Bio-Engineered Skin and Soft Tissue Substitutes

Policy Number: MM.06.018

Original Effective Date: 06/01/2012

Line(s) of Business: HMO; PPO; QUEST Integration

Current Effective Date: 09/01/2016

Section: Surgery

Place(s) of Service: Outpatient/Office

I. Description

Bio-engineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (eg, dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. The various acellular dermal matrix products can differ in a number of ways, including as species source (human, bovine, porcine), tissue source (eg dermis, pericardium, intestinal mucosa), additives (eg antibiotics, surfactants), hydration (wet, freeze dried) and required preparation (multiple rinses, rehydration).

Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species (eg, bovine, porcine). Skin substitutes may also be composed of dermal cells, epidermal cells, or a combination of dermal and epidermal cells and may provide growth factors to stimulate healing. Tissue-engineered skin substitutes can be used as either temporary or permanent wound coverings.

There are a large number of potential applications for artificial skin and soft tissue products. One large category is nonhealing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, nonhealing lower-extremity wounds represent an ongoing risk for infection, sepsis, limb amputation, and death. Bio-engineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

The preferred outcome for the healing of lower-extremity ulcers is the percentage of patients with complete wound healing and the time to complete wound healing. The percentage of patients with 50% wound healing and time to 50% wound healing have also been considered to be appropriate outcomes for this condition. The percent change in wound area at 4 weeks is predictive of complete healing at 12 weeks in patients with diabetic foot ulcers. Thus, minimal improvement at 30 days can be considered as an indicator that a wound is unlikely to heal in patients with comorbidities that are known to affect wound healing.

Other situations in which bio-engineered skin products might substitute for living skin grafts
include certain postsurgical states such as breast reconstruction, in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Certain primary dermatologic conditions that involve large areas of skin breakdown, such as bullous diseases, may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. Acellular dermal matrix products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and a variety of other conditions.

Summary
Bio-engineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman tissue (xenographic), synthetic materials, or a composite of these materials. Bio-engineered skin and soft tissue substitutes are being evaluated for a variety of conditions, including breast reconstruction and to aid healing of lower-extremity ulcers and severe burns.

Acellular dermal matrix products are also being evaluated in the repair of a variety of soft tissues. Overall, the number of bio-engineered skin and soft-tissue substitutes is large, but the evidence is limited for any specific product. Relatively few products have been compared with the standard of care, and then only for some indications. A few comparative trials have been identified for use in lower-extremity ulcers (diabetic or venous) and for treatment of burns. In these trials, there is a roughly 15% to 20% increase in the rate of healing. Several other products/indications are supported by either clinical input or by an FDA humanitarian device exemption.

Breast Reconstruction
Given the extensive data from controlled cohorts and case series, as well as the clinical input obtained about the usefulness of this procedure in providing inferolateral support for breast reconstruction, use of allogeneic acellular dermal matrix (ADM) products (ie, AlloDerm, AlloMax, DermaMatrix, FlexHD, GraftJacket) may be considered medically necessary in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis, or when the inframammary fold and lateral mammary folds have been undermined during mastectomy and re-estabishment of these landmarks is needed.

Interpositional Graft After Parotidectomy
Two lower quality controlled trials were identified that demonstrated a reduction in the incidence of Frey syndrome with use of an interpositional ADM graft. Neither study described the method of group assignment or blinding of patients and assessors. In addition, clinical input regarding the use of an interpositional spacer after parotidectomy was not uniform. Therefore, bio-engineered skin and soft tissue substitutes are not covered to fill in contour defects and prevent Frey syndrome after parotidectomy.

Fistula Repair
One RCT was identified that used an ADM product that has not been cleared for marketing in the United States. Therefore, the use of this product for fistula repair is not covered.

Surgical Repair of Hernias
The limited evidence available does not support the efficacy of any tissue-engineered skin.
substitute for surgical repair of hernias. Therefore, this use is not covered.

Laryngoplasty
The effect of micronized AlloDerm (Cymetra) in laryngoplasty has been reported in case series. Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure and to evaluate the safety of repeat injections.

Tympanoplasty
AlloDerm has been compared with native tissue grafts in a non-RCT. There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia), and there was no significant difference in hearing between the groups at follow-up. Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure.

