



# Medical Coverage Policy

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 Coverage Policy Number ..... 0068

## Tissue-Engineered Skin Substitutes

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### Related Coverage Resources

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- [Breast Reconstruction Following Mastectomy or Lumpectomy](#)
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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. 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.

### Coverage Policy

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

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

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

Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
AlloDerm®	Breast	Considered medically necessary when	15777	Q4116

Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
	reconstruction	used in association with a covered, medically necessary breast reconstruction procedure		
AlloMax™	Breast reconstruction	Considered medically necessary when used in association with a covered, medically necessary breast reconstruction procedure	15777	Q4100 C1781
AlloPatch Pliable®	Diabetic foot ulcer	<p>Considered medically necessary when ALL of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• full-thickness diabetic foot ulcer of greater than six weeks duration for which standard therapy has failed</li> <li>• type I or type II diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• 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)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status</p>	15275-15278	Q4128
AmnioBand®	Diabetic foot ulcer	<p>Considered medically necessary when ALL of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• full-thickness diabetic foot ulcer of greater than six weeks duration for which standard therapy has failed</li> <li>• type I or type II diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, the following</p>	15275-15278	Q4151 Q4168

Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
		<p>conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• 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)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>		
Apligraf®	Diabetic foot ulcer	<p>Considered medically necessary when ALL of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• full-thickness diabetic foot ulcer of greater than three weeks duration for which standard wound therapy has failed</li> <li>• type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• 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)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>	15275-15278	Q4101
Apligraf®	Venous stasis ulcer	<p>Considered medically necessary when BOTH of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• partial- or full-thickness venous stasis ulcer of greater than four weeks duration for which standard wound therapy has failed</li> <li>• treated foot has adequate blood</li> </ul>	15271-15278	Q4101

Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
		<p>supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></p> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• 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)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>		
Biobrane	Burn wound	Considered medically necessary when used for temporary covering of a partial-thickness freshly debrided or excised burn wound	Not Applicable	Q4100 C9399
Biobrane-L	Burn wound	<p>Considered medically necessary when BOTH of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• temporary covering of a partial-thickness freshly debrided or excised burn wound</li> <li>• adjunct to meshed autograft</li> </ul>	Not Applicable	Q4100 C9399
DermACELL™	Breast reconstruction	Considered medically necessary when used in association with a covered, medically necessary breast reconstruction procedure	15777	Q4122
DermACELL™	Diabetic foot ulcer	<p>Considered medically necessary when ALL of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• partial or full-thickness diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed</li> <li>• type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, treatment is limited to</p>	15275-15278	Q4122

Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
		<p>a total of two applications.</p> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>		
Dermagraft®	Diabetic foot ulcer	<p>Considered medically necessary when ALL of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• full-thickness diabetic foot ulcer of greater than six weeks duration for which standard therapy has failed</li> <li>• type I or type II diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• 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)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>	15275-15278	Q4106
Epicel	Burn wound	<p>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%</p>	15150-15157 C5271-C5278	Q4100 C9399
EpiFix® Amniotic Membrane	Diabetic foot ulcer	<p>Considered medically necessary when ALL of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• partial or full-thickness, diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed</li> <li>• type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood</li> </ul>	15275-15278	Q4131

Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
		<p>supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></p> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• additional applications may be applied at a minimum of one week intervals, for up to a maximum of four in 12 weeks are considered medically necessary when evidence of wound healing is present (e.g., signs of epithelialization and reduction in ulcer size)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>		
EpiFix® Amniotic Membrane	Venous stasis ulcer	<p>Considered medically necessary when BOTH of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• partial- or full-thickness venous stasis ulcer of greater than four weeks duration for which standard wound therapy has failed</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• 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)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>	15271-15278	Q4131
FlexHD® Acellular	Breast	Considered medically necessary when	15777	Q4128

Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
Hydrated Dermis	reconstruction	used in association with a covered, medically necessary breast reconstruction procedure.		
Grafix®	Diabetic foot ulcer	<p>Considered medically necessary when ALL of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• partial or full-thickness diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed</li> <li>• type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• 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)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>	15275-15278	Q4132 Q4133
GraftJacket® Regenerative Tissue Matrix	Diabetic foot ulcer	<p>Considered medically necessary when ALL of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• partial or full-thickness, diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed</li> <li>• type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, one application is</p>	15275-15278	Q4107

Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
		considered medically necessary.		
Integra® Dermal Regeneration Template	Burn wound	Considered medically necessary when BOTH of the following criteria are met: <ul style="list-style-type: none"> <li>• postexcisional treatment of a full-thickness or deep partial-thickness burn</li> <li>• sufficient autograft is not available at time of excision or is contraindicated</li> </ul>	15271-15278	Q4105
Integra™ Bilayer Matrix Wound Dressing				Q4104
Integra™ Matrix Wound Dressing				Q4108
Integra™ Meshed Bilayer Wound Matrix				C9363
Integra® Dermal Regeneration Template/ Omnigraft Dermal Regeneration Matrix	Diabetic Foot Ulcer	Considered medically necessary when ALL of the following criteria are met: <ul style="list-style-type: none"> <li>• partial or full-thickness diabetic foot ulcer of greater than six weeks duration for which standard wound therapy has failed</li> <li>• type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• 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)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status</p>	15275-15278	Q4105
NeoForm™ Dermis	Breast reconstruction	Considered medically necessary when used in association with a covered, medically necessary breast reconstruction procedure	15777	Q4100 C1781
Oasis® Wound	Diabetic foot	Considered medically necessary when		Q4102



Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
<p>Matrix</p> <p>Oasis® Ultra Tri-Layer Matrix</p>	<p>ulcer</p>	<p>ALL of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• partial or full-thickness, diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed</li> <li>• type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• 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)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status</p>	<p>15275-15278 C5275-C5278</p>	<p>Q4124</p>
<p>Oasis Wound Matrix</p> <p>Oasis® Ultra Tri-Layer Matrix</p>	<p>Venous stasis ulcer</p>	<p>Considered medically necessary when BOTH of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• partial or full-thickness, lower extremity venous stasis ulcer of four weeks duration for which standard wound therapy has failed</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• additional applications at a minimum of one week intervals, for up to a maximum of four in 12 weeks are considered medically</li> </ul>	<p>15271-15278 C5271-C5278</p>	<p>Q4102 Q4124</p>

Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
		<p>necessary when evidence of wound healing is present (e.g., signs of epithelialization and reduction in ulcer size)</p> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status</p>		
Suprathel®	Burn	Considered medically necessary when used for the treatment of first- and second-degree burns.	Not Applicable	Q4649
TheraSkin®	Diabetic foot ulcer	<p>Considered medically necessary when ALL of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• partial or full-thickness, diabetic foot ulcer of greater than four weeks duration for which standard wound therapy has failed</li> <li>• type 1 or type 2 diabetes mellitus with a hemoglobin A1c (HbA1C) less than 12%</li> <li>• treated foot has adequate blood supply as evidenced by either the presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></li> </ul> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>• treatment is limited to one initial application</li> <li>• additional applications may be applied at a minimum of one week intervals, for up to a maximum of four in 12 weeks are considered medically necessary when evidence of wound healing is present (e.g., signs of epithelialization and reduction in ulcer size)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>	15275-15278	Q4121
TheraSkin®	Venous stasis ulcer	<p>Considered medically necessary when BOTH of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• partial- or full-thickness venous stasis ulcer of greater than four weeks duration for which standard wound therapy has failed</li> <li>• treated foot has adequate blood supply as evidenced by either the</li> </ul>	15271-15278	Q4121

Skin Substitute	Indication	Criteria	Application CPT®/HCPCS Codes	Product HCPCS Codes
		<p>presence of a palpable pedal pulse or an ankle-brachial index (ABI) of <math>\geq 0.70</math></p> <p>When the above medical necessity criteria are met, the following conditions of coverage apply:</p> <ul style="list-style-type: none"> <li>treatment is limited to one initial application</li> <li>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)</li> </ul> <p>Additional applications beyond 12 weeks are considered not medically necessary regardless of wound status.</p>		
Transcyte®	Burn wound	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.	C5271-C5278	Q4182

**Each of the products listed above for ANY unlisted indication is considered experimental, investigational, or unproven.**

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

Skin Substitute	Reason(s) for Request (this list may not be all inclusive)	Application CPT®/HCPCS Codes	Product HCPCS Codes
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
Adherus Dural Sealant®	Dural repair	No specific code	Q4100
Affinity	Wound care	15271-15278	Q4159
Allopatch HD™	Tendon augmentation	No specific code	Q4128
AlloSkin™	Wound care	15271-15278 C5271-C5278	Q4115 Q4141
AlloSkin™ RT	Wound care	15271-15278	Q4123
Allowrap™	Wound care	15271-15278	Q4150

<b>Skin Substitute</b>	<b>Reason(s) for Request (this list may not be all inclusive)</b>	<b>Application CPT/HCPCS Codes</b>	<b>Product HCPCS Codes</b>
AmnioBand® Particulate	Wound Care	15271-15278 C5271-C5278	Q4168
AmnioCare®	Tendon/nerve repair	No specific code	Q4100 C9399
AmnioClear®	Wound care Surgical barrier	15271-15278	Q4100
AmnioClear LTC flowable	Knee pain and inflammation	No specific code	J3590
AmnioExCel/BioDExCel™	Wound care Soft tissue repair	15271-15278	Q4137
Amniofix® Amniotic Membrane	Tendon/nerve repair	No specific code	Q4100 C9399
AmnioHeal® Plus	Wound care	15271-15278 C5271-C5278	Q4100 C9399
AmnioMatrix®	Wound care Soft tissue repair	15271-15278 C5271-C5278	Q4139
AmnioMTM Injectable	Wound care Soft tissue repair	No specific code	Q4100 C9399
AmnioPro Membrane	Wound care	15271-15278	Q4163
AmnioPro Flow	Wound care	No specific code	Q4162
Amnio Wound	Wound care	15271-15278 C5271-C5278	Q4181
Amniovo™	Soft tissue repair Tendon repair	No specific code	Q4100 C9399
Architect™ Biomatrix	Wound care	15271-15278	Q4147
Artacent™	Surgical barrier	No specific code	Q4169
ArthroFlex™ (FlexGraft®)	Shoulder reconstruction Achilles tendon repair	No specific code	Q4125
Avance Nerve Graft	Peripheral nerve repair	64912 64913	Q4100 C9399
AxoGuard® Nerve Connector	Peripheral nerve repair	64999	Q4100 C9399
Bio-ConneKt®	Wound care	15271-15278	Q4161
BioDfactor™	Wound care Soft tissue repair	15271-15278 C5271-C5278	Q4100 C9399
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	Q4161
Biodesign® (Surgisis®) AFP™ Anal Fistula Plug	Anal and rectal fistula repair	46707	Q4100 C1781
Biodesign® (Surgisis®) Hiatal	Hernia repair	49568	Q4100

<b>Skin Substitute</b>	<b>Reason(s) for Request (this list may not be all inclusive)</b>	<b>Application CPT/HCPCS Codes</b>	<b>Product HCPCS Codes</b>
Hernia Matrix			C1781
Biodesign® (Surgisis®) Inguinal Hernia Matrix	Hernia repair	49568	Q4100 C1781
Biodesign® (Surgisis®) RVP™ Recto-Vaginal Fistula Plug	Recto-vaginal fistula repair	No specific code	Q4100 C1781
BioFix®	Wound care	15271-15278 C5271-C5278	Q4100 C9399
BioVance®	Wound care	15271-15278	Q4154
CardioCel®	Pericardial closure Cardiac or vascular defect repair	No specific code	Q4100 C9399
Clarix® Regenerative Matrix	Surgical covering/wrap/barrier	No specific code	Q4100 C9399
Clarix® Flo	Integumental tissue repair	No specific code	Q4155
Conexa™	Tendon repair	No specific code	Q4100 C1781
Cormatrix CanGaroo™ Protect ECM Envelope	Implantable electronic device pocket	No Specific Code	Q4100 C9399
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
Cortiva®	Soft tissue repair Breast reconstruction	15777 17999	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	C5271-C5278	Q4166
Cymetra™	Integumental tissue repair	No specific code	Q4112
DermaMatrix Acellular Dermis	Facial soft tissue defects Breast reconstruction	15275-15278 15777	Q4100 C1781
DermaPure™	Wound care	15271-15278	Q4152
DermaSpan™	Wound covering Tendon repair	15271-15278	Q4126
Dermavest	Wound care	15271-15278	Q4153
Duraform™	Dural repair	No specific code	Q4100 C9399
DuraGen®	Dural repair	No specific code	Q4100 C9399
DuraGuard	Dural repair	No specific	Q4100

