed Purified Amniotic Fluid for any indication.

XCellerate™
XCellerate™ (Precise Bioscience, Hinsdale IL) is a lyophilized amniotic membrane allograft proposed for the treatment of non-healing wounds and burn injuries (Precise Bioscience, 2024). XCellerate is a human cellular and tissue-based product. XCellerate is provided in the following sizes: 2x2 cm, 2x4 cm, 4x4 cm, 4x7 cm and 6 mm, 9 mm, 12 mm discs (CMS, 2020). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of XCellerate for any indication.

XCelliStem® Wound Powder
XCelliStem® Wound Powder (Stemsys® Bio, Sunrise, FL) is an extracellular matrix composed of porcine collagen that is designed to break down rapidly after application to the wound site to promote host site remodeling and regeneration (Stemsys Bio, 2023). It is proposed for the management of wounds including: partial and full-thickness wounds, pressure ulcers, diabetic ulcers, venous 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, and skin tears), and draining wounds. XCelliStem Wound Powder received FDA 510(k) (K172593) approval in 2018 (FDA, 2022). Evidence in the published peer-reviewed literature to support the clinical effectiveness of XCelliStem Wound Powder for any indication is lacking.

Xenform®
Xenform Soft Tissue Repair Matrix (TEI Biosciences Inc., Boston, MA), a bovine, acellular collagen matrix, is FDA 510(k) approved for "use as a soft tissue patch to reinforce soft tissue where weakness exists and for the surgical repair of damaged or ruptured soft tissue membranes. It is specifically indicated for the repair of colon, rectal, urethral, and vaginal prolapse; reconstruction of the pelvic floor; and procedures such as sacrocolposuspension and urethral sling" (FDA, 2006). It is available in 2x7 cm, 4x7 cm, 6x10 cm and 8x12 cm sizes. On April 16, 2019, the U.S. Food and Drug Administration (FDA) ordered manufacturers of surgical mesh intended for transvaginal repair of pelvic organ prolapse (POP) to stop selling and distributing these products. Boston

Scientific stopped global sales of its transvaginal mesh products indicated for pelvic organ prolapse: Xenform™ Soft Tissue Repair Matrix (Boston Scientific, 2019).

There is limited evidence primarily in the form of case series with small patient populations (n=28-45) and one year follow-ups to support the safety and efficacy of Xenform. Studies investigated Xenform for the treatment of cystocele and/or rectocele defects and Peyronie's disease (Caraceni, et al., 2016; Goldstein, et al., 2010). Goldstein et al. noted that this clinical trial was the first study to investigate XenForm for pelvic floor reconstruction among patients with pelvic organ prolapse.

XenMatrix™ Surgical Graft
XenMatrix (Becton, Dickinson and Company [BD], Franklin Lakes, NJ) 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 (BD, 2024; 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 Patch (formerly PeriPatch)
XenoSure Biologic 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, renal and tibial patching, profundaplasty, and arteriovenous access revisions (LeMaitre Vascular, 2024; FDA, 2004). There is insufficient evidence to support the safety and efficacy of Xenosure.

Zenith™ Amniotic Membrane
Zenith™ Amniotic Membrane (Legacy Medical Consultants, Houston, TX) is a dehydrated amniotic membrane allograft. It is proposed for use as a barrier and covering for acute and chronic non-healing wounds and burn injuries. It is regulated as a human cell, tissue, or cellular or tissue-based product (HCT/P) under Section 361 of the Public Health Service Act. Zenith Amniotic Membrane allograft is available in the following sizes: 1x1 cm, 2x2 cm, 2x3 cm, 4x4 cm, 4x6 cm, 4x8 cm, 8x8 cm, 10x10 cm, 10x12 cm, and 10x20 cm (Legacy Medical Consultants, 2023; CMS, 2021). There is insufficient evidence in the published peer-reviewed scientific literature to support the efficacy of Zenith Amniotic Membrane for all indications.

Literature Review – Systematic Reviews 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.

Amniotic Allografts for Use in Bariatric and Gynecological Procedures: Abstracts included a Cochrane review (Bosteels, et al., 2017) on anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility. Studies using human amniotic membrane grafting vs. no grafting were included. The authors concluded that the clinical effectiveness of anti-adhesion treatment for improving key reproductive outcomes or for decreasing intrauterine adhesions (IUAs) following operative hysteroscopy in subfertile women remained uncertain. A pilot randomized controlled trial (n=45) of women with severe adhesions allocated the women to one of three groups—insertion of intrauterine balloon only, fresh amnion graft or dried amnion graft. Outcomes were significantly better with amnion graft that intrauterine balloon alone (p=0.003) and outcomes were better with fresh amnion than with dried amnion (p=0.01). Additional studies with larger patient populations are needed to validate the effectiveness of amniotic graft for this indication. No evidence was found to support the use of amniotic membrane in bariatric surgery.