Diabetic Lower-Extremity Ulcers
RCTs have demonstrated the efficacy of Apligraf and Dermagraft over the standard of care, and of EpiFix in comparison with Apligraf. Use of these products may be considered medically necessary for the treatment of diabetic lower extremity ulcers. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

Lower-Extremity Ulcers Due to Venous Insufficiency
RCTs have demonstrated the efficacy of Apligraf and Oasis Wound Matrix over the standard of care. Use of these products may be considered medically necessary for lower-extremity ulcers due to venous insufficiency. In a large RCT, Dermagraft was not shown to be more effective than controls in the primary or secondary end points for the entire population, and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

Dystrophic Epidermolysis Bullosa
OrCel has received approval via an HDE. As this is a rare disorder and it is unlikely that there will be RCTs, OrCel is considered medically necessary for this indication.

This policy does not address products used in the treatment of burns, tendon/ligament repair or products supplied in an inpatient setting.

II. Criteria/Guidelines
A. Allogeneic acellular dermal matrix products (i.e., AlloDerm, DermaMatrix, FlexHD, Graftjacket, AlloMax) or Strattice are covered (subject to Limitations and Administrative Guidelines) in breast reconstructive surgery when one of the following criteria is met:
   1. There is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required;
   2. There are viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis; or
   3. The infra-mammary fold and lateral mammary folds have been undermined during
B. The use of allograft products is covered (subject to Limitations and Administrative Guidelines) for shoulder tendon repair.

B.C. Treatment of chronic, non-infected, full-thickness diabetic lower extremity ulcers using Apligraf, Dermagraft, Integra Dermal Regeneration Template, Amniotic Membrane Graft (e.g., OrBiovance, Epifix, Grafix) is covered (subject to Limitations and Administrative Guidelines) for the treatment of chronic, non-infected, full-thickness diabetic lower extremity ulcers when all of the following criteria are met:
1. The ulcers have not adequately responded after six weeks of standard wound therapy*; *
2. The patient is on a comprehensive diabetic management program; and
3. Reduction in pressure on a foot ulcer has been accomplished with appropriate modalities.

B.D. Treatment of chronic, non-infected, partial or full-thickness lower extremity skin ulcers due to venous insufficiency with Apligraf, Epifix or Oasis Wound Matrix is covered (subject to Limitations and Administrative Guidelines) for the treatment of chronic, non-infected, partial or full-thickness lower extremity skin ulcers due to venous insufficiency when all of the following criteria are met:
1. The ulcers have not adequately responded after six weeks of standard wound therapy*; *
2. Compression bandages and/or graduated compression garments have been consistently applied; and
3. Leg elevation and exercise have been encouraged.

E. Treatment of dystrophic epidermolysis bullosa with OrCel is covered (subject to Limitations and Administrative Guidelines) for the treatment of dystrophic epidermolysis bullosa.

F. Treatment of second- and third-degree burns using the following tissue-engineered skin substitutes is covered (subject to Limitations and Administrative Guidelines).
1. Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30% when provided in accordance with the HDE specifications of the FDA).
2. Integra Dermal Regeneration Template™
3. TransCyte™

* Standard wound therapy includes:
- Evaluation of wound with documentation of measurements (length, width and depth) at baseline and at least weekly by a licensed medical professional;
- Application of moist topical dressings;
- Debridement of necrotic tissue, if present;
- Treatment of infection, if present;
- Evaluation and provision of adequate nutrition;
- Management of diabetes mellitus, if applicable; and
- Evaluation and management of peripheral artery disease, if applicable.

III. Limitations
A. Bio-engineered skin and soft tissue substitutes have not been shown to improve health outcomes for all other conditions not listed under Criteria/Guidelines.