<b>Skin Substitute</b>	<b>Reason(s) for Request (this list may not be all inclusive)</b>	<b>Application CPT/HCPCS Codes</b>	<b>Product HCPCS Codes</b>
		code	C9399
DuraMatrix™	Dural repair	No specific code	Q4100 C9399
DuraSeal™ Dural Sealant System	Dural repair	No specific code	Q4100 C9399
DuraSeal™ Spine Sealant System	Dural repair	No specific code	Q4100 C9399
Durepair Regeneration Matrix®	Dural repair	No specific code	Q4100 C9399
Endoform Dermal Template™	Wound care	15271-15278 C5271-C5278	Q4100 C9399
Epifix® Injectable	Wound care	No specific code	Q4145
EpiCord™	Wound care	15271-15278	Q4131
Excellagen®	Wound care	15271-15278 C5271-C5278	Q4149
EZ Derm™	Wound care	C5271-C5278	Q4136
FloGraft™ flowable	Tendonitis Soft tissue trauma	No specific code	Q4100 C9399
FlowerDerm™	Wound care	15271-15278 C5271-C5278	Q1479
FLowerFlow™	Wound care	15271-15278 C5271-C5278	Q4177
FlowerPatch™	Wound care	15271-15278 C5271-C5278	Q4178
Fortaderm™/Puraply™	Wound care	15271-15278	Q4172
GammaGraft	Wound care	C5271-C5278	Q4111
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
hMatrix®	Integumental tissue repair	No specific code	Q4134
Hyalomatrix® PA	Wound care	15271-15278 C5271-C5278	Q4117
HydroFix® Vaso Shield	Vessel guard	No specific code	Q4100 C9399
Integra™ Flowable Wound Matrix	Wound care	No specific code	Q4114
Interfyl™	Integumental tissue repair	No specific code	Q4171
Keramatrix®	Wound care	15271-15278	Q4165

<b>Skin Substitute</b>	<b>Reason(s) for Request (this list may not be all inclusive)</b>	<b>Application CPT/HCPCS Codes</b>	<b>Product HCPCS Codes</b>
		C5271-C5278	
Lyoplast®	Dural repair	No specific code	Q4100 C9399
MariGen/Kerecis® Omega3 Wound	Wound care	15271-15278	Q4158
MatriStem®	Wound care	15271-15278 C5271-C5278	Q4118
Matrix HD™	Wound care Tendon repair	15271-15278	Q4128
Mediskin™	Wound care	15271-15278 C5271-C5278	Q4135
MemoDerm™	Wound care Tendon repair	15271-15278	Q4126
Miroderm™	Wound care	15271-15278	Q4175
NeoPatch™	Wound care	15271-15278 C5271-C5278	Q4176
Neox® Wound Matrix	Wound care	15271-15278	Q4148 Q4156
Neox® 100	Wound care	15271-15278	Q4156
Neox® Cord 1K	Wound care	15271-15278	Q4148
Neox® Flo	Wound care	No specific code	Q4155
NeuraGen® Nerve Guide	Peripheral nerve repair	64910	C9352
NeuraWrap™ Nerve Protector	Peripheral nerve repair	64999	C9353
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
OrthADAPT™ Bioimplant	Soft tissue reinforcement	15777 17999	Q4100 C1781
OsseoGuard®	Oral defects	15275-15278 C5275-C5276	Q4100 C9399
Ovation®	Wound healing	15271-15278 C5271-C5278	Q4100 C9399
PalinGen® Flow	Soft tissue repair	No specific code	Q4174
PalinGen® Xplus	Soft tissue repair	No specific code	Q4173

<b>Skin Substitute</b>	<b>Reason(s) for Request (this list may not be all inclusive)</b>	<b>Application CPT/HCPCS Codes</b>	<b>Product HCPCS Codes</b>
Peri-Guard® Repair Patch	Soft tissue repair Pericardial and intracardiac repair	No specific code	Q4100 C1781
Peri-Strips® Dry	Staple line reinforcement	No specific code	Q4100
Permacol™	Soft tissue reinforcement/repair	15777 17999	C9364
Phasix Mesh	Soft tissue reinforcement/repair	15777 17999	C1781
Phasix™ Plug and Patch	Soft tissue reinforcement/repair	15777 17999	C1781
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
Preserve™ Paraderm™ Dermal Tissue Matrix	Integumental tissue repair	No specific code	Q4100 C9399
PriMatrix™	Wound care	15271-15278	Q4110
ProMatriX™	Wound care	No specific code	Q4174
Puracol®	Wound care	15271-15278 C5271-C5278	Q4100 C9399
PX50®/PX50® Plus	Damaged or inadequate tissue repair	No specific code	Q4100 C9399
Repliform™	Integumental tissue repair	No specific code	C1762
Repriza®	Reconstructive surgery Breast reconstruction Abdominal wall repair	15271-15278 15777	Q4143
Restore® Orthobiologic Soft Tissue Implant	Soft tissue reinforcement	17999	Q4100 C1781
Revita	Wound care	15271-15278 C5271-C5278	Q4180
Revitalon™	Wound care	15271-15278	Q4157
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
SJM™ Pericardial Patch with EnCap™ AC Technology	Pericardial repair	No specific code	Q4100 C9399
SportMesh™	Soft tissue reinforcement	15777 17999	Q4100 C1781
SteriShield™	Soft tissue reinforcement/repair	15777 17999	Q4100 C9399
Strattice™ Reconstructive Tissue	Soft tissue reinforcement/repair	15777	Q4130



<b>Skin Substitute</b>	<b>Reason(s) for Request (this list may not be all inclusive)</b>	<b>Application CPT/HCPCS Codes</b>	<b>Product HCPCS Codes</b>
Matrix		17999	
Stravix™	Integumental tissue repair	No specific code	Q4100 C9399
SurgiMend®	Breast reconstruction	15777	C9358; C9360
Symbotex™ Composite Mesh	Soft tissue reinforcement	15777 17999	Q4100 C9399
Talymed™	Wound care	15271-15278	Q4127
tarSys™	Eyelid reconstruction	67961-67966	Q4100 C9399
TenoGlide® Tendon Protector Sheet	Tendon repair	No specific code	C9356
TenSIX™	Wound care Tendon repair	15271-15278	Q4146
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
TruSkin™	Wound care	15271-15278 C5271-C5278	Q4167
Unite® Biomatrix	Wound care	15271-15278 C5271-C5278	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 17999	Q4100 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
WoundEx® Membrane	Wound Care	15271- 15278	Q4163
WoundEx® Flow	Integumental tissue repair	No specific code	Q4162
XCM Biologic Vascular Patch	Soft tissue reinforcement/repair	15777 17999	Q4142
XCeed™	Wound care	No specific code	Q4100 C9399
Xenform®	Soft tissue reinforcement/repair	15777 17999	C1763
XenMatrix™ Surgical Graft	Soft tissue reinforcement/repair	15777 17999	C1781
XenoSure® Biologic Vascular Patch	Cardiac reconstruction/repair Vascular reconstruction/repair	No specific code	Q4100 C1781

## Overview

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

## General Background

### Autologous Skin Grafts and Cadaver-Derived Skin Grafts

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

### Tissue Engineered Skin Substitutes

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

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

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  $\geq 0.70$ .

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 for banked human tissue. AATB oversees a voluntary accreditation program and the FDA focuses on preventing the transmission of communicable diseases by requiring donor screening and testing. Tissue establishments must register with the FDA and list each cell or tissue produced. An example of a banked human tissue product is AlloDerm, an acellular dermal matrix (FDA, 2004).

### **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, et al., 2007; Salzberg, 2006; Breuing, et al., 2005; Nahabedian, 2005; Gamboa-Bobadilla, 2006. Various forms of AlloDerm are available including AlloDerm™ Regenerative Tissue Matrix, AlloDerm Select™ Tissue Matrix and AlloDerm Select Duo™ Tissue Matrix Bilateral Pair (Allergan, 2017; Hayes, 2017).

### **AlloDerm – Other Indications**

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

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

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

**Frey's syndrome:** 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 quasi-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. (2000) reported a 17.1% overall hernia recurrence rate, 40% surgical site infections, and 11.6% postoperative fistulas. Other studies reported postoperative ileus (24.2%), wound seroma (12.9%), and intrabdominal abscess (9.6%). In one study, seven of nine patients required reoperation due to postoperative abdominal wall laxity which was associated with infection and larger defects. Outcomes varied based on the type of surgical procedure performed, the type and number of AlloDerm sheets used, presence or absence of fecal contamination, and patient comorbidities (e.g., diabetes mellitus). The evidence in the published peer-reviewed scientific literature does not support the efficacy of AlloDerm for hernia repair.

**Lower Eyelid Surgery:** AlloDerm is proposed as an alternative to hard palate grafting used in the surgical repair of lower eyelid retraction following blepharoplasty. However, studies are primarily in the form of retrospective reviews with small patient populations and the authors reported less than 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 (Bard, 2017).

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 (Bard, 2017). 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. It 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 1.5x1.5 cm to 4x8 cm. (MTF, 2017).

Zelen et al. (2017) conducted a multicenter, randomized controlled trial to investigate 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<sup>2</sup>; 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 ( $4.7 \text{ cm}^2$ ) compared with the SOC group ( $2.7 \text{ cm}^2$ ).

### **AmnioBand® or Guardian**

AmnioBand or Guardian (Musculoskeletal Transplant Foundation, Edison, NJ), is an allograft made of human amnion and chorion and proposed as a covering for internal and external wounds. 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 (Musculoskeletal Foundation, 2017; Centers for Medicare and Medicaid, 2014).

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  $\geq 18$  years, type 1 or type 2 diabetic, had at least one unhealed neuropathic DFU  $\geq 1 \text{ cm}^2$  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  $\geq 30 \text{ mm Hg}$ ; or ABI with results of  $\geq 0.7$  and  $\leq 1.2$ ; 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.  $2.0 \text{ cm}^2$ ).

### **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 1 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  $\geq 0.70$ ) 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, 2010; 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  $\geq 0.70$ . Apligraf is used in conjunction with standard wound care therapy. One initial application is used and the wound is

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

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

### **Biobrane®/Biobrane®-L**

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

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

### **DermACELL™**

DermACELL (LifeNet Health®, Virginia Beach, VA) is an acellular human dermis allograft collagen scaffold proposed for the treatment of second and third degree burns, breast reconstruction, chronic non-healing wounds, dehisced wound sites and cosmetic reconstruction after traumatic burn injuries. LifeNet Health is registered with the FDA as an establishment producing tissue- and cellular-based products. 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 (NOVADAQ, 2017). The evidence in the published peer-reviewed literature supports DermACELL for the treatment of diabetic foot ulcer. The use of DermACELL for breast reconstruction has evolved into an accepted standard of practice. DermACELL is unproven and is not an established tissue substitute for all other indications.

**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  $\geq 1 \text{ cm}^2$  or  $\leq 25 \text{ cm}^2$ , wound depth  $\leq 9 \text{ mm}$ , 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 (Advanced Tissue Sciences., LaJolla, CA) is a cryopreserved dermal substitute approved by the FDA PMA process for the treatment of lower extremity full-thickness diabetic foot ulcers on the fore foot, toes or heel, 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  $\geq 0.70$ ) should be present in order for healing to occur. When Dermagraft is indicated, treatment is limited to one initial application. If evidence of healing is seen (e.g., signs of epithelialization and reduction in ulcer size) a maximum of eight applications for up to a total of 12 weeks are considered appropriate (Advanced Biohealing, 2013; FDA, 2001). The FDA Humanitarian Device Exemption (HDE) process for the treatment of dystrophic epidermolysis bullosa (EB) was withdrawn by the manufacturer. Randomized controlled trials and case series have demonstrated improved outcomes when Dermagraft was used for the treatment of these ulcers (Marston, et al., 2003, Gentzkow, et al., 1999).

### **Epicel**

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

### **EpiFix®**

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- $\alpha$ , TRF- $\beta$ ], fibroblast growth factor [bFGF], platelet derived growth factor [PDGF], and vascular endothelial growth factor [VEGF]), cytokines (e.g., interleukin 1 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, laminin7, and proteoglycans). EpiFix is proposed to promote cellular migration to enhance soft tissue repair in acute and chronic wounds free of necrotic tissue and infection; partial- and full-thickness wounds; venous, diabetic, pressure, and chronic vascular ulcers; trauma wounds, including burns; and surgical wounds. EpiFix membranes/sheets come in 14 mm and 16 mm disks as well as, 2X3 cm, 4X4 cm and 5X6 mm sheets. Randomized controlled trials support EpiFix for the treatment of 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. A Hayes brief (2015; reviewed 2017) on EpiFix stated that there was insufficient evidence to assess the effectiveness of safety of EpiFix on other types of nonhealing wounds (e.g., surgical wounds, traumatic wounds, pressure ulcers).

**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).

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<sup>2</sup>) 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 AlloDerm patients was 402 cm<sup>2</sup> and the mean mesh size used to repair the defect was 318 cm<sup>2</sup>. 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 complications included five seromas, seven intra-abdominal abscesses and two enterocutaneous fistulas. In the FlexHD group, mean hernia size was 388 cm<sup>2</sup> and the mean size of the mesh used to repair the defect was 389 cm<sup>2</sup>. 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.

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 from published clinical trials are lacking. Studies have primarily been in the form of retrospective reviews and case series with small patient populations.

### **Grafix®**

Grafix Cellular Repair Matrix (Osiris Therapeutics, Inc., Columbia, MD) 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 (GrafixPRIME™, GrafixCORE™) 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, 2015). In a randomized controlled trial (Lavery, et al., 2014). GrafixPI Prime and GrafixPI Core are also Grafix Prime products (Centers for Medicare and Medicaid Services [CMS], 2017). Grafix has been shown to significantly improve wound healing overall and to shorten the time to wound healing for partial and full-thickness diabetic foot ulcers and is an accepted therapy for a select subgroups of patient. However, at this time, 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.