Dural Sealants: Kinaci et al. (2018) conducted a systematic review of the literature to evaluate the efficacy of dural sealants in preventing cerebrospinal fluid (CSF) leakage following cranial surgery. Studies describing regular cranial procedures combined with the use of any dural sealant reporting CSF leakage were included. The primary outcome measure was CSF leakage of any origin. Secondary outcomes were incidental leakage through the skin, pseudomeningocele formation (subcutaneous or epidural collection of CSF) and surgical-site infection. Twenty studies (n=3682 procedures) met inclusion criteria and were primarily in the form of retrospective reviews and case series. Ten comparative studies (n=2321), including three randomized controlled trials, comparing sealant vs no sealant were included in the meta-analysis. There was no significant difference between the two groups in CSF leakage. Meta-analyses for secondary outcomes showed no significant difference between the number of incisional CSF leakage or in the pseudomeningocele formation. Surgical-site infection was seen less in the sealant group than the control group. The number of patients with surgical-site infection in the sealant group was 10 of 1006 (1.0%) versus 60 of 1062 (5.6%) in the control group. Overall, adverse events were not reported and when they were, the direct relationship between sealant use and adverse event was not objectively confirmed. Author-noted limitations of this systematic review included: lack of randomized controlled trials; patients receiving rescue therapy in the control group with other types of sealants or grafts to obtain watertight closure were not excluded; high risk of bias in the comparative cohort studies; heterogeneity of the patient populations and sealants used; variation in the number of CSF leakages; and differentiation in leakage between supra- and infratentorial

craniotomies could not be made. The authors concluded that studies with greater methodologic quality, including randomized controlled trials are warranted.

Fibrin Sealants: Esposito et al. (2016) conducted a systematic review of the literature to investigate the safety and efficacy of fibrin sealants that are used as dural sealants to prevent and/or treat cerebrospinal fluid leaks. Thirty-two studies enrolled 2935 patients who were exposed to fibrin sealant. Seven studies that only included safety data were included and used for safety analysis. Three studies were randomized controlled trials. The remaining studies were prospective case series and retrospective reviews. The studies investigated fibrin glue for the treatment of acute intraoperative CSF leaks, prevention of postoperative CSF leaks, and treatment of persisting CSF leaks. Overall, few or no adverse events were reported in most of the studies. Limitations of the studies included: limited number of randomized controlled trials, heterogeneity in the definition of postoperative CSF leak; limited number of studies (n=2) that discussed fibrin sealants for persistent CSF leaks; variations in surgical technique; variety of fibrin glues that were used did not allow comparison of products; heterogeneity in patient populations (e.g., age, sex, race, medical condition); and variation in use of secondary treatments (i.e., medical therapies, interventional strategies). Due to the limitations of the studies, firm conclusions could not be made regarding the benefit of fibrin sealants. Well-designed and powered randomized clinical trials are needed to support the safety and establish the efficacy of these sealants.

Fistula Plugs: Nasseri et al. (2016) conducted a systematic review to evaluate the evidence on the efficacy of fistula plugs (AFPs) in treating fistula-in-ano in patients with Crohn's disease. Twelve studies met inclusion criteria. Eight were nonrandomized prospective and four were retrospective reviews. A total of 84 patients (n=1–20 per study), age 18–72 years (median 45 years) and follow-up of 3–24 months (median nine months) were included in the analysis. The total success rate (i.e., closure of the fistula tract) was achieved by 49/84 patients. Two out of five patients had success with recurrent fistula., The overall success rate with Surgisis was 48/80 and one out of four patients for Gore Bio-A. Five studies reported a recurrence rate of 13.6% (3/22 patients). The authors were unable to draw firm conclusions due to the limitations of the studies. The procedure appeared safe with little morbidity and low risk of incontinence. Limitations of the studies as noted by the authors included; heterogeneity of study design; small patient population; lack of statistical significance in outcomes; grouping of fistulas in Crohn's disease with other types of anal fistulas introducing ambiguity; short-term follow-up and heterogeneity of follow-up times; and various confounding factors (e.g., use of steroids or immunosuppresants, previous use of seton stitch to aid in healing and variation in surgical technique) and lack of reporting of these factors. The authors noted that the outcomes may have been worse if longer follow-ups had been reported and that it was unclear whether failure occurred as a result of technical error or owing to the pathology of the fistula despite use the correct surgical technique.