B. All other bio-engineered skin and soft tissue substitutes have not been shown to...
improve health outcomes, this includes, but is not limited to:

1. ACell® UBM Hydrated Wound Dressing
2. ACell® UBM Lyophilized Wound Dressing
3. Affinity™
4. AlloPatch HD™
5. AlloSkin™
6. AlloSkin™ RT
7. AlloWrap™
8. Alphaplex™ with MariGen Omega3™
9. AmnioFix®
10. Aongen™ Collagen Matrix
11. ArthroFlex™ (Flex Graft)
12. Atlas Wound Matrix
13. Avagen Wound Dressing
14. Avaulta Plus™
15. Biobrane®
16. BioDfence/BioDfactor
17. CellerateRX®
18. Clarix® Flo
19. Collagen Sponge (Innocoll)
20. Collagen Wound Dressing (Oasis Research)
21. CollaGUARD®
22. CollaSorb™
23. CollaWound™
24. Collexa®
25. Collieva®
26. Conexa™
27. Coreleader Colla-Pad
28. CorMatrix®
29. CRXa™
30. Cymetra®
31. Dermadapt™ Wound Dressing
32. DermaPure™
33. DressSkin
34. Dermavest™
35. Durepair Regeneration Matrix®
36. Endoform Dermal Template™
37. ENDURAGen™
38. Excellagen
39. E-Z Derm™
40. FortaDerm™ Wound Dressing
41. GammaGraft
42. Graftjacket® Xpress, injectable
43. GUARDIAN
44. HA Absorbent Wound Dressing
45. Helicoll
46. Hyalomatrix® (Laserskin®)
47. Hyalomatrix® PA
48. hMatrix®
49. Integra™ Flowable Wound Matrix
50. Integra™ Bilayer Wound Matrix
51. Jaloskin®
52. MariGen
53. MatriDerm®
54. MatriStem® Burn Matrix
55. MatriStem® Micromatrix
56. MatriStem® Wound Matrix
57. Matrix Collagen Wound Dressing
58. Matrix HD™
59. MediHoney®
60. Mediskin®
61. MemoDerm™
62. Neox® Flo
63. NuShield™
64. Oasis® Burn Matrix
65. Oasis® Ultra Tri-Layer Matrix
66. Permacol™
67. PriMatrix™
68. PriMatrix™ Dermal Repair Scaffold
69. Puros® Dermis
70. Repliform®
71. Repriza™
72. Revitalon™
73. SIS Wound Dressing II
74. SS Matrix™
75. Stimulen™ Collagen
76. StrataGraft®
77. Suprathel®
78. SurgiMend®
79. Talymed®
80. TenoGlide™
81. TheraForm™ Standard/Sheet
82. TheraSkin®
83. Unite™ Biomatrix
84. Veritas® Collagen Matrix
Bio-Engineered Skin and Soft Tissue Substitutes

<table>
<thead>
<tr>
<th>AmnioBand, Guardian</th>
<th>Amnioexcel-or-Biodexcel</th>
<th>Amniomatrix-or-Biodmatrix</th>
<th>Architect-extracellular-matrix</th>
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</thead>
<tbody>
<tr>
<td>Arthroflex</td>
<td>Biodfence-Dryflex</td>
<td>Biovance-1</td>
<td>Cymetra</td>
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<tr>
<td>Dermapure</td>
<td>Dermavest</td>
<td>E-Z-Derm</td>
<td>Excellagen</td>
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<td>Gammagraft</td>
<td>Grafix-prime</td>
<td>Hyalomatrix</td>
<td>hMatrix</td>
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<tr>
<td>MariGen</td>
<td>MatriStem-Micromatrix-and-Wound-Matrix</td>
<td>Mediskin</td>
<td>Memoderm</td>
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<tr>
<td>Neox</td>
<td>Neox Flo or ClarixFlo</td>
<td>Nushield</td>
<td>Primatrix</td>
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<tr>
<td>Repriza</td>
<td>Revitalon</td>
<td>SurgiMend</td>
<td>Talymed</td>
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<tr>
<td>Tensix</td>
<td>Theraskin</td>
<td>TissuMend</td>
<td>Unite Biomatrix</td>
</tr>
<tr>
<td>XCM-Biologic-Tissue-Matrix</td>
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</tr>
</tbody>
</table>

IV. Administrative Guidelines

A. Precertification is required for the application of Apligraf, Dermagraft, Epicel, OrCel, Integra Dermal Regeneration Template, Amniotic Membrane graft (e.g., Biovance, Epifix, Grafix), TransCyte, and Oasis Wound Matrix. Complete HMSA’s Precertification Request and mail or fax the form as indicated. Include the following information if applicable:
   1. Clinical notes documenting patient’s compliance with a diabetic management program.
   2. The exact location of the ulcer and initial ulcer size.
   3. Duration and description of the standard treatments that were tried and failed.
   4. Documentation of the presence of dystrophic epidermolysis bullosa if this is the indication.