Lavery et al. (2014) conducted a multicenter, randomized controlled trial to compare the safety and efficacy of Grafix (n=50) to standard wound care (SWC) (n=47) for the treatment of chronic diabetic foot ulcers. Subjects had type I or type II diabetes, with a 1–15 cm<sup>2</sup> wound, present for 4–52 weeks. The wound was located below the malleoli on the plantar (n=85) or dorsal surface (n=12) of the foot. Grafix patients received an application of

Grafix once a week ( $\pm$  3 days) for up to 84 days. Both groups received SWC including surgical wound debridement at each visit, a non-adherent dressing and an off-loading device. The primary outcome measure was complete wound closure (100% re-epithelialization with no drainage). Significantly more patients received complete wound closure with Grafix than SWC ( $p=0.0001$ ). The median time to healing was significantly shorter in the Grafix group than the SWC group (42 days vs. 69.5 days) ( $p=0.019$ ). A total of 23/28 healed Grafix-treated wounds vs. 7/10 SWC wounds remained closed at the 12 week post-closure follow-up ( $p=0.419$ ). There was a lower incidence of wound-related infections in the Grafix group ( $p=0.044$ ).

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  $\leq 15$  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)  $\geq 0.5$  and  $\leq 1.2$  or toe systolic pressure  $\geq 40$  mmHg or transcutaneous tissue oxygen tension (tcpO<sub>2</sub>)  $>30$  mmHg or skin perfusion pressure of  $>30$  mmHg. The patients had significant comorbidities (hypertension, current or former smoker, heart disease and/or partial foot 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® Regenerative Tissue Matrix (RTM)**

GraftJacket Regenerative Tissue Matrix (RTM) (Wright Medical Technology, Inc., Arlington, TN) is an acellular human dermal collagen template indicated for the repair or replacement of damaged or inadequate integumental tissue. GraftJacket Regenerative Tissue Matrix is regulated by the FDA as human tissue for transplantation and indicated for the treatment of diabetic foot ulcers. GraftJacket Regenerative Tissue Matrix MaxForce Extreme and GraftJacket Matrix Maxstrip are variations of the size and thickness of this tissue matrix. There are also products specific for other types of surgery including hand and shoulder surgery (Wright Medical Technologies, 2017). 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 any other indication including breast reconstruction is lacking and its role is unclear.

GraftJacket has also been investigated for use during tendon/rotator cuff repair. Published studies have been primarily in the form of case reports, case series, and retrospective reviews. Barber et al. (2012) conducted a randomized controlled trial ( $n=42$ ) to evaluate the safety and effectiveness of Graftjacket used in arthroscopic repair of large rotator cuff tears. Patients underwent repair of two-tendon rotator cuff tears measuring greater than three centimeters (cm) with ( $n=22$ ) (group 1) and without Graftjacket ( $n=20$ ) (group 2). Exclusion criteria included: irreparable massive rotator cuff tears measuring greater than five cm; subscapularis tendon disruptions; revision surgery; inflammatory or autoimmune diseases; evidence of active infection, cancer, or highly communicable diseases; and smokers. Follow-up ranged from 12–38 months (mean 24 months). The primary outcome measure was the presence of retears independently seen on gadolinium-enhanced magnetic resonance imaging (MRI) at least 12 months postoperatively. Secondary endpoints were clinical outcomes

measured by the American Shoulder and Elbow Surgeons (ASES) scores, Constant scores and the University of California, Los Angeles (UCLA) scores. MRIs showed intact cuffs in 85% of group 1 (n=17) and 40% of group 2 (n=6), statistically significant (p<0.01). With Graftjacket, there was a significant improvement in the ASES score (p=0.035) and the Constant score (p=0.08). There were no significant differences in the UCLA scores between the two groups. No adverse events were attributed to the use of Graftjacket. Operative time was increased 30–60 minutes with Graftjacket application. Limitations of the study include the small patient population, short-term follow-up, and loss of patients to MRI follow-up.

### **Integra®**

**Integra Dermal Regeneration Template** (Integra LifeSciences Corp., Plainsboro, NJ), 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 (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 Omnigraft 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 ARegeneration 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 improvements were reported following applications of IDRT in wound closure, physical functioning, pain and less chance of reoccurrence. 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 burns, 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  $\geq 0.70$ ) 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; Niezgodna, et al., 2005; Mostow, et al., 2005; Demling, et al., 2004).

### **Suprathel®**

Suprathel® (PolyMedics Innovations GmbH, 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 burns, partial thickness burns, 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.

Iqbal et al. (2017) conducted a case series to investigate Suprathel for the treatment of burns in 65 children aged four months to 11 years. The burns were superficial scald (n=51) and flame (n=14) burns including dermal (n=16), mid-dermal (n=34) and deep dermal (n=15). The total body surface area (TBSA) was 23.6% (range 8%-45%). Suprathel was applied to the wound after debridement, followed by Vaseline gauze, dry gauze and crepe bandage. The outer dressings were changed every 4-5 days unless clinical problems indicated otherwise. Median healing time was 15 days (range 10-35 days). A total of 20 patients took longer than 21 days to heal, of whom 13 were flame burns and developed hypertrophic scarring, associated with wound infection. Healing time of superficial dermal and mid-dermal burns was not significantly different. Burns with TBSA less than 30% were healed before median time. The TBSA was positively correlated with healing time in days. Limitations of the study are the small patient population and lack of a comparator.

Highton et al. (2013) prospectively evaluated the use of Suprathel for the treatment of partial thickness burns in 33 children, age five months to 11 years. The majority of burns affected the trunk (n=21), upper limbs (n=13) and lower limbs (n=8). Burns were assessed as being mostly superficial partial thickness (n=18) or mid-dermal (n=15). Suprathel was applied 0–7 days post-burn. Following debridement, Suprathel was applied followed by Vaseline gauze, dry gauze and crepe bandage. A total of 1–8 applications of Suprathel were required (median 2) and time to healing ranged from 9–38 days (median 16 days). Ten patients took longer than 21 days to heal. Four patients developed hypertrophic scarring, which was strongly associated with wound infection ( $p < 0.05$ ). Healing time of superficial partial thickness and mid-dermal burns was not significantly different ( $p = 0.494$ ). Limitations of the study are the small patient population and lack of a comparator.

Rahmanian-Schwarz et al (2011) conducted a prospective comparison study to evaluate the effectiveness of Biobrane1 (n=17) vs. Suprathel1 (n=17) for the treatment of adults with superficial partial-thickness burns of face or of the dorsum of the hand. Average follow-up after initial treatment was 8.4 months. The Vancouver Scar

Scale (VSS) was used for the clinical assessment of burned skin characteristics (e.g., height, pliability, vascularity and pigmentation). The Cutometer SEM 5751 (MPA 580, Courage & Khazaka Electronic GmbH, Koln, Germany) was used to evaluate scar elasticity. Complete epithelialization on average was 23 days (range, 13–43 days) postoperatively with Biobrane vs. 24.8 days (range, 14–53 days) for Suprathel ( $p>0.05$ , not significant). There were no significant differences between the two products for skin elasticity. The data showed a decrease of elastic function on average of 30% after Biobrane compared to 35.5% after Suprathel. For gross elasticity a decrease of 35% for Biobrane and 44% for Suprathel were reported. For biological elasticity Biobrane showed a 35% decrease and Suprathel showed a 42.5% decrease. Biological elasticity showed a decrease of 44% with Biobrane and 44% for Suprathel. The drop of viscoelastic ratio was closer to the normal skin with Biobrane (44%) vs. Suprathel (55%). Limitations of the study include the small patient population and lack of randomization.

Keck et al. (2012) reported on a case series of 18 adults, ages 25–83 years, who were treated with Suprathel for deep-partial thickness burns. Median total burned body surface area was 17.5% & 11% were deep dermal burns. Following excision, matched burn wounds were covered with 0.1 mm meshed autologous split-thickness skin grafts (STSG) and Suprathel (two areas of at least 100 cm<sup>2</sup>) for direct intra-individual comparison. Scars were evaluated by the Vancouver Scar Scale (VSS), the Patient and Observer Scar Assessment Scale (POSAS) and suction cutometry (MPA 580, Courage and Khazaka Electronic GmbH, Cologne, Germany) on days 30 and 90, postoperatively. Fifteen days following surgery, complete wound closure was present in 44.4% (8/18) of all areas covered with Suprathel and 88.9% (16/18) in the split-thickness skin graft (STSG) area ( $p=0.008$ ). On day thirty all areas were completely closed in all patients ( $n=17$ ). Regarding scar evaluation, on day 90, median total VSS was 3 (range, 0–9) in STSG areas and 2 (range, 2–5) in Suprathel areas. The STSG had a significantly higher pliability scores ( $p=0.0293$ ). Suprathel had higher pigmentation scores ( $p=0.1247$ ) (not significant) and a significantly higher vascularity score ( $p=0.0114$ ). No adverse reactions to Suprathel were recorded. A limitation of the study is the small patient population and short-term follow-up.

To assess the effectiveness of Suprathel, Madry et al. (2011) prospectively reported on 21 patients treated with Suprathel for the treatment of partial burns ( $n=15$ ), frostbites ( $n=5$ ) and one case of Lyell's syndrome (toxic epidermal necrolysis). Treatment results depended on the time of Suprathel application to the wound and on the type of injury. Nine partial-thickness burn patients had Suprathel applied within 24 hours and seven reached epithelialization within 14 days, one within 21 days and one deep burn patients required grafting. In the two patients in whom applications were made on the second day after injury, one obtained epithelialization within 21 days and one required dressing removal. Applications were made more than 48 hours after injury in four patients and two patients had epithelialization of the wound within 21 days and two required dressing removal. One frostbite patient experienced epithelialization within 14 days (Suprathel applied within 24 hours) and the patient with Lyell's syndrome healed after three weeks with application on the third day of symptoms. Limitations of the study include the small patient population and lack of a comparator.

### **TheraSkin®**

TheraSkin (LifeNet Health, Inc., Virginia Beach, VA) is a human skin allograft with epidermis and dermis layers. As a human skin product, TheraSkin is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. Proposed indications for TheraSkin include ulcers (i.e., diabetic foot ulcers, venous stasis ulcers, stage II and greater pressure ulcers) and dehisced surgical burns with or without exposed tendon, muscle or bone. It is also proposed for the treatment of wounds that might otherwise require autografts. The allograft is to be used in conjunction with conventional therapies (Soluble Solutions, 2015). Randomized controlled trials have reported significant improvement following treatment of partial and full-thickness diabetic foot ulcers with TheraSkin (Sanders, et al., 2014; DiDomenica, et al., 2011). TheraSkin is an established human skin allograft for the treatment of diabetic and venous stasis lower extremity ulcers.

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 extremity 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. 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.

### **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 5 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 (Skye Biologics, 2017). 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) 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, 5 x7.5 cm, 3x3 cam) (Gore, 2015). There is insufficient evidence to support the safety and efficacy of the Patch.

### **Adherus Dural Sealant®**

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

the PMA process (HyperBranch, 2015). 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. One size (2.5 X 2.5 cm) is available (Organogenesis, 2016; Centers for Medicare and Medicaid [CMS], 2014).

### **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, 2017). 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.

### **AlloSkin™/AlloSkin RT/AlloSkin AC**

AlloSkin (AlloSource, Centennial, CO) is a cryopreserved, allograft composed of epidermal and dermal cadaveric tissue proposed for use with partial and full thickness wounds and is regulated by the American Association of Tissue Banks (AATB) and the FDA guidelines for banked human tissue (AlloSource, 2016). AlloSkin products include the AlloSkin Wound Care, AlloSkin RT Wound Care at Room Temperature, and the AlloWrap Natural Wound cover. AlloSkin AC is a meshed dermis-only graft. The difference in these grafts includes whether they are frozen or irradiated and whether they are single layered or double layered. Published data supporting the safety and efficacy of AlloSkin are lacking.

### **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 different 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, 2016). 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 Moravv.

### **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 40mg to 160mg (Musculoskeletal Foundation [MTF], 2017; 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 AFCCell Medical, West Conshohocken, PA) is a placental amniotic 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 Bioscience, 2015). 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.

### **AmnioExCel® and AmnioMTM/AmnioMatrix®**

AmnioExCel or BioDExCel™ (AmnioGenix™, LLC, Collierville, TN) is a non-crosslinked, dehydrated, human amniotic extracellular matrix that acts as a scaffold for cellular attachment. The product includes EGF, TGF-β, 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 arterial ulcers, pressure ulcers, traumatic injuries, burns, surgical wounds), ridge augmentation, soft tissue repair, periodontal defects, bony defects and sinus coverage. AmnioMTM™ or AmnioMatrix® is the injectable form of the amnion allograft (AmnioGenix, 2014). 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<sup>2</sup> 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 closure 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, 2017).

Other AmnioFix products include: AmnioFix injectable which is a powder form intended for treatment of “tendon and soft tissue injuries, such as patellar tendon inflammation, tendonitis, tendonosis, plantar fasciitis, tennis elbow”. AmnioFix Sports Med and AmnioFix Wrap are for nerve and tendon protection (MiMedx, 2017). There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of Amniofix products.