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 validate that grafts are effective in preventing Frey syndrome.

Hernia Repairs: Trippoli et al. (2018) conducted a systematic review of the literature to evaluate the differences in various biological products for the treatment of primary and incisional ventral hernias. Included studies met the following criteria: treatment of primary and incisional abdominal hernia; mesh derived from porcine dermis or porcine intestinal submucosa or bovine pericardium or bovine or fetal dermis; may or may not involve ''cross-linking of collagen''; end-point was 30-day follow-up of surgical site infection and/or relapse rate after follow-up of at least 12 months. The five available biological meshes of porcine derivative available in the market at the time of the analysis were Strattice, Permacol, Fortiva, Surgisis, and Xenmatrix. The four available bovine meshes were Peri-guard, Veritas, Bioripar and Tutomesh. Eleven trials that evaluated five meshes met inclusion criteria. Nine studies were single-arm (prospective or retrospective), and two studies were based on a comparative design. The meshes included in the studies were: Permacol (n=706), Strattice (n=324), Surgisis (n=44), Tutomesh (n=38) and Xenmatrix (n=22). No published studies were found investigating Fortiva, Veritas, Bioripar and Tutomesh. Among all comparisons carried out within these biological meshes, one significant difference was found. Permacol (a crosslinked mesh) showed a lower recurrence rate at 12 months than Strattice (a non-cross-linked mesh) ($p=0.001$), suggesting that crosslinking may strengthen a mesh. Overall the studies generally showed a poor methodological quality. There was wide variability in the surgical wound infections between studies and the 12-month relapse rates (n=4 studies). Additional author-noted limitations of the studies included the limited available clinical information, small patient populations, short-term follow-ups, and uncontrolled study designs. Other limitations are the heterogeneity of the wound types and retrospective study designs. In conclusion, there is insufficient evidence in the published literature to support the use of biological mesh for hernia repair. Data do not indicate if a porcine vs. bovine or cross-linked vs non-crosslinked mesh should be used. Patient selection criteria have not been established.

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, and 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 dermal 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 report was found for Allomax, FlexHD, FortaGen, Peri-Guard, SurgiMend and Tutopatch.

Hyaluronic Acid: Shaharudin et al. (2016) conducted a systematic review to assess the evidence on the effectiveness of hyaluronic acid (HA) compared to placebo or other agents for promoting chronic wound healing. Nine randomized controlled trials (n=865) met inclusion criteria. The authors noted that there was better quality of evidence for mixed arterial and venous ulcers than for venous leg ulcers and diabetic foot ulcers. Overall, the studies provided little evidence regarding the claimed effects of HA for this indication. Some mixed evidence suggested that HA reduced the intensity of pain for mixed arterial and venous ulcers. There is insufficient evidence to support the use of HA for the treatment of chronic wound healing.

Laryngotracheal and Pharyngeal Reconstruction: Hui et al. (2017) conducted a systematic review to evaluate the safety and efficacy of acellular dermal matrices in laryngotracheal and pharyngeal reconstruction. Eleven studies (n=170) including three retrospective review, five case series and three case reports met inclusion criteria. Eight studies reported on ADM use in oncological reconstruction. Seven studies used AlloDerm, three studies used Heal-All Oral Biofilm (Zhenghai Biotech, Yantai, China) and one case report used Permacol. Follow-ups varied from two weeks to 42 months. The methodology of the studies was poor. Other limitations included the small patient populations, and heterogeneity of surgical procedures and diagnosis. Overall, the studies provided incomplete descriptive detail concerning peri-operative radiation dosing and scheduling, the surgeon's experience using dermal grafts, graft thickness, and defect size. The authors stated that due to the limited number and heterogeneity of the cases, conclusions could not be made regarding the impact of acellular dermal matrix use on post-operative stricture and stenosis rates in tracheal or pharyngeal reconstruction.

Orthopedic Sports Medicine: Riboh et al. (2016) conducted a systematic review of the literature to assess the evidence for amniotic membrane products used in orthopedic sports medicine. Eighty articles were considered relevant to the study. Fifty-five of the articles were narrative and 25 articles described preclinical and clinical trials of amniotic products for orthopedic sports medicine. The primary indications being explored included: cartilage restoration, ligament and tendon healing, nonoperative treatment of knee osteoarthritis, and plantar fasciitis. Due to the low quality of the studies, a systematic review summary and meta-analysis for the use of these products for this indication could not be conducted. According to the authors the current body of evidence in is heavily biased toward in vitro and animal studies, with little to no human clinical data.