B. Precertification is not required for acellular dermal matrixes products or Strattice when used in breast reconstruction surgery. HMSA reserves the right to perform retrospective reviews using the above criteria to validate if services rendered met payment determination criteria.

B.C. Precertification is not required for allograft products used in shoulder tendon repair. HMSA reserves the right to perform retrospective reviews using the above criteria to validate if services rendered met payment determination criteria.

C.D. Applicable HCPCS codes:

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
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<tr>
<td>Q4100</td>
<td>Skin substitute, not otherwise specified</td>
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<tr>
<td>Q4101</td>
<td>Apligraf, per square centimeter</td>
</tr>
<tr>
<td>Q4102</td>
<td>Oasis Wound Matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4105</td>
<td>Integra Dermal Regeneration Template (DRT), per square centimeter</td>
</tr>
<tr>
<td>Q4106</td>
<td>Dermagraft, per square centimeter</td>
</tr>
<tr>
<td>Q4107</td>
<td>Graftjacket, per square centimeter</td>
</tr>
<tr>
<td>Q4116</td>
<td>AlloDerm, per square centimeter</td>
</tr>
<tr>
<td>Q4122</td>
<td>Dermacell, per square centimeter</td>
</tr>
<tr>
<td>Q4124</td>
<td>Oasis Ultra Tri-Layer Wound Matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4128</td>
<td>Flex HD, Allopatch HD or Matrix HD, per square centimeter [when used for</td>
</tr>
</tbody>
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### Bio-Engineered Skin and Soft Tissue Substitutes

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tr>
<td>Q4130</td>
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<tr>
<td>Q4131</td>
<td>Epifix, per square centimeter</td>
</tr>
<tr>
<td>Q4132</td>
<td>Grafix core, per square centimeter</td>
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<td>Q4133</td>
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<tr>
<td>Q4145</td>
<td>Epifix, injectable, 1 mg</td>
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<tr>
<td>Q4154</td>
<td>Biovance, per square centimeter</td>
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**HCPCS codes that do not meet payment determination criteria:**