A Hayes clinical research response (2016) on the use of AmnioFix following prostatectomy reported that there was insufficient published evidence to assess the safety and clinical outcomes for AmnioFix for this indication. Only one study was found that was a matched analysis comparing outcomes related to continence and potency in 116 patients undergoing robotic-assisted radical prostatectomy and receiving an unidentified human amnion allograft wrap versus those who did not receive a graft.

Zelen et al. (2013) conducted a single-center randomized controlled trial to examine the effectiveness of AmnioFix injectable amniotic membrane for the treatment of refractory plantar fasciitis (n=45). Recruited patients were 18 years or older and were recalcitrant to three of the following treatments: rest, ice, compression, and elevation (RICE); corticosteroid injection; stretching exercises; nonsteroidal oral 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 1 week and at eight weeks follow-up (p<0.001, each). No significant treatment response was reported in patients injected with saline. No adverse events related to AmnioFix were reported. Limitations of the study include the short-term follow-up and small patient population.

#### **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, 2017). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of AmnioHeal Plus.

#### **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; HRT, 2016). 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.

#### **Amnio Wound**

Amnio Wound (Alpha Tissue, LLC.) is a lyophilized (freeze dried) human amniotic membrane allograft comprised of an epithelial layer and two fibrous connective tissue layers. It is proposed for the treatment of neuropathic ulcers, venous stasis ulcers, post-traumatic wounds, pre-and post-surgical wounds, pressure ulcers, diabetic wounds, burn wounds, scar tissue, scarring, and as an adhesion barrier. The graft is administered by placing the stromal side onto the external wound area (CMS, 2017). There is insufficient evidence to support the safety and effectiveness of Amnio Wound.

### **Amniovo™**

Amniovo (Tri-State Biologics, Secaucus, NJ) 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. 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 (Tri-State Biologics, 2016). There is insufficient evidence in the published peer-review literature to support the safety and clinical effectiveness of Amniovo.

### **Architect™ Biomatrix**

Architect Biomatrix (Harbor MedTec, Inc., Irvine, CA) is an equine, pericardial, extracellular collagen matrix. It was approved by the FDA 510 (k) process in 2013 as Harbor MedTech BriDGE Extracellular Collagen Matrix (ECM) Wound Dressing. FDA approved indication is for the local management of moderately to heavy exuding wounds including: partial and full thickness wounds, draining wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds and surgical wounds. Architect is processed by a proprietary patented BriDGE™ process. The matrix is available in four sizes in standard and fenestrated sheets (FDA, 2013; Harbor MedTec, 2017). Architect PX ECM was FDA 510(k) approved in 2014 for the same indications as the Biomatrix. The difference is that the PX matrix compared to the Biomatrix has a lower concentration of the BDDGE solution used in manufacturing the product. It is a partially stabilized matrix which is proposed to maintain its natural ECM tissue regeneration properties longer on the wound. Architect PX ECM is available in 11 sizes. Harbor MedTech has a third product called Architect FX ECM which is proposed to more quickly adhere to the wound bed than the Biomatrix. Architect FX is not currently FDA approved (FDA, 2015; CMS, 2014). Evidence supporting the safety and efficacy of Architect products is lacking. Studies are primarily in the form of case reports.

### **Artacent™**

Artacent Wound (Tides Medical, Lafayette, LA) is an amniotic patch derived from the submucosa of donated human placenta. The product is proposed for chronic wound covering (diabetic ulcers, pressure ulcers, venous stasis ulcers, burns). One of the proposed advantages of this amniotic product is that either side can be placed on the wound. It consists of collagen layers, including basement membrane, stromal matrix and growth factors. Artacent Flex is proposed for use as a surgical barrier for the following types of surgeries: extremity, orthopedic, spinal, urological, vascular, ophthalmic, and plastics. The patches are available in 1X1 cm, 2X2 cm, 2X3 cm, 4X4 cm, 4X6 cm and 4X8 cm sizes (CMS, 2016; Tides Medical, 2009a; Tides Medical 2009b). Evidence supporting the safety and efficacy of these Artacent 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, Afkex400, Aflex 401, Aflex500 (LifeNet Health, 2017). Data in the peer-reviewed scientific literature supporting the safety and effectiveness of Arthroflex are lacking.

### **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-dimension 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, 2017).

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. A Hayes Clinical Research Response on Avance (2015) stated that this is the only commercially available nerve allograft for use in surgical repair of nerves and that published evidence is very limited.

### **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., 2016; Cook Biotech, 2017, 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).

#### **bio-ConneKt® Wound Matrix**

bio-Connect (MLM Biologics, Alachua, FL) is an FDA 510(k) approved, reconstituted collagen-based wound dressing derived from equine tendon. The FDA indications for use state that bio-ConneKt is used for the “local management of moderately to heavily exuding wound, including: partial and full thickness wounds; draining wounds; tunneling wounds; pressure sores/ulcers; venous ulcers; chronic vascular ulcers; diabetic ulcers; trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears); and surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Mohs' surgery, podiatric wounds, dehisced surgical incisions)”. Bio-ConneKt is radiation (E-beam) sterilized. The device was approved as being substantially equivalent to other similar devices (predicate device). The matrix is placed directly into the wound site and incorporated into the wound as healing occurs. It is supplied in 6X7 cm, 5X5 cm, 3X3 cm, and 2X2 cm sizes (CMS; 2015; FDA, 2014). There is insufficient evidence to support the safety and efficacy of bio-ConneKt.

#### **BioDfactor™/BioDfence™/BioDfence™ DryFlex/BioDRestore™**

Amedico Corporation (Salt Lake City, UT) provides three products proposed for use as physical barriers between the dura and soft tissue of the paraspinal muscles to reduce fibroblast infiltration into the epidural space and postoperative scarring. The products are human amniotic tissue allografts that are resorbed into the body during healing. They are regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. BioDfactor is a cryopreserved liquid form of the allograft extracellular matrix and comes in 0.25 ml, 0.5 ml and 1.25 ml. BioDfence Resorbable Adhesion Barrier comes in sheets 1x2 cm, 2x2cm, 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 0.5cc, 1.0cc and 2.0 cc sizes (BioD, LLC, 2014).

There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of these products. In a Clinical Research Response, Hayes (2015) stated that no published evidence regarding these BioD products was identified.

#### **Biodesign® Dural Graft**

Biodesign® Dural Graft (Cook Medical, 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. 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) (FDA. 2013; Cook Medical, 2016). There is insufficient evidence to support the safety and efficacy of Biodesign Dural Graft for a dural repair.

#### **Biodesign® (Surgisis®) AFP™ Anal Fistula Plug**

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

Evidence in the published peer-reviewed scientific literature does not support the safety and efficacy of the Surgisis AFP. Studies have primarily been in the form of case series and retrospective reviews with small,

heterogeneous patient populations, and short-term follow-ups (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%.

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. Per the FDA 510(k) (2006) approval for SIS Hernia Repair Device and Surgisis Gold Hernia Repair Graft, the devices are "intended to be implanted to reinforce soft tissue where weakness exists. Indications for use include the repair of a hernia and body wall defect." There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of Surgisis Hiatal Hernia Graft. Studies are primarily in the form of case reports, retrospective reviews and case series with small patient populations (n=5-6) and short-term follow-ups, reporting a high hernia recurrence rate.

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

#### **Biodesign® (Surgisis®) Inguinal Hernia Graft**

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

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

### **Biodesign® (Surgisis®) RVP™ Recto-Vaginal Fistula Plug™**

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

### **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 (Integra LifeSciences, 2017). There is insufficient evidence to support the effectiveness of the BioFix products.

### **BioVance®**

BioVance (Alliqua™ Biomedical, Langhorne, PA) is a dehydrated amniotic membrane allograft proposed for the treatment of acute and chronic wounds including burns, diabetic ulcer, venous leg ulcers, pressure ulcers and surgical wounds. The product is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. BioVance is available in eight sizes (Alliqua Biomedical, 2017). There is insufficient evidence in the published peer-reviewed literature to support the efficacy of BioVance. Studies are primarily in the form of case series with small patient populations.

### **CardioCel®**

CardioCel (Admedus Innovative Health Solutions, Minneapolis, MN) is an acellular, collagen cardiovascular patch prepared from glutaraldehyde-crosslinked bovine pericardium using a patented ADAPT® process. 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". It is supplied in three sizes: 4x4 cm, 5x8 cm and 14x7 cm (FDA, 2014; Admedus Innovative Health Solutions, 2016).

To date, studies are primarily in the form of animal studies and small patient populations. 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.

A Hayes clinical research response (2015) on the CardioCel Bovine Pericardial Patch concluded that evidence is insufficient to allow conclusions regarding long-term safety and clinical efficacy of this device. Other than the Neethling et al. study above, Hayes found four articles that were either animal studies or laboratory-based experimental studies.

### **Clarix® Regenerative Matrix**

Clarix Regenerative Matrix (AmnioX Medical, Inc., Marietta, GA) 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 CORD 1K (4 sizes) and Clarix 100 (3 sizes) (AmnioX Medical, 2017). Additional products are Clarix Cord RT and Clarix 100 (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. In a 2015 Clinical Research Response on Clarix, Hayes reported that no published studies were found on this product and that the published evidence on the cryopreservation process used by AmnioX was insufficient to determine if this process was superior to the dehydration process used by other manufacturers. Hayes also noted that published evidence on human amniotic products is "very limited". Studies are primarily animal or laboratory based.

### **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 (AmnioX Medical, 2014). The data supporting the clinical utility of Clarix Flo is lacking.

### **Conexa™ Reconstructive Matrix**

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

### **CorMatrix®**

Cormatrix CanGaroo™ Protect ECM Envelope (Cormatrix Cardiovascular, Inc., Roswell, GA) was FDA 510(k) Class II 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 (Cormatrix, 2015). CorMatrix ECM® products are a 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).

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.

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.

### **Cortiva®**

Cortiva is a non-crosslinked, donated 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 hernia repair (CMS, 2015). The manufacturer proposes that the graft be used for breast reconstruction. There are two products: Cortiva and Cortiva 1.0 mm. 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., 2017; CMS, 2015; RTI, Inc. 2014). Studies investigating the clinical outcomes of Cortiva are primarily in the form of retrospective reviews with short-term follow-ups (Keifer, et al., 2016). There is insufficient evidence to support Cortiva for any indication.

### **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 (Matricel GmbH, Germany) for “use during the process of guided bone regeneration and guided tissue regeneration” for multiple conditions. 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, 2016). 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. (Skye Biologics, 2017). 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 undifferentiated 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® Biomedical, Inc., Atlanta, GA) 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). The three Cygnus products are the Cygnus Solo™, Cygnus Matrix™, and Cygnus Max™. Cygnus Solo is a single layer amnion proposed for topical wounds and burns or dermatologic applications. Cygnus Matrix is a medium thickness allograft and 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. 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 1x1 cm to 10x12 cm and three thicknesses (Vivex Biomedical, 2017). Evidence in published peer-review literature supporting the safety and efficacy of Cygnus products is lacking.

### **Cytal®**

Cytal Wound Matrix (ACell® Inc., 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 (CMS, 2016; ACell, 2015; FDA, 2015). There is insufficient evidence to support the safety and efficacy of Cytal for all indications.

### **Cymetra™**

Cymetra (LifeCell Corporation, Branchburg, NJ) is a micronized form of AlloDerm. It is processed from human tissue obtained from tissue banks and is therefore, classified by the FDA as human tissue for transplantation. The allograft tissue is processed into a particulate acellular dermal matrix, dried and placed in a syringe. It is to be used in transplantation for the repair or replacement of damaged or inadequate integumental tissues (e.g., injection laryngoplasty) (LifeCell, 2017). Cymetra is proposed for the treatment of vocal fold scars, presbyphonia, Parkinson-related dysphonia, and medialization of vocal folds following thyroplasty. Due to resorption, repeated injections may be indicated (Simpson, et al., 2008; Remacle and Lawson, 2007; Simpson, 2006). Cymetra is also proposed for use for smoothing deep wrinkles, nasolabial lines, lip enhancement, and repair of acne scarring.

Studies evaluating the efficacy of Cymetra injections for vocal fold immobility are primarily in the form of case series or retrospective reviews with small patient populations (n=6–34) and short-term follow-ups. A 2015 Hayes search and summary identified one prospective study (n=6) and four retrospective review studies. Hayes concluded that the evidence was insufficient to support Cymetra for vocal cord paralysis.

### **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 Wound Care [TRWC], Inc., 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) (TRWC, 2017). 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 (BioMet® Biologics Inc., Warsaw, IN) is an acellular dermal matrix derived from allograft human skin. The product is regulated by the FDA's American Association of Tissue Banks and regulatory process for testing and donor screening and prepared by a Biologics proprietary process. DermaSpan is proposed for repair or replacement of damaged or inadequate integumental tissue (wound coverage), and as supplemental support, protection, reinforcement or covering of tendons (BioMet, 2017). There is insufficient evidence to support the safety and efficacy of DermaSpan.