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, Surgisis, 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.

Professional Societies/Organizations
American Society of Colon and Rectal Surgeons
In 2016, the American Society of Colon and Rectal Surgeons published clinical practice guidelines for the management of anorectal abscess, fistula-in-ano, and rectovaginal fistula (Vogel, et al). The guidelines states that the fistula plug is a relatively ineffective treatment for fistula-in-ano. The guidelines did not include the use of collagen plug for rectvaginal fistulas as they state the success of of this intervention has proven to be prohibitively poor.

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."

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Porcine Skin and Gradient Pressure Dressings (270.5)	Longstanding, no date
LCD	CGS Administrators	Wound Application of Cellular and/or Tissue Based Products (CTPs), Lower Extremities (L36690)	9/01/2022
LCD	First Coast Service Options	Application of Skin Substitute Grafts for Treatment of DFU and VLU of Lower Extremities (L36377)	1/08/2019

	Contractor	Determination Name/Number	Revision Effective Date
LCD	Novitas	Application of Bioengineered Skin Substitutes to Lower Extremity Chronic Non-Healing Wounds (L35041)	9/26/2019

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare and Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered Tissue Engineered Skin Substitutes Application and Product Codes

Considered Medically Necessary when criteria in the applicable policy statement listed above are met and when used to report the application and/or the product of a covered skin substitute:

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

CPT®* Codes	Description
	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)

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)

HCPCS Codes	Description
A2012	Suprathel, per square centimeter
A4649	Surgical supply; miscellaneous
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)

HCPCS Codes	Description
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
C9399	Unclassified drugs or biologicals
Q4100	Skin substitute, not otherwise specified
Q4101	Apligraf, per square centimeter
Q4102	Oasis Wound Matrix, per square centimeter
Q4104	Integra Bilayer Matrix wound dressing (BMWD), per square centimeter
Q4105	Integra Dermal Regeneration Template (DRT), per square centimeter or Integra omnigraft dermal regeneration matrix, per square centimeter.
Q4106	Dermagraft, per square centimeter
Q4107	Graftjacket, per square centimeter
Q4108	Integra Matrix, per square centimeter
Q4110	Primatrix, per square centimeter
Q4116	Alloderm, per square centimeter
Q4121	TheraSkin, per square centimeter
Q4122	Dermacell, Dermacell AWM or Dermacell AWM Porous, square centimeter
Q4124	Oasis Ultra Tri-layer Wound Matrix, per square centimeter
Q4128†	FlexHD, allopatch HD, per square centimeter
Q4132	Grafix core and GrafixPL core, per square centimeter
Q4133	Grafix prime and GrafixPL prime, stravix and stravixpl, per square centimeter
Q4151	Amnioband or Guardian, per sq cm
Q4168	AmnioBand, 1 mg
Q4182	Transcyte, per sq cm
Q4186	Epifix, per square centimeter
Q4203	Derma-gide, per square centimeter

†Note: Considered Experimental/Investigational/Unproven when used to report Allopatch HD

Not Covered Tissue Engineered Skin Substitutes Application and Product Codes

Considered Not Medically Necessary when used to report a tissue-engineered skin substitute not covered in the policy statement above:

CPT®* Codes	Description
C1781	Mesh (implantable)
C9399	Unclassified drugs or biologics
Q4100	Skin substitute, not otherwise specified

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

CPT®* Codes	Description
15778	Implantation of absorbable mesh or other prosthesis for delayed closure of defect(s) (i.e., external genitalia, perineum, abdominal wall) due to soft tissue infection or trauma
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue
46707	Repair of anorectal fistula with plug (eg: porcine small intestine submucosa [SIS])
64910	Nerve repair; with synthetic conduit or vein allograft (eg, nerve tube), each nerve
64912	Nerve repair; with nerve allograft, each nerve, first strand (cable)
64913	Nerve repair; with nerve allograft, each additional strand (List separately in addition to code for primary procedure)
64999	Unlisted procedure, nervous system