<table>
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<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<tr>
<td>C9349</td>
<td>Puraply, and Puraply Antimicrobial, any type, per square centimeter</td>
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<tr>
<td>C9354</td>
<td>Acellular pericardial tissue matrix of nonhuman origin (Veritas), per square centimeter</td>
</tr>
<tr>
<td>C9356</td>
<td>Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per square centimeter</td>
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<td>C9358</td>
<td>Dermal substitute, native, non-denatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters</td>
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<td>C9360</td>
<td>Dermal substitute, native, non-denatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters</td>
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<tr>
<td>C9363</td>
<td>Skin substitute, Integra Meshed Bilayer Wound Matrix, per square centimeter</td>
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<td>C9364</td>
<td>Porcine implant, Permacol, per square centimeter</td>
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<td>Q4103</td>
<td>Oasis Burn Matrix, per square centimeter</td>
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<td>Q4104</td>
<td>Integra Bilayer Matrix Wound Dressing (BMWD), per square centimeter</td>
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<td>Q4108</td>
<td>Integra Matrix, per square centimeter</td>
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<td>Q4110</td>
<td>PriMatrix, per sq. cm.</td>
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<td>Q4111</td>
<td>GammaGraft, per sq. cm.</td>
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<td>Q4112</td>
<td>Cymetra, injectable, 1 cc</td>
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<td>Graftjacket XExpress, injectable, 1 cc</td>
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<td>Integra Flowable Wound Matrix, injectable, 1 cc</td>
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<td>AlloSkin, per square centimeter</td>
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<td>AlloDerm, per square centimeter</td>
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<td>Q4117</td>
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<td>Q4118</td>
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<td>Q4119</td>
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<td>Alloskin RT, per sq. cm.</td>
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<td>Arthroflex, per sq. cm.</td>
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<td>Memoderm, Dermaspan, Transgraft or Integuply, per sq. cm.</td>
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<td>Q4127</td>
<td>Talymed, per sq. cm.</td>
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<tr>
<td>Q4128</td>
<td>Flex HD, Allopatch HD or Matrix HD, per sq. cm. [when used for Allopatch HD or Matrix HD]</td>
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<tr>
<td>Q4129</td>
<td>Unite Biomatrix, per sq. cm. square centimeter</td>
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<tr>
<td>Q4132</td>
<td>Grafix core, per sq. cm.</td>
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<td>Q4133</td>
<td>Grafix prime, per sq. cm.</td>
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<tr>
<td>Q4134</td>
<td>hMatrix, per sq. cm. square centimeter</td>
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<td>Q4135</td>
<td>Mediskin, per sq. cm. square centimeter</td>
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<td>Q4136</td>
<td>EZ-derm, per sq. cm. square centimeter</td>
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<td>Q4137</td>
<td>Amnioexcel or BioDExexCel, per sq. cm square centimeter</td>
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<td>Q4138</td>
<td>Biodfence Dryflex, per sq. cm square centimeter</td>
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<td>Q4139</td>
<td>Amniomatrix or BioDMDmatrix, injectable, 1 cc</td>
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<td>Q4140</td>
<td>Biodfence, per sq. cm square centimeter</td>
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<td>Q4141</td>
<td>Alloskin AC, per sq. cm square centimeter</td>
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<td>Q4142</td>
<td>XcmCM biologic tissue matrix, per sq. cm square centimeter</td>
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<td>Q4143</td>
<td>Repriza, per sq. cm square centimeter</td>
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<td>Q4146</td>
<td>TenSIX, per square centimeter</td>
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<td>Q4147</td>
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<td>Q4148</td>
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<td>Q4151</td>
<td>Amniband or, Guardian, 1 per sq. cm square centimeter</td>
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<td>Q4152</td>
<td>Dermapure, 1 per sq. cm square centimeter</td>
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<td>Q4153</td>
<td>Dermavest and Plurivest, 1 per sq. cm square centimeter</td>
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<td>Q4154</td>
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<td>Q4155</td>
<td>Neox fFlo Oor Clarix fFlo, 1 Mmg</td>
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<td>MariGgen, 1 Per sq. cm square centimeter</td>
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<td>Affinity, 1 Per sq. cm square centimeter</td>
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<td>NuSshield, 1 Per sq. cm square centimeter</td>
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<td>Bio-connekt wound matrix, per square centimeter</td>
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<td>Q4163</td>
<td>Amnioproc, bioskin, biorenew, woundex, amniogen-45, amniogen-200, per square centimeter</td>
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<td>Q4164</td>
<td>Helicoll, per square centimeter</td>
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<tr>
<td>Q4165</td>
<td>Keramatrix, per square centimeter</td>
</tr>
</tbody>
</table>

V. Background Regulatory Status

Bio-engineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (i.e., cadaveric human dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. The various acellular dermal matrix (ADM) products can differ in a number of ways, including as species source (human, |
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Regulatory Status

There are a large number of artificial skin products that are commercially available or in development. The following summary of commercially available skin substitutes describes those products that have substantial relevant evidence on efficacy. This list demonstrates the wide range of types of products available.

Acellular Dermal Matrix

Allograft acellular dermal matrix (ADM) products derived from donated human skin tissue are supplied by U.S. AATB-compliant tissue banks using the standards of the American Association of Tissue Banks (AATB) compliant tissue banks and federal U.S. Food and Drug Administration’s (FDA) guidelines. The processing removes the cellular components (i.e., epidermis and all viable dermal cells) that can lead to rejection and infection. Acellular dermal matrix ADM products from human skin tissue are regarded as minimally processed and not significantly changed in structure from the natural material; the FDA classifies it as banked human tissue and therefore, does not require FDA approval.
- **AlloDerm® (LifeCell Corp.)** is an acellular dermal matrix ADM (allograft) tissue-replacement product that is created from native human skin and processed so that the basement membrane and cellular matrix remain intact. Originally, AlloDerm required refrigeration and rehydration before use. It is currently available in a ready-to-use product that is stored at room temperature. An injectable micronized form of AlloDerm (Cymetra) is also available.

- **AlloMax™ Surgical Graft (Bard Davol)** is an acellular non-cross-linked human dermis allograft. (AlloMax was previously marketed as NeoForm™.)