#### **Dermavest**

Dermavest (AediCell, Inc., Jersey City, NJ) is a decellularized, human placenta skin replacement product. The product is comprised of different sources of human connective tissue and is FDA-regulated as a Human Cell, Tissue, and Cellular and Tissue-Based Product. It is proposed as an advanced wound care product for burns, chronic diabetic ulcers, decubitus/pressure ulcers, and venous stasis ulcers. It is supplied as a single dehydrated 2x3 cm sterile pad (Aedicell, 2016; CMS, 2014). Data supporting the clinical utility of Dermavest is lacking.

#### **Duraform™**

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

#### **DuraGen®**

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

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

#### **Dura-Guard®**

Dura-Guard (Synovis® Surgical Innovations, St. Paul, MN) is prepared from a bovine pericardium cross-linked with glutaraldehyde. It is a 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 (Synovis, 2010; FDA, 1998). There is insufficient evidence to support the safety and efficacy of Dura-Guard. As noted above in DuraGen, Williams et al. (2013) compared DuraGen to Dura-Guard and found no significant differences between the products.

#### **DuraMatrix™**

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

#### **DuraSeal™ Dural Sealant System**

The DuraSeal Dural Sealant System (Confluent Surgical, Inc., Waltham, MA) consists of synthetic absorbable sealant materials and an applicator used to apply the sealant to an incision site. The sealant is approved by the FDA premarket approval (PMA) process “for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure. DuraSeal should only be used with autologous duraplasty.” The sealant is composed of a polyethylene glycol (PEG) ester solution and a trily sine 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).

Osburn 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™ Spine Sealant System**

DuraSeal™ Spine Sealant System (Covidien, Waltham, MA) is FDA PMA approved “for use as an adjunct to sutured dural repair during spinal surgery to provide watertight closure” to prevent CSF leakage through the suture pinholes and gaps between stitches. The system is composed of two solutions, a PEG ester solution and a Trily sine amine solution. When mixed together, the precursors polymerize to form the hydrogel sealant. The sealant is sprayed or layered on the sutured site. Since the sealant is more than 90% water, it is absorbed within four to eight weeks following surgery. The hydrogel may swell up to 50% of its size in any dimension (FDA 2009).

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

the study are the unequal number of patients in the groups and the short-term follow-up. Additional studies are needed to support the safety and efficacy of DuraSeal Spinal Sealant.

### **Durepair® Regeneration Matrix**

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

### **Endoform Dermal Template™**

Endoform Dermal Template (Mesynthes Ltd, Wellington, New Zealand) is an ovine (sheep)-derived extracellular matrix that is FDA 510(k) approved for single use in the treatment of “partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns; and skin tears) and draining wounds” (FDA, 2010). Endoform is prepared from propria 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 proposed 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 heterogeneity of wound types (e.g., diabetic foot ulcers, venous leg ulcers, heel pressure ulcers) (Ferrerias, et al., 2017; Lullove, 2017; Bohn and Gass, 2013).

### **EpiCord™**

EpiCord (MiMedx Group, Kennesaw, GA) is a minimally manipulated, dehydrated, non-viable cellular 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 2x3 cm and 3x5 cm sizes (Mimedex, 2017; CMS, 2016). Evidence supporting the safety and effectiveness for EpiCord for all indications is lacking.

### **Epifix® Injectable**

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

### **Excellagen®**

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

### **EZ Derm™**

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

### **FloGraft™**

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

### **FlowerFlo™, FlowerPatch™, FlowerDerm™**

FlowerFlo, FlowerPatch and FlowerDerm (Flower Orthopedics Corp., Horsham, PA) are three products proposed for wound healing. FlowerFlo is a liquid placental tissue matrix allograft intended to replace or supplement damaged or inadequate integumental tissue. FlowerFlo is available in 0.5 cc, 1.0 cc and 2.0 cc vials.

FlowerPatch is a dehydrated amniotic membrane allograft that comes in two thicknesses and is available in 2x4 cm, 4x4 cm, 4x6 cm and 4x8 cm sizes. FlowerDerm is a hydrated acellular (human) dermal allograft matrix used for the treatment of non-healing wounds and burn injuries. FlowerDerm is supplied as a 0.5 mm or 1.0 mm allograft, meshed and unmeshed, in a variety of sizes. All three products are proposed for treatment of chronic, non-infected, full thickness diabetic lower extremity ulcers; chronic, non-infected, partial or full-thickness diabetic lower extremity skin ulcers due to venous insufficiency which have not adequately responded to conventional ulcer therapy; and patients with second and third degree burns (Flower Orthopedics, 2017a; Flower Orthopedics, 2017b; CMS, 2017). Clinical trials supporting the safety and effectiveness of these products are lacking.

### **Fortaderm™ (Puraply™)**

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 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. FortaDerm Wound Dressing is supplied in dry sheets in sizes ranging from 5X5 cm to 12X36 cm. FortaDerm PHMB is supplied in dry sheets in various sizes (4x4 cm to 12x36 cm). Per the FDA, Puraply is the proprietary name for FortaDerm (Organogenesis, 2017; CMS, 2014; FDA, 2005; FDA 2001). Organogenesis stated that they do not currently offer these products. There is insufficient evidence in the peer-reviewed literature to support the clinical utility of the Fortaderm products.

### **GammaGraft**

GammaGraft (Promethean Lifesciences Inc., Pittsburg, PA) is an irradiated human skin allograft harvested from cadaveric donors and contains epidermal and dermal layers of skin. It is a temporary graft proposed for the treatment of venous stasis ulcers; diabetic foot ulcers; full-thickness ulcers; Mohs surgery sites; skin graft donor sites; partial thickness wounds; burns; areas of dermabrasion; temporary coverage of exposed abdominal viscera, including small bowel and liver; exposed pericranium and cranium; fasciotomy sites; as a test on a wound bed before autografting; and areas of excision which are not closed pending final pathology report. GammaGraft is regulated by the FDA as human tissue because it is donated human skin and not an engineered product (Promethean Lifesciences, 2017). Evidence in the published peer-reviewed scientific literature does not support the efficacy of GammaGraft.

### **Gentrix®**

Gentrix (ACell, Inc., Columbia, MD) 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. 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 (FDA, 2016; Acell, 2015; Acell, 2017). There is insufficient evidence to support Gentrix for any indication.

### **GORE® BIO-A® Fistula Plug**

The GORE BIO-A Fistula Plug (W.L. Gore & Associates, Inc., Elkton, MD) is FDA approved as a Class II, 510(k) synthetic bioabsorbable scaffold intended for use in the reinforcement of soft tissue for repair of anorectal

fistulas. Cell migration into the scaffold and tissue is generated as the body gradually absorbs the synthetic material (FDA, 2009). There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of this device. Studies are primarily in the form of case reports and case series with small patient populations and short-term follow-up.

Narange 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 (W.L. Gore & Associates, Inc., Flagstaff, AZ) is a synthetic bioabsorbable copolymer fiber (polyglycolide acid:trimethylene carbonate [PGA:TMC]) 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, 2015; FDA, 2012). The safety and efficacy of this product has not been established. Studies are primarily in the form of case reports and case series with small patient populations and short-term follow-up.

### **GraftJacket® Xpress**

GraftJacket Xpress (Wright Medical Technology, Inc., Arlington, TN), a flowable soft-tissue scaffold, is a powdered form of the GraftJacket tissue matrix. Using saline, it is reconstituted and injected into a wound. The scaffold is proposed for filling deep tunneling-type chronic wounds such as those found in chronic diabetic foot ulcers. The skin substitute is packaged in a syringe and intended for one time use. This product is regulated by the FDA as human tissue for transplantation. There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of GraftJacket Xpress. Studies have primarily been in the form of retrospective reviews with small patient populations and short-term follow-ups (Brigido, et al., 2009).

### **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/grfts, 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 2017; Dhanraj, et al., 2015; FDA, 2004). Data supporting the safety and efficacy of HeliColl is lacking.

### **hMatrix®**

hMatrix Acellular Dermis (Bacterin International Holdings Inc., Belgrade, MT) is an acellular dermal scaffold processed from donated human skin. The dermis is processed using a proprietary method and the matrix is packaged and sterilized using low-dose gamma irradiation. hMatrix is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. The product is stored and supplied frozen. Bacterin offers three hMatrix preparations: hMatrix Acellular Dermis for wound applications; hMatrix PR for breast augmentation, abdominal wall repair, and facial reconstruction; and SportMatrix onlay for tendon augmentation (Bacterin, 2015). There is insufficient evidence to support the safety and efficacy of hMatrix as a skin substitute.

### **Hyalomatrix PA®**

Hyalomatrix PA (Anika Therapeutics, S.r.l., Padova, Italy) is a bilayered, biodegradable acellular dermal skin substitute composed of hyaluronic acid and a semipermeable silicone membrane that acts as a scaffold for cellular invasion and capillary ingrowth. The matrix is FDA 510(k) approved “for the management of wounds including: partial and full-thickness wounds; second and third-degree burns; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undetermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, skin tears); and draining wounds” (FDA, 2007). There is insufficient evidence in the peer-reviewed scientific literature to support the safety and effectiveness of Hyalomatrix PA.

Studies evaluating Hyalomatrix have primarily been in the form of case series and retrospective reviews with small patient populations and heterogeneous diagnosis. In general, randomized controlled trials have not supported the effectiveness of hyaluronic acid for the treatment of chronic ulcers (Shaharudin, et al., 2016).

In a search and summary report, Hayes (2017) concluded that there was insufficient evidence to assess the safety and/or impact of Hyalomatrix for the treatment of burns. Studies were primarily in the form of retrospective reviews.

Observational case series using Hyalomatrix have been reported for the treatment of non-melanoma skin cancer (n=10) (Dessy, et al. 2016), upper and lower limb trauma (n=15) (Vaianti, et al., 2013), venous ulcers (n=16) (Motolese, et al., 2013), coverage of cancellous bone exposure in diabetic foot ulcers (n=23) (Caravaggi, et al., 2009), and pediatric burns (n=300) which was one centers experience in using Hyalomatrix PA as a bridge to remove necrotic debris and stimulate regeneration (Gravante, et al., 2007). Randomized controlled trials comparing Hyalomatrix PA to established standard of care for these conditions are needed to assess the safety and efficacy of this product.

Caravaggi et al. (2011) conducted an observational study (n=262) for the use of Hyalomatrix PA (HPA) for the treatment of multiple types of chronic wounds including vascular ulcers, diabetic foot ulcers, pressure ulcers, traumatic wounds and others (vasculitic ulcers and iatrogenic). Ninety-five of the ulcers had tendon, joint, or bone exposure. Patients had failed at least two months of conventional therapy. The main endpoint of this study was the reduction in threshold area ( $\geq 10\%$ ). At the baseline visit, HPA was applied along with a non-adherent dressing which were left undisturbed for at least one week. The nonadherent dressing was changed weekly or as needed. HYAFF (derivative of hyaluronic acid) was completely absorbed by the 15<sup>th</sup> day. At that point, if a suitable dermal layer had been restored, a thin autograft was applied or for smaller wounds, healing was reached spontaneously. The “wound edge effect” was assessed by measuring advancement of the wound edge. A threshold area reduction of the ulcer (epithelial advancement) of  $\geq 10\%$  was an endpoint measure. Re-epithelialization was achieved in 83% of ulcers in a median of 16 days. Twenty-six percent of wounds achieved 75% re-epithelialization within the 60-day follow-up period with HPA only treatment. A follow-up showed that 84% of ulcers achieved complete re-epithelialization by secondary intention. Limitations of the study include lack of a comparator and randomization; and heterogeneity of type, size, location, depth and duration of ulcers.

Gravante et al. (2007) conducted a prospective case series (n=300) to assess the outcomes of a “bridge” treatment for deep-partial thickness burn patients. The treatment involved removing necrotic debris by dermabrasion followed by the application of Hyalomatrix PA on the third to fifth hospital day. Dressings were changed every seven days and areas without signs of recovery on day 21 were removed with escharectomy and covered with thin skin grafts. A total of 183 patients required only one treatment, 67 required more than one treatment and 50 patients required escharectomy. A total of 83% of patients healed within 21 days. A limitation of the study is the lack of a control or comparison group. Prospective randomized controlled trials are needed to validate the outcomes of this study and evaluation of the recurrence rate.

### **HydroFix® Vaso Shield**

HydroFix Vaso Shield (the “Vaso Shield”) (MiMedx® Group, Inc., Marietta, GA) is a vessel guard made of hydrogel material using proprietary technology. Protection of veins and arteries is a common issue associated with many types of surgeries. Protection of the aorta, vena cava, iliac vessels and other anatomy is particularly important in anterior spine surgery. HydroFix® Vaso Shield was designed to help physicians protect vessels during anterior vertebral surgery. The Shield is FDA 510(k) approved “as a cover for vessels during anterior

vertebral surgery". Intended uses include: fusion surgery, adjacent level surgery, artificial disc implantation, implant or hardware removal, trauma, and vascular surgery in the spine (FDA, 2011). Data in the form of clinical trials supporting the safety and effectiveness of HydroFix are lacking.