HCPCS Codes	Description
A2004	Xcellistem, 1mg
A2005	Microlyte matrix, per square centimeter
A2019	Kerecis omega3 marigen shield, per square centimeter
A2020	Ac5 advanced wound system (ac5)
A2021	Neomatrix, per square centimeter
A6010	Collagen based wound filler, dry form, sterile, per gram of collagen
C1762	Connective tissue, human (includes fascia lata)
C1763	Connective tissue, nonhuman (includes synthetic)
C1768	Graft, vascular
C1832	Autograft suspension, including cell processing and application, and all system components
C9352	Microporous collagen implantable tube (NeuraGen Nerve Guide), per centimeter length
C9353	Microporous collagen implantable slit tube (NeuraWrap Nerve Protector), per centimeter length
C9354	Acellular pericardial tissue matrix of nonhuman origin (Veritas), per square centimeter
C9355	Collagen nerve cuff (NeuroMatrix), per 0.5 centimeter length
C9356	Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per square centimeter
C9358	Dermal substitute, native, nondenatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeter
C9360	Dermal substitute, native, nondenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeter
C9361	Collagen nerve cuff (NeuroMend Collagen Nerve Wrap), per 0.5 centimeter length
C9364	Porcine implant, Permacol, per square centimeter
J3590	Unclassified biologics

HCPCS Codes	Description
Q4103	Oasis burn matrix, per square centimeter
Q4113	Graftjacket Xpress, injectable, 1cc
Q4114	Integra Flowable Wound Matrix, injectable, 1cc
Q4118	MatriStem micromatrix, 1 mg
Q4125	Arthroflex, per square centimeter
Q4126	Memoderm, dermaspan, tranzgraft or integuply, per square centimeter
Q4128†	FlexHD, Allopatch HD, per square centimeter
Q4130	Strattice TM, per square centimeter
Q4137	Amnioexcel, amnioexcel plus or biodexcel, per square centimeter
Q4138	Biodfense dryflex, per square centimeter
Q4139	Amniomatrix or biodmatrix, injectable, 1 cc
Q4140	Biodfense, per square centimeter
Q4148	Neox cord 1K, Neox cord RT, or Clarix cord 1K, per square centimeter
Q4150	AlloWrap DS or dry, per square centimeter
Q4152	DermaPure, per square centimeter
Q4155	Neoxflo or clarixflo, 1 mg
Q4156	Neox 100 or Clarix 100, per sq cm, per square centimeter
Q4158	Kerecis Omega3, per square centimeter
Q4159	Affinity, per square centimeter
Q4160	NuShield, per square centimeter
Q4162	Woundex flow, BioSkin flow, 0.5cc
Q4163	Woundex, BioSkin, per square centimeter
Q4164	Helicoll, per square centimeter
Q4166	Cytal, per square centimeter
Q4168	AmnioBand, 1 mg
Q4170	Cygnus, per square centimeter
Q4173	PalinGen or PalinGen XPlus, per square centimeter
Q4174	Palingen or promatrx, 0.36 mg per 0.25 cc
Q4180	Revita, per square centimeter
Q4187	Epicord, per square centimeter
Q4189	Artacent ac, 1 mg
Q4192	Restorigin, 1 cc
Q4193	Coll-e-derm, per square centimeter
Q4195	Puraply, per square centimeter
Q4196	Puraply am, per square centimeter
Q4210	Axolotl graft or axolotl dualgraft, per square centimeter
Q4215	Axolotl ambient or axolotl cryo, 0.1 mg
Q4222	Progenamatrix, per square centimeter
Q4227	Amniocore, per square centimeter
Q4229	Cogenex amniotic membrane, per square centimeter
Q4234	Xcellerate, per square centimeter
Q4235	Amniorepair or Altiply, per square centimeter
Q4236	Carepatch, per square centimeter
Q4239	Amnio-Maxx or amnio-maxx lite, per square centimeter
Q4246	Coretext or protext, per cc
Q4250	Amnioamp-mp, per square centimeter
Q4253	Zenith amniotic membrane, per square centimeter
Q4254	Novafix dl, per square centimeter
Q4262	Dual layer impax membrane, per square centimeter

HCPCS Codes	Description
Q4263	Surgraft tl, per square centimeter
Q4264	Cocoon membrane, per square centimeter
Q4265	Neostim tl, per square centimeter
Q4266	Neostim membrane, per square centimeter
Q4267	Neostim dl, per square centimeter
Q4268	Surgraft ft, per square centimeter
Q4269	Surgraft xt, per square centimeter
Q4270	Complete sl, per square centimeter
Q4271	Complete ft, per square centimeter
Q4272	Esano a, per square centimeter
Q4273	Esano aaa, per square centimeter
Q4274	Esano ac, per square centimeter
Q4275	Esano aca, per square centimeter
Q4276	Orion, per square centimeter

†Note: Considered Experimental/Investigational/Unproven when used to report Allopatch HD

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Revision Details

Type of Revision	Summary of Changes	Date
Annual review	• Revised noncoverage policy statement • Removed policy statement for numerous products	3/15/2024