- **DermaCell** is an allogeneic ADM processed with proprietary technologies MATRACELL and PRESERVON.

- **DermaMatrix** is a freeze-dried acellular dermal matrix (allograft) derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation (MTF).

- **DermaPure** is a single layer decellularized human dermal allograft for the treatment of acute and chronic wounds.

- **FlexHD (Ethicon)** is an acellular hydrated dermis derived from donated human allograft skin. The Musculoskeletal Transplant Foundation acquires and processes the tissue.

- **DermaCell** is an allogeneic ADM processed with proprietary technologies MATRACELL and PRESERVON.

- **DermaMatrix** is a freeze-dried acellular dermal matrix (allograft) derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation (MTF).

- **DermaPure** is a single layer decellularized human dermal allograft for the treatment of acute and chronic wounds.

- **Graftjacket Regenerative Tissue Matrix (also called Graftjacket Skin Substitute, KCI)** is an acellular regenerative tissue matrix that has been processed from screened donated human skin supplied from U.S. tissue banks. The allograft is processed-minimally processed to remove the epidermal and dermal cells while preserving dermal structure. Graftjacket Xpress® is an injectable product.

**Xenogenic**

Keramatrix® (Keraplast Research) is an open-cell foam comprised of freeze-dried keratin that is acellular animal-derived. In 2009, it was cleared for marketing by FDA through the 510(k) marketing process under the name of Keratec. The wound dressings are indicated in the management of the following types of dry, light, and moderately exuding partial and full-thickness wounds, pressure (stage I-IV) and venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, donor sites, and grafts.

Helicoll (Encol) is an acellular collagen matrix from bovine dermis. In 2004, it was cleared by FDA through the 510(k) process for topical wound management that includes partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (eg, abrasions, lacerations, second-degree burns, skin tears), and surgical wounds including donor sites/grafts.

Permacol™ (Covidien) is xenogeneic and composed of cross-linked porcine dermal collagen. Cross-linking improves the tensile strength and long-term durability, but decreases pliability.
PriMatrix™ is a xenogeneic acellular dermal matrix (ADM) processed from fetal bovine dermis. It is indicated was cleared for marketing by FDA through the U.S. Food and Drug Administration’s (FDA)-510(k) process for partial- and full-thickness wounds; diabetic, pressure, and venous stasis ulcers; surgical wounds; and tunneling, draining, and traumatic wounds.

SurgiMend® PRS (TEI Biosciences) is a xenogeneic ADM processed from fetal bovine dermis. This product is currently undergoing an FDA-regulated investigational device exemption (IDE) trial for breast reconstruction.

Strattice™ Reconstructive Tissue Matrix (LifeCell Corp.) is a xenogenic non-cross-linked porcine-derived ADM. There are pliable and firm versions, which are stored at room temperature and come fully hydrated.

OASIS™ Wound Matrix (Cook Biotech) is a xenogeneic collagen scaffold derived from porcine small intestinal mucosa. In 2000, it was cleared for marketing by FDA through the 510(k) process for the management of partial- and full-thickness wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds.

**Amniotic Membrane**

Amniotic membrane consists of 2 conjoined layers, the amnion and chorion, and forms the innermost lining of the amniotic sac or placenta. It is harvested immediately after birth, cleaned, sterilized, and either fresh frozen or dehydrated. Human amniotic membrane is considered to be minimally processed and not significantly changed in structure from the natural material; the FDA classifies it as banked human tissue and therefore, it does not require FDA approval. Epifix and Amniofix are commercially available sources of dehydrated human amniotic membranes. Epifix is provided in sheets and Amniofix is an injectable form of micronized amniotic membrane. Other Amniotic membrane sheet products include Affinity™ (NuTech Medical), AlloWrap™ (AlloSource), AlloWrap, AmnioBand, and GUARDIAN, (Musculoskeletal Transplant Foundation), AmnioGraft® (Bio-Tissue), BioDfence™ and Biodefense, BioDDryFlex® (both from BioD), Biovance® (Alliqua Biomedical), Dermavest™ and Plurivest™ (Aedicell), EpiFix® (dehydrated- MiMedix), Neox® Flo, Clarix Flo, Neox 1000® (Amniox® Medical), Grafix® Prime and Grafix® Core (cryopreserved, Osiris), NuShield™ (NuTech Medical), and Revitalon™ (previously known as AmnioClear, Medline Industries).