### **Integra™ Flowable Wound Matrix**

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

### **Interfyl™**

Interfyl Human Connective Tissue Matrix (Alliqua® Biomedical, Yardley, PA) is an allogeneic, decellularized, particulate human tissue derived from the placenta. Because it is not cross-linked and does not contain cells, Interfyl is proposed to reduce the likelihood of immunogenic and inflammatory responses. It is proposed as a supplement or replacement for damaged or inadequate integumental. Interfyl is recommended for the treatment of deep dermal wounds, irregularly-shaped and tunneling wounds, augmentation of deficient/inadequate soft tissue, and the repair of small surgical defects. It is available in 1.5 ml flowable form in 3 cc syringe and in 50 mg and 100 mg particulate in vials (Alliqua, 2017; CMS, 2016). There is insufficient evidence to support the safety and efficacy of Interfyl for any indication.

### **Keramatrix®**

Keramatrix (Keraplast Technologies, LLC, Antonio, TX) is an absorbable matrix, rich in keratin protein, proposed to deliver Replicine™ Functional Keratin® into the wound as the Matrix dissolves. The keratin protein is derived from sheep's wool. Keramatrix is indicated for the treatment of chronic wounds, with low to high exudate, including: pressure ulcers, venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers and donor sites and grafts (Keraplast, 2016; CMS, 2015).

The FDA 510(k) approval included three different wound dressings. Keratec Keragel, Kerafoam and Keraderm. These products are indicated for "dry, light and moderately exudating partial and full thickness wounds such as: first and second degree burns; severe sunburns; and superficial injuries, cuts, abrasions and surgical wounds". The Keratec Wound dressing may also be used in the management of dry, light and moderately exudating partial and full thickness wounds including pressure (stage I-IV) and venous stasis ulcers; ulcers caused by mixed vascular etiologies; diabetic ulcers; and donor sites and grafts. The Keratec Wound Dressings are not intended to be used on third degree burns (FDA, 2009)

Keramatrix is supplied in a 10x10 cm size. Kerasorb® is a multilayer dressing with a keratin wound contact surface backed with an absorbent polyurethane foam and two gel dressings (keragel®, keragelIT®) (Keraplast,, 2016; CMS, 2015; FDA, 2009).

There is insufficient evidence to support the safety and efficacy of Keramatrix and Keratec keratin products for any indications. Studies are primarily in the form of case reports and case series with small patient populations, heterogeneity of the types of wounds treated and heterogeneity of the type of keratin products used (Batzer, et al., 2016; Loan, et al., 2016; Hammond, et al., 2010).

Davidson et al. (2016) conducted a randomized controlled trial (n=26) to compare wound healing using a standard of care (SOC) dressing vs. Keramatrix for the treatment of partial-thickness donor site wounds. Part of their own donor site was used as the control for each patient. The proximal or distal location of each dressing type was randomized. The middle third of the wound was ignored as it potentially may have been influenced by both dressings. A calcium alginate dressing was used as the control dressing. For analysis, 15 patients were placed into the old group (age >50 years) and 11 patients were placed in the young group (age ≤50 years). The median epithelialization at 7 days was 80% for the young group and there was no significant difference between



the treatment and control portions of the wounds. In the older group, the majority of each wound was unhealed at day seven. There was a significant difference ( $p=0.23$ ) between epithelialization in the control vs. the treatment portion of the wound in favor of the treated portion. Limitations of the study include the small patient population and short-term follow-up. The authors noted that a weakness of the assessment technique was that it was difficult to repeat the results of digital images which were unable to capture the detail necessary to make the assessments of percentage epithelialization.

### **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. 2017; 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 2.5X2.5 cm to 10X12.5 cm (Aesculap, Inc. 2017; FDA, 2013). There is insufficient evidence to support the safety and effectiveness of the LyoPlant substitutes (Hayes, 2015; reviewed 2017).

### **MariGen/Kerecis™ Omega3 Wound**

MariGen wound dressing (Kerecis Ltd., Reykjavik, Iceland), also known as Kerecis Omega3 Wound, is a processed, fish (piscine) dermal matrix composed of fish collagen. The device is FDA 510(k) 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. As part of the processing, cells and antigenic materials are extracted. The fish skin is derived from cod farmed in the North Atlantic Ocean. MariGen 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, MariGen contains omega3 polyunsaturated fatty acids. In comparison to porcine grafts, fish skin is proposed to have lower risk of disease. Kerecis distributes seven additional products which are available in various countries and may have different names. These other products include: Kerecis Omega3 Dura for reconstruction of dura mater, Kerecis Omega3 Hernia for abdominal repair, Kerecis Omega3 Pectus for breast reconstruction and four dermatologic products proposed for the treatment of abnormal skin conditions (e.g., psoriasis, eczema, dermatitis, keratosis pilaris and pseudofolliculitis). These additional products are not FDA approved and are in various stages of development (Kerecis, 2017; FDA, 2013). There is insufficient evidence in the published peer-reviewed literature to support the clinical utility of MariGen/Kerecis Omega3 Wound product. Kerecis has been tested on animals and small patient populations ( $n=581$ ) with short-term follow-up (Yang, et al., 2016; Baldursson, et al., 2015; FDA, 2013).

### **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 (ACell, 2015). 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 (Acell, 2017).

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 stasis and decubitus ulcers. Studies investigating Matristem for these conditions are primarily in the form of retrospective 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  $\leq 30\%$  or increased by  $\leq 50\%$  and met other inclusion criteria were enrolled in the study. Other inclusion criteria included: ulcer present for  $\geq 4$  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-brachial index (ABI) of  $\geq 0.7$  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.

A Hayes Clinical Research Response on MatriStem (2015; updated 2017) evaluated eleven abstracts including including one prospective randomized controlled trial (RCT) (n=17); one prospective randomized comparative study (n=56); and eight retrospective uncontrolled studies. MatriStem was used for the treatment of chronic, nonhealing wounds unresponsive to other therapy, esophageal indications and head/neck flap procedures. No studies were identified for pelvic floor reconstruction. No adverse events were noted. Hayes concluded that there is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of MatriStem.

### **Matrix™ HD**

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

### **Mediskin™**

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

### **MemoDerm™**

MemoDerm (Memometal, Inc., Memphis, TN) is a sterile acellular dermal matrix derived from human allograft skin tissue and is regulated by AATB and FDA requirements for tissue processing. The matrix is proposed for

use in various orthopedic procedures involving rotator cuff, anterior shoulder capsule, flex/extension tendons, ulnar collateral ligament, Achilles tendon, or lateral ankle complex, as well as for treatment of chronic diabetic foot ulcers. There is insufficient evidence in the peer-reviewed literature to support the safety and efficacy of Memoderm.

#### **Miroderm™**

Miroderm Biologic Wound Matrix (Miromatrix Medical, Inc. Eden Prairie, MN) is an acellular, porcine-derived matrix proposed for wound care. According to the manufacturer this is the first and only matrix derived from porcine liver. It retains an intact extracellular matrix with epithelial base-membrane on the outside and an open collagen matrix that is placed on the wound. The matrix is FDA 510(k) approved for the management of wounds including: partial and full thickness wounds; venous stasis ulcers; pressure 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, and skin tears); and draining wounds. The dressing comes in fenestrated and non-fenestrated patches ranging in size from 3x3 cm to 8x15 cm (CMS, 2016; Micromatrix, 2016). There is insufficient evidence to support the safety and efficacy of this porcine liver matrix for any indication.

#### **NeoPatch™ Chorioamniotic Membrane Allograft**

NeoPatch Chorioamniotic Membrane Allograft (Cryolife, Inc. Kennesaw, GA) is a dehydrated human placental membrane tissue comprised of both amnion and chorion. The constituent epithelium, basement membrane and collagen-rich extracellular matrix is proposed to provide a protective covering to the wound. NeoPatch is proposed for the treatment of wounds, including lower extremity ulceration caused by diabetes; chronic venous disease; other chronic conditions; or some acute wounds. NeoPatch is supplied in the following sizes: 14 mm round, 18 mm round, 24 mm round, 2X3 cm, 3x5 cm, 4x4 cm and 5x6 cm (CMS, 2017). There is insufficient evidence to support the safety and effectiveness of NeoPatch.

#### **Neox™ Wound Matrix/Neox 1k/Neox 100**

Neox Wound Matrix, previously Neox 1K, (Amnio Medical™, Marietta, GA) 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 Cryotek™ 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 peel is available in three sizes (Amnio Medical, 2017). An additional 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 (Hayes, Inc., 2017; Caputo, et al., 2016; Raphael, 2016).

#### **Neox® Flo**

Neox Flo (Amnio 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) (Amnio Medical, 2017). 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, 2017). NeuraGen Nerve Guide is FDA 510(k) approved "for repair of peripheral nerve discontinuities where gap closure can be achieved by flexion of the extremity". NeuraWrap is 510(k) approved "for the management of peripheral nerve injuries in which there has been no substantial loss of nerve tissue".

There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of NeuraGen and NeuraWrap. Studies are primarily in the form of case series and retrospective reviews with small patient populations (n=8–96) (Hayes, Apr 2016a; Hayes, Apr 2016b).

#### **NuCel™/NuCel Bioactive Amniotic Suspension/NuShield™ Spine/NuShield™ Orthopaedics/**

NuShield Spine (Nutech Medical, Birmingham, AL) is a bioabsorbable amniotic membrane proposed for use in various spinal surgeries including: decompression, foraminotomy, microdiscectomy, anterior lumbar interbody fusion (ALIF); laminectomy, discectomy, posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF) and lateral lumbar interbody fusion (XLIF). It is a biologic scaffold used as a barrier interface between the dura and surrounding musculature. Nutech Medical is registered as a tissue bank with the U.S. Food and Drug Administration (FDA). NuShield Orthopaedics, an amniotic membrane, is proposed for use as a scaffold for cellular migration and as a protective barrier for tendons and nerves following tendon repair. NuCel is a liquid form of amniotic membrane proposed for use in situations where a patch covering is “inadequate or inconvenient”. The product is mixed with the patient’s own blood and applied to the surgical site. NuTech noted that “there are no studies specifically related to the spine and/or orthopedics” using NuCel for these conditions. 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 (Nutech Medical, 2012).

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). In a Search and Summary Report on NuCel BioActive Amniotic Suspension, Hayes (2015) reported that no published clinical studies or review articles were found.

#### **Oasis® Burn Matrix**

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

#### **OrCel™**

OrCel (Forticell Bioscience, Inc., New York, NY) (formerly called Composite Cultured Skin [CCS]) is an allogeneic, bilayered cellular matrix, Type I bovine collagen sponge with FDA PMA approval for the treatment of split-thickness donor site wounds in burn patients. There is limited evidence to support the efficacy of OrCel compared to the standard of care for the treatment of split-thickness donor sites. Therefore, OrCel is considered investigational for this indication. FDA-HDE approval was granted for OrCel for use as an adjunct in the treatment of mitten-hand deformity surgery of epidermolysis bullosa. Published studies are in the form of case series with small patient populations (n=7). There is insufficient evidence to support the use of OrCel for any indication.

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

#### **OrthADAPT™ Bioimplant**

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

repair surgery including reinforcement of rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons” (FDA, 2007; Coons and Barber, 2006).

### **OsseoGuard®**

The OsseoGuard Membrane (Biomet, Inc., Palm Beach Gardens, FLA) is a protective barrier made from bovine Type I Achilles tendon collagen proposed for the regeneration of hard and soft tissue in various dental defects including: localized ridge augmentation/future site preparation, peri-implant bone defects, extraction sockets, bone regeneration after root resection and sinus window coverage. The 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 (Biomet, 2017). 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 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.

### **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 (Amnio Regen Solutions, 2015). A wet form of PalinGen, the Xplus Hydro Membrane, is also available. The Membranes come in ten sizes and can be customized (BioPro, 2016). There is insufficient evidence in the published studies to support the effectiveness of these products for their proposed use.

In a clinical research response on PalinGen for orthopedic indications, Hayes (2015) concluded that the evidence was insufficient to make an informed decision regarding the application of amniotic-derived tissue products in general, and PalinGen specifically, in the orthopedic setting. Studies were primarily in the form of retrospective reviews, observational studies and cases series with small patient populations and heterogeneous diagnosis. Hayes also noted that recent scrutiny by the FDA has raised concerns regarding the regulatory process for amniotic products and the potential need for FDA Biologics Licensure Applications (BLA) for these products.

### **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 strips 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, 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; inguinal, Littre’s, and paraesophageal hernia repairs; hernias in contaminated fields; various urological, gynecological and plastic surgery indications and urodynamic stress incontinence (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=15-65) and short-term follow-ups lack the data needed to support the efficacy of Permacol in the treatment of these conditions.

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

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 (Davol, 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, 2017; FDA, 2012).

There is insufficient evidence in the published peer-reviewed literature to support the safety and effectiveness of the Phasix products. Studies have primarily been in the form of animal and laboratory studies. A 2017 Hayes Clinical Research Response stated that literature specifically addressing Phasix mesh in the setting of hernia repairs was very limited, consisting of a review, an in vitro study and an animal study.

### **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<sup>®</sup> Dura is a smooth surface barrier proposed to minimize tissue attachment to allow easy re-operation following craniectomy procedures. Preclude<sup>®</sup> MVP<sup>®</sup> is for procedures in which immediate, watertight closure is needed during dura repair and reconstruction techniques. Preclude PDX Dura Substitute, a temporary or permanent prosthesis, is proposed to minimize cerebrospinal fluid leakage and tissue attachment during duraplasty procedures. PDX consists of a polytetrafluoroethylene (ePTFE) and elastomeric fluoropolymer three-layer construct. There is insufficient evidence in the published peer-reviewed literature to support the efficacy of these products.