**Collagen Scaffold**

OASIS Wound Matrix is a xenogeneic collagen scaffold derived from porcine small intestinal mucosa. It was cleared by the FDA’s 510(k) process in 2000 for the management of partial and full-thickness wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds.

**Living Cell Therapy**

Apligraf® (Organogenesis) is a bilayered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. It is supplied as needed, in one size, with a shelf-life of 10 days. In 1998, it was FDA-approved in 1998 by FDA for use in conjunction with compression therapy for the treatment of non-infected, partial and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic ulcers.
lower extremity ulcers nonresponsive to standard wound therapy.

Dermagraft® (Organogenesis) is composed of cryopreserved human-derived fibroblasts and collagen applied to derived from newborn human foreskin and cultured on a bioabsorbable polyglactin mesh scaffold. Dermagraft has been approved by the FDA for repair of diabetic foot ulcers and for use in the treatment of wounds related to dystrophic epidermolysis bullosa.

TheraSskin® (Soluble Systems) is a cryopreserved human skin allograft composed of living fibroblasts and keratinocytes and an extracellular matrix in epidermal and dermal layers. TheraSskin® is derived from human skin allograft in compliance with the American Association of Tissue Banks (AATB) and U.S. Food and Drug Administration's (FDA) guidelines. It is considered a minimally processed human cell, tissue, and cellular- and tissue-based product (HCT/P) by the FDA.

OrCel™ (Forticell Bioscience; formerly Composite Cultured Skin) is an absorbable allogeneic bilayered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. It was approved by the FDA pre-market approval for healing donor site wounds in burn victims and under an humanitarian device exemption (HDE) for use in patients with recessive dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites.

Biosynthetic

Biobrane®/Biobrane-L (Smith and Nephew) is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially imbedded into the film. The fabric creates a complex 3-dimensional structure of tri-filament thread, which chemically binds collagen. Blood/secreta clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs.

Integra® Dermal Regeneration Template (marketed as Omnigraft Dermal Regeneration Matrix, Integra LifeSciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It was approved by FDA for use in postexcisional treatment of life-threatening 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 physiologic condition of the patient. Integra™ Matrix Wound Dressing and Integra™ meshed Bilayer Wound Matrix are substantially equivalent skin substitutes approved by FDA through the 510(k) process for other indications. Integra® Bilayer Wound Matrix (Integra LifeSciences) is designed to be used in conjunction with negative pressure wound therapy. The meshed bilayer provides a flexible wound covering and allows drainage of wound exudate. FDA product code: MDD.

TransCyte™ (Advanced Tissue Sciences) consists of human dermal fibroblasts grown on nylon mesh, combined with a synthetic epidermal layer and was approved by FDA in 1997. TransCyte is intended to be used as a temporary covering over burns until autografting is possible. It can also be used as a temporary covering for some burn wounds that heal without autografting.

Synthetic

Suprathel® (PolyMedics Innovations) is a synthetic copolymer membrane fabricated from a tripolymer of polylactide, trimethylene carbonate, and s-caprolactone. It is used to provide temporary coverage of superficial dermal burns and wounds. Suprathel® is covered with gauze and a dressing that is left in place until the wound has healed.
VI. Rationale:

This evidence review was developed based on a literature search using MEDLINE in November 2007 for use of an allogeneic tissue-engineered skin substitute (AlloDerm) in breast reconstructive surgery. At the time this review was created, the available data on use of this technology were limited. In particular, there were no comparative studies to evaluate possible changes of the reconstructive time or to evaluate changes in esthetics. In addition, the duration of follow-up was limited, so the impact on longer-term complications such as severe contractures could not be determined. Finally, criteria to determine those who were candidates for use of this procedure had not been established.

In 2011 this evidence review was expanded to address additional bio-engineered skin and soft tissue substitutes and other indications. The most recent literature update was performed through October 30, 2015. Following is a summary of key literature to date.