### **Preclude<sup>®</sup> Pericardial Membrane**

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

### **Preclude<sup>®</sup> 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) (Gore Medical, 2015). There is insufficient evidence in the published clinical studies to support the safety and efficacy of the Preclude Vessel Guard.

### **Preserve<sup>™</sup> Paraderm<sup>™</sup> Dermal Tissue Matrix**

Paraderm Dermal Tissue Matrix (Paragon<sup>®</sup> 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 (Paragon 28, 2017). There is insufficient evidence to support the safety and effectiveness of this matrix.

### **PriMatrix**

PriMatrix (TEI Biosciences, Inc., Boston, MA) is an acellular dermal tissue matrix derived from fetal bovine dermis. It is 510(k) FDA approved for the "management of wounds that include: "partial and full thickness wounds; pressure, diabetic, and venous ulcers; second-degree burns; surgical wounds-donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds-abrasions, lacerations, and skin tears; tunneled/undermined wounds and draining wounds" (FDA, 2008). There is insufficient evidence in the published peer-reviewed scientific literature supporting the efficacy of Primatrix. Studies are primarily in the form of case reports, case series (n=20-55) and retrospective reviews (Hayes, 2016; Kavros, et al., 2014; Hayn, 2013; Lullove, 2012; Strauss, et al., 2012; Karr, 2011).

### **ProMatriX<sup>™</sup>**

ProMatrX ACF (BioPro Inc., Port Huron, MI) is a human liquid allograft comprised of amnion and amniotic fluid 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<sup>™</sup> 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 (BioPro, 2016, CMS 2016). There is insufficient evidence in the published peer reviewed literature to support the safety and efficacy of ProMatrX.

### **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 2017; 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).

### **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 and PX50 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) (Skye Biologics, 2015; 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).

### **Repliform™**

Repliform Tissue Regeneration Matrix (Boston Science, Natick, 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. Boston Scientific distributes Repliform Tissue Regeneration Matrix on behalf of LifeCell Corp (Boston Science, 2017; Boston Science 2015). 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; Criveliaro, 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.

### **Repriza® Acellular Dermal Matrix**

Repriza (Promethean Lifesciences Inc., Pittsburg, PA) is a human skin, acellular dermal matrix. The product is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. Repriza is membrane free and proposed for implantation for reconstructive surgery including breast reconstruction, abdominal wall reconstruct and augmentation of soft tissue irregularities. The matrix is provided in 4x12 cm and 6x16 cm sheets. It can also be custom made. The product is marketed by Specialty Surgical Products, Inc. (SSP). There is insufficient evidence to support the safety and efficacy of Repriza for reconstructive surgery.

### **Restore® Orthobiologic Soft Tissue Implant**

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

### **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, 2017; CMS, 2017). Data supporting the safety and effectiveness of Revita are lacking.

### **Revitalon™**

Revitalon (Medline Industries, Inc., Mundelein, Ill.) is an amnionic allograft consisting of the amnion and chorion of placental tissue proposed for the treatment of chronic, non-healing wounds. The product contains growth factors and cytokines. Tissue is procured from the Musculoskeletal Transplant Foundation (MTF) and FDA-regulated as a Human Cell, Tissue, and Cellular and Tissue-Based Product. Revitalon comes in three sheet sizes and as a one centimeter dot (Global Health, 2016). There is insufficient evidence in the peer-reviewed literature to support the clinical utility of Revitalon.

#### **RX Membrane and RX Flow**

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 (Skye Biologics, 2017).

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 (Skye Biologics, 2017).

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® and Associates, Inc., Flagstaff AZ) is a bioabsorbable membrane of synthetic polyglycolic acid and trimethylene carbonate copolymer for use in surgical staplers. The material is FDA 510(k) approved for use in surgical procedures in which soft tissue transection or resection with staple line reinforcement is needed (e.g., hysterectomy, lung resection, liver resection, bladder reconstruction, bronchial, bariatric, colon, colorectal, esophagus, gastric, mesentery, pancreas, small bowel, and spleen procedures) (Gore Medical, 2015; 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., Cambridge, 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. 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.

In May 2015 the FDA issued a warning letter to Allergan stating that the FDA approval of SERI Surgical Scaffold did not include the use of SERI Surgical Scaffold 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 reconstruction using a tissue expander or implant". The FDA requested Allergan "immediately cease activities that result in the misbranding or adulteration of the Strattice Reconstructive Tissue Matrix" for breast reconstruction" (FDA, 2015).

#### **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, 2017; FDA 1997). Published clinical trials supporting the safety and effectiveness of SJM are lacking.

### **SportMesh™**

SportMesh (Biomet Sports Medicine, Warsaw, IN) is a synthetic device made from Artelon® (Artimplant, AB, Vastra Frolunda, Sweden) fibers. The device is a biodegradable temporary scaffold that is proposed to allow the body’s cells to regenerate and heal. SportMesh is FDA 510(k) approved for “use in general surgical procedures for reinforcement of soft tissue where weakness exists” and “for reinforcement of soft tissues that are repaired by suture or suture anchors, limited to the supraspinatus, during rotator cuff repair surgery” (FDA, 2006). A second product, SportsMesh or Artelon Tissue Reinforcement mesh, is also FDA 510(k) approved based on the SportMesh predicate device for the same indications. Data supporting the safety and efficacy of SportMesh is lacking. Studies have primarily been in vitro or in the form of case reports with small patient populations (n=4) and short-term follow-ups (i.e., two weeks) (Huss, et al., 2008).

### **SteriShield™**

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

### **Strattice™ Reconstructive Tissue Matrix**

Strattice Reconstructive Tissue Matrix (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” (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 ( $\leq 30$  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, Somerville, NJ) (n=88) when used in a Lichtenstein's tension-free hernioplasty. Ultrapro is a lightweight, partially absorbable, polypropylene mesh. Subjects were adult males, age  $\geq 18$  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  $\geq 18$  years with hernias  $\geq 9$  centimeters<sup>2</sup> (cm<sup>2</sup>) and repairable 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) 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 (WoundSource, 2017). There is insufficient evidence to support the safety and effectiveness of Stravix.

### **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, 2017; 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 (Hayes, 2017; 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; TEI Biosciences, 2015). There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of SurgiMend for these other 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, 2017; FDA, 2013). There is insufficient evidence to support the safety and efficacy of Symbotex.

### **Talymed™**

Talymed (Marine Polymer Technologies, Inc., Danvers, MA) is a wound healing matrix comprised of shortened fibers of poly-N-acetyl glucosamine (pGlcNAc) isolated from microalgae. The dressing is FDA 510(k) approved and “indicated for the management of wounds including: diabetic ulcers, venous ulcers, pressure wounds, ulcers caused by mixed vascular etiologies, full thickness and partial thickness wounds, second degree burns, surgical wounds-donor sites/grafts, post-Mohs’ surgery, post-laser surgery, and other bleeding surface wounds, abrasions, lacerations, traumatic wounds healing by secondary intention, chronic vascular ulcers, and dehisced surgical wounds” (Marine Polymer Technologies, 2016; FDA 2010).

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

healed wounds compared to the control group (p=0.005). Limitations of the study include the small patient population and the number of patients lost/withdrawn/discontinued intervention in the study group (n=11).

### **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 (IOP Ophthalmics, 2013; 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. 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.

### **TenSIX™ Acellular Dermal Matrix**

TenSIX Acellular Dermal Matrix (Solana Surgical, LLC, Memphis, TN) is derived from donated human tissue and sterilized via a Gamma Precision Dose Sterilization proprietary process. The product is regulated by the American Association of Tissue Banks and the FDA guidelines for banked human tissue. TenSIX has a basement membrane and dermal sides. The matrix is proposed for repair or replacement of tissue lost from foot ulcers or amputation or for protection, reinforcing and covering tendons. TenSIX is available in meshed (4x4 cm, 4x8 cm) and non-meshed forms (2x4 cm, 4x7 cm, 5x10 cm). There is insufficient published evidence to support the safety and efficacy of TenSIX. Studies are primarily in the form of case reports (Solana Surgical, 2014).

### **TissueMend Soft Tissue Repair Matrix**

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

### **Tornier® BioFiber™ Scaffold and Tornier® Collagen Coated BioFiber Scaffold**

There are two Tornier BioFiber Scaffolds (Tornier, Inc. Edina MN). The Tornier Collagen Coated BioFiber Scaffold is a bi-layer, synthetic absorbable reinforced woven fabric made from poly (4-hydroxybutyrate) fibers. The device is FDA 510(k) approved for “use where temporary wound support is required to reinforce soft tissues where weakness exists or for the repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result”. The 510(k) FDA approved predicate device is the BioFiber Absorbable Biological Scaffold for soft tissue repair and reinforcement. BioFiber is an orthopedic absorbable polymer soft tissue scaffold proposed for reinforcement of suture-tendon interface and tendon repair. BioFiber is proposed for a wide range of orthopedic indications including repairs of the shoulder, knee, hip, and foot/ankle (Tornier, Inc. 2015; FDA, 2012). There is insufficient evidence supporting the safety and efficacy of the Tornier BioFiber Scaffolds.

### **TruSkin™**

TruSkin (Osiris Therapeutics, Inc., Columbia, MD) is a split-thickness, cryopreserved, human cadaver skin allograft with dermis and epidermis. The allograft retains the extracellular matrix, growth factors, and endogenous living skin cells of the native tissue. It is a mesh proposed for repair of acute and chronic wounds (e.g., diabetic foot ulcers, venous leg ulcers, pressure ulcers, surgical wounds, and wounds with exposed bone and tendon). TruSkin is proposed as an alternative to fresh skin allograft and prepared using a proprietary process (CMS, 2016). There is insufficient evidence to support the safety and effectiveness of TruSkin.

### **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 exuding wounds, including: partial and full thickness wounds, draining wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, partial thickness [second degree] burns, skin tear, surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, dehisced surgical incisions) (FDA, 2011). Because studies are primarily in the form of case reports, there is insufficient data to support the safety and efficacy of Unite Biomatrix.

### **Vascu-Guard®**

Vascu-Guard (Synovis® Surgical Innovations, St. Paul, MN, previously Bio-Vascular, Inc.) is a bovine pericardium cross-linked matrix with glutaraldehyde. It is 510(k) FDA approved as an intracardiac patch and proposed for use in peripheral vascular reconstruction including the carotid, renal, iliac, femoral, profunda and tibial blood vessels and arteriovenous access revisions. 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. VersaShield 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, 2017). There is insufficient evidence in the published clinical trials to support the efficacy of VersaShield 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 Peri-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 and ViaFlow C (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). ViaFlow Flowable Placental Tissue Matrix 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 Technology, 2017; Wright Medical Technology, 2015).

In a clinical research response, Hayes (2016; reviewed 2017) stated no information was found in the peer-reviewed literature for ViaFlow and ViaFlow C. There is insufficient evidence available to make informed decisions regarding either safety or clinical effectiveness of these two products.

### **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). 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 (Sky Biologics, 2017). 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).

### **XCM Biologic Vascular Patch**

XCM Biologic Vascular Patch (Kenny Nash Corp., Exton PA) is a non-cross-linked 3-D matrix derived from porcine dermis using the Optrix™ process. The dermis is composed of cells and extracellular matrix (ECM). The matrix is FDA 510(k) approved as Medeor Matrix (Kenny Nash Corp., Exton PA) and indicated “for the reinforcement and repair of soft tissue where weakness exists including, but not limited to: defects of the thoracic wall, suture line reinforcement, muscle flap reinforcement, hernia repair, soft tissue reconstructive procedures including plastic and reconstructive surgical applications, and reinforcement of the soft tissues, which are repaired by suture or suture anchors, including but not limited to, rotator cuff, patellar, Achilles, biceps, quadriceps and other tendons. Medeor Matrix is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Sutures, used to repair the tear, and sutures or bone anchors used to attach the tissue to the bone, provide biomechanical strength for the tendon repair”. The product is distributed by Synthes® (Synthes, 2017; FDA, 2011). There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of XCM Biologic.

### **Xceed™**

Xceed Purified Amniotic Fluid (AmnioLife Corporation [now Alaris], 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 (AmnioLife Corporation, 2016). There is a lack of evidence in the published peer reviewed literature to support the use of Xceed Purified Amniotic Fluid for any indication.

### **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 (Boston Scientific, 2016). 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 (C.R. Bard, Inc. Covington, GA) is an acellular non-crosslinked regenerative porcine collagen matrix proposed for hernia and abdominal wall repair. The grafts are created using a patented AquaPure™ Process that removes the cells, leaving an open collagen scaffold. Brennan Medical received FDA 510(k) approval for porcine dermal matrix “intended for implantation to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue membranes. XenMatrix is specifically indicated for: plastic and reconstructive surgery; muscle flap reinforcement; hernia repair including abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, and incisional hernias; suture-line reinforcement; reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Porcine Dermal Matrix is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the rotator cuff, patellar Achilles, biceps, quadriceps, or other tendons (C.R. Bard, 2017; FDA, 2011). Clinical trials with data supporting the safety and efficacy of XenMatrix are lacking. Studies are primarily in the form of retrospective reviews and in vitro studies.

### **XenoSure® Biologic Vascular Patch (formerly PeriPatch)**

XenoSure Biologic Vascular Patch (LeMaitre Vascular, Inc., Ontario, Canada), a processed bovine pericardial patch was FDA approved as PeriPatch™ (PM Devices Inc., British Columbia, Canada). The device is intended for use as a surgical patch for cardiac and vascular reconstruction and repair as well as, soft tissue repair and reinforcing suture lines during general surgical procedures. Per LeMaitre applications include carotid endarterectomy, iliac artery stenting, femoral, iliac, renal and tibial patching, profundoplasty, and arteriovenous access revisions (LeMaitre Vascular, 2017; FDA, 2004). There is insufficient evidence to support the safety and efficacy of Xenosure.

### **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:** In a clinical research response, Hayes (2016) assessed the available evidence on amniotic allografts for bariatric surgery and gynecological procedure. Evidence regarding the use of amniotic membrane or other amniotic tissue products for gynecological indications is lacking. Studies using amniotic products for vaginoplasty, cervicoplasty and adhesion prevention were primarily in the form of case reports, retrospective reviews and small case series (n=3–27). Although positive outcomes were reported, the studies were limited by lack of a control group, short-term follow-up and small patient populations. Abstracts included a Cochrane review (Bosteels, et al., 2015) 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.

**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:** Nasser et al. (2015) 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 immunosuppressants, 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 Frey 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 dermis matrix was compared to a muscle flap graft. ( $p=0.70$ ). No serious adverse events were reported. Frey syndrome had an incidence of 8.3% in the acellular dermis group and 11.1% in the muscle flap group. Limitations of the analysis include a discrepancy in the number of subjects with Frey syndrome dependent on whether a subjective vs. objective assessment was made. Very mild Frey syndrome cannot be detected by a subjective assessment. Other limitations include heterogeneity in the types of parotid lesions and surgical procedures, small patient populations and possibility of selection bias of the included studies. More RCTs with large, homogeneous patient populations and long-term follow-up are needed to valid that grafts are effective in preventing Frey syndrome.

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

Ferzoco (2013) conducted a systematic review to assess outcome in patients who underwent repair of contaminated or infected ventral incisional hernias using a biologic mesh. The eleven studies that met inclusion criteria used the following products: AlloDerm (n=7), Surgisis (n=2); CollaMend (n=2), Permacol (n=2), Strattice (n=1), and Veritas (n=1). All studies were retrospective chart reviews and included a total of 677 patients. Reported hernia recurrence varied widely and ranged from 0%–50%. Wound dehiscence rates varied from 0%–35.5% and mesh explantation ranged from 0%–23%. Occurrence rates for seroma, fistula, evisceration, intrabdominal bleeding, repeat surgery, 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 be 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 methodological weaknesses exist” representing a low level of evidence. Outcomes with Surgisis were also conflicting. Some studies reported a recurrence rate of 0%–5.3% regardless of whether the surgery was performed in a clean or infected field, while other studies reported a recurrent rate as high as 39% in dirty fields. One study was terminated early due to the high recurrence rates in a Surgisis group with clean cases. According to the authors, insufficient or minimal data in the form of retrospective reviews were found for Veritas, Xenmatrix, CollaMend and Strattice and only case reports were found for Allomax, FlexHD, FortaGen, Peri-Guard, SurgiMend and Tutopatch.

**Hyaluronic Acid:** Shaharudin et al. (2016) conducted a Cochrane 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.

**Orthopedic Sports Medicine:** Riboh et al. (2015) 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.

### Technology Assessments

**Hayes Directory Report:** Hayes (2015; reviewed 2017) conducted a review of the literature to determine if synthetic dural tissue substitutes were safe and effective for dural repair following surgery or trauma. Ten retrospective reviews and five randomized or quasi-randomized controlled trials met inclusion criteria. Follow-ups ranged from one week to 33 months. The comparators included autologous graft (n=3 studies), other substitutes (n=2 studies) or various surgical technique using a synthetic product (e.g., AlloDerm, DuraGen, DuraGen Plus). The remaining studies involved products that were no longer commercially available or involved unique comparisons used in only one study. Similar types and rates of complications were reported for synthetic tissue versus autologous grafts. Due to the overall low level of evidence, Hayes concluded that there is a lack of evidence to support the safety and efficacy of these products for dural repair and patient selection criteria has not been established. Limitations of the studies included: small patient populations, lack of comparators, short-term follow-ups, conflicting evidence, and the heterogeneity of the product types and surgical procedures.

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

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

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

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

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

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

**Canadian Agency for Drugs and Technologies:** In a Rapid Respond Report on biological mesh, the Canadian Agency for Drugs and Technologies in Health (CADTH) (2010; updated 2015) presented a summary of findings on biological mesh for breast reconstruction, pelvic organ prolapse, mucogingival surgery, inguinal hernia repair, urethroplasty, diabetic foot ulcers, and decompressive hemicraniectomy. The report included systematic reviews, meta-analyses, technology assessments, randomized and non-randomized clinical trials, economic studies and guidelines. CADTH stated that the evidence of clinical effectiveness and safety was generally positive or neutral. However, the studies were of insufficient high quality to support the use of these products and their optimal place in therapy has not been established. Examples of commercially available products noted by CADTH included:

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

### **Professional Societies/Organizations**

**American Society of Plastic Surgeons (ASPS):** In the evidence based clinical practice guideline for breast reconstruction with expanders and implants (2013), ASPS stated that “evidence on acellular dermal matrix (ADM) in post-mastectomy expander/implant breast reconstruction is varied and conflicting. Surgeons should evaluate each clinical case individually and objectively determine the use of ADM”. Clinicians should be flexible



in their decision-making regarding appropriate practice, although they may set bounds on alternatives; patient preference should be have a substantial influencing role.

**American Urogynecologic Society (AUGS):** In the Choosing Wisely recommendations (2015), AUGS stated that synthetic or biologic grafts should not be used during posterior vaginal repair of rectocele for women with symptoms of a posterior vaginal wall bulge or difficulty with defecation. AUS stated that the use of these products does not improve patient outcomes.

**Use Outside of the US**

Tissue-engineered skin substitutes are offered outside the US by several companies. Products approved in the US may not be approved for use outside of the US and products approved outside the US may not be approved for use in the US. Also, the approved indications for the products may not be the same within and outside of the US. Integra LifeSciences has CE Mark approval for Surgimend PRS Mesh for pre- and sub-pectoral breast reconstruction in Europe. Strattice has CE Mark approval by the Netherlands-based notified body, KEMA, for its Strattice® Reconstructive Tissue Matrix. The CE Mark allows Strattice to be marketed in 27 European Union member states. Strattice is proposed for use in hernia repair and breast reconstruction. Native® (mbp, Germany) porcine acellular dermal matrix is proposed for use in Europe for breast reconstruction. DuralSeal dural sealant systems are available in Canada and Europe. Medtronic offers products in Canada, Europe, Asia, Japan, Middle East, Africa, Latin America, Australia and New Zealand. Biomet 3i™ also offers products worldwide.

**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.”

The National Institute for Health and Clinical Excellence (NICE) (United Kingdom) (2015) guidance on the management of diabetic foot ulcers states that dermal or skin substitutes should be considered as an adjunct to standard care only when healing of treated ulcers does not progress and should only be used on the advice of a multidisciplinary foot care service. NICE does not recommend any specific products.

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

**Coding/Billing Information**

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

**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 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15130	Dermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
15131	Dermal autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15135	Dermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
15136	Dermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15150	Tissue cultured skin autograft, trunk, arms, legs; first 25 sq cm or less
15151	Tissue cultured skin autograft, trunk, arms, legs; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
15152	Tissue cultured skin autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15155	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 25 sq cm or less
15156	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
15157	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15200	Full thickness graft, free, including direct closure of donor site, trunk; 20 sq cm or less
15201	Full thickness graft, free, including direct closure of donor site, trunk; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
15220	Full thickness graft, free, including direct closure of donor site, scalp, arms, and/or legs; 20 sq cm or less
15221	Full thickness graft, free, including direct closure of donor site, scalp, arms, and/or legs;

	each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
15240	Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; 20 sq cm or less
15241	Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
15260	Full thickness graft, free, including direct closure of donor site, nose, ears, eyelids, and/or lips; 20 sq cm or less
15261	Full thickness graft, free, including direct closure of donor site, nose, ears, eyelids, and/or lips; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
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)

<b>HCPCS Codes</b>	<b>Description</b>
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)
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
Q4116	Alloderm, per square centimeter
Q4121	TheraSkin, per square centimeter
Q4122	Dermacell, per square centimeter
Q4124	Oasis ultra tri-layer wound matrix, per square centimeter
Q4128†	Flexhd, allopatch hd, or matrix hd per square centimeter
Q4131	EpiFix, or epicord per square centimeter
Q4132	Grafix core, per square centimeter
Q4133	Grafix prime, per square centimeter
Q4151	AmnioBand or Guardian, per sq cm
Q4168	AmnioBand, 1 mg
Q4182	Transcyte, per sq cm

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

**Not Covered Tissue Engineered Skin Substitutes Application and Product Codes**

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

<b>CPT®* Codes</b>	<b>Description</b>
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue
46707	Repair of anorectal fistula with plug (eg: porcine small intestine submucosa [SIS])

49568	Implantation of mesh or other prosthesis for open incisional or ventral hernia repair or mesh for closure of debridement for necrotizing soft tissue infection (List separately in addition to code for the incisional or ventral hernia repair)
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
C1762	Connective tissue, human (includes fascia lata)
C1763	Connective tissue, nonhuman (includes synthetic)
C1768	Graft, vascular
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
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
C9364	Porcine implant, permacol, per square centimeter
J3590	Unclassified biologics
Q4103	Oasis burn matrix, per square centimeter
Q4110	Primatrix, per square centimeter
Q4111	Gammagraft, per square centimeter
Q4112	Cymetra, injectable, 1cc
Q4113	Graftjacket express, injectable, 1cc
Q4114	Integra flowable wound matrix, injectable, 1cc
Q4115	Alloskin, per square centimeter
Q4117	Hyalomatrix, per square centimeter
Q4118	MatriStem micromatrix, 1 mg
Q4123	Alloskin RT, per square centimeter
Q4125	Arthroflex, per square centimeter
Q4126	Memoderm, dermaspan, tranzgraft or integuply, per square centimeter
Q4127	Talymed, per square centimeter
Q4130	Strattice tm, per square centimeter
Q4131	EpiFix, or Epicord per square centimeter
Q4134	hMatrix, per square centimeter
Q4135	Mediskin, per square centimeter
Q4136	E-Z Derm, per square centimeter
Q4137	Amnioexcel or biodexcel, per square centimeter
Q4138	Biodfence dryflex, per square centimeter
Q4139	Amniomatrix or biodmatrix, injectable, 1 cc
Q4140	Biodfence, per square centimeter
Q4141	Alloskin AC, per square centimeter
Q4142	Xcm biologic tissue matrix, per square centimeter
Q4143	Repriza, per square centimeter
Q4145	Epifix, injectable, 1 mg
Q4146	Tensix, per square centimeter
Q4147	Architect, architect px, or architect fx, extracellular matrix, per square centimeter
Q4148	Neox 1k, per square centimeter

Q4149	Excellagen, 0.1 cc
Q4150	Allowrap ds or dry, per square centimeter
Q4152	Dermapure, per square centimeter
Q4153	Dermavest and plurivest, per square centimeter
Q4154	Biovance, per square centimeter
Q4155	Neoxflo or Clariflo, 1 mg
Q4156	Neox 100, per square centimeter
Q4157	Revitalon, per square centimeter
Q4158	MariGen, per square centimeter
Q4159	Affinity, per square centimeter
Q4160	NuShield, per square centimeter
Q4161	Bio-Connekt wound matrix, per square centimeter
Q4162	Amniopro flow, bioskin flow, biorenew flow, woundex flow, amniogen-a, amniogen-c, 0.5cc
Q4163	Amniopro, bioskin, biorenew, woundex, amniogen-45, amniogen-200, per square centimeter
Q4164	Helicoll, per square centimeter
Q4165	Keramatrix, per square centimeter
Q4166	Cytal, per square centimeter
Q4167	Truskin, per square centimeter
Q4168	Amnioband, 1 mg
Q4169	Artacent wound, per square centimeter
Q4170	Cygnus, per square centimeter
Q4171	Interfyl, 1 mg
Q4172	Puraply or puraply am, per square centimeter
Q4173	Palingen or palingen xplus, per square centimeter
Q4174	Palingen or promatrix, 0.36 mg per 0.25 cc
Q4175	Miroderm, per square centimeter
Q4176	Neopatch, per square centimeter
Q4177	Floweramnioflo, 0.1 cc
Q4178	Floweramniopatch, per square centimeter
Q4179	Flowerderm, per square centimeter
Q4180	Revita, per square centimeter
Q4181	Amnio wound, per square centimeter

**\*Current Procedural Terminology (CPT®) ©2017 American Medical Association: Chicago, IL.**

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