Breast Reconstruction

AlloDerm

Systematic Reviews:

Two systematic reviews from 2012 found an increased rate of complications with acellular dermal matrix (ADM)-assisted breast reconstruction. One meta-analysis of 16 retrospective studies found a higher likelihood of seroma (pooled odds ratio [OR], 3.9; 95% confidence interval [CI], 2.4 to 6.2), infection (pooled OR = 2.7; 95% CI, 1.1 to 6.4) and reconstructive failure (pooled OR = 3.0; 95% CI, 1.3 to 6.8) when compared to with breast reconstruction using traditional musculofascial flaps. Another meta-analysis that compared 19 studies using acellular dermal matrix ADM (n=2,037) with 35 studies using submuscular reconstruction (n=12,847) found an increased risk of total complications (relative risk [RR], 2.05; 95% CI, 1.55 to 2.70), seroma (RR = 2.73; 95% CI, 1.67 to 4.46), infection (RR = 2.47; 95% CI, 1.71 to 3.57) and reconstructive failure (RR = 2.80; 95% CI, 1.76 to 4.45) with acellular dermal matrix ADM. These meta-analyses are limited by the poor quality of included studies and significant heterogeneity.

Randomized Controlled Trials:

In 2012, McCarthy et al. reported a multicenter blinded randomized controlled trial (RCT) of AlloDerm in 2-stage expander/implant reconstruction. Seventy patients were randomized to AlloDerm acellular dermal matrix ADM-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. There were no significant differences between the groups in the primary outcomes of immediate postoperative pain (54.6 AlloDerm and 42.8 control on a 100-point visual analog score) or pain during the expansion phase (17.0 AlloDerm and 4.6 control), or in the secondary outcome of rate of tissue expansion (91 days AlloDerm and 108 days control) and patient reported physical well-being. There was no significant difference in adverse events (AEs), although the total number of AEs adverse events was small. Phase 2 of the study will evaluate long-term outcomes.

Controlled Studies:

Preminger and colleagues et al evaluated the impact of AlloDerm on expansion rates in immediate tissue expander/implant reconstruction in a retrospective matched cohort study. Forty-five patients had reconstruction with AlloDerm and 45 had standard reconstruction. Subjects
were matched for expander size (±100 mL), history of irradiation, and indication for mastectomy. There were no significant differences in initial filling volume, mean rate of postoperative expansions, or in the incidence of postoperative complications. Aesthetic outcomes were not addressed. In 2008 Colwell and Breuing reported on 10 patients who had mastopexy with dermal slings; 5 patients were given AlloDerm and 5 were given autologous tissue. Patients maintained projection and breast base width after 6 months to 3 years.

**Uncontrolled Studies:**
A number of case series have also demonstrated that this approach can provide tissue coverage of implants and tissue expanders. AlloDerm has been reported in nipple reconstructive surgery in a case series on 30 nipple reconstructive procedures performed at one institution. Use of AlloDerm has also been reported in a small series (n=3) to correct breast implant-related problems (malposition, symmastia, and rippling).

**Strattice**
Given the extensive data from case series as well as the clinical input obtained about the usefulness of this procedure in providing inferolateral support for breast reconstruction, use of AlloDerm may be considered medically necessary in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis; or when the infra-mammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed. The expanding body of literature for Strattice as well as the wide acceptance of its use by the reconstructive surgery community makes it a medically necessary alternative to Alloderm under similar circumstances.

**Other:**
Liu et al. reported postoperative complications in breast reconstruction with (n=266) or without (n=204) AlloDerm in 2011. Radiation therapy, body mass index (BMI), intraoperative use of tumescent solution, and medical comorbidities were similar between the 2 groups, but there were twice as many smokers and the implants were larger in the AlloDerm group. There was a trend for a higher rate of major infections that required prosthesis removal in the AlloDerm group (4.9% vs 2.5%, p=0.172) and a statistically significant increase in overall wound infection rate (6.8% vs 2.5%). The overall surgical complication rate was significantly higher in the AlloDerm group (19.5% vs 12.3%). Multivariate analysis indicated that the use of ADM (acellular dermal matrix), smoking, higher BMI, higher initial volume, and bigger implant size were associated with a higher overall surgical complication rate. This study is limited by the retrospective analysis and differences between groups at baseline.

Bindingnavele et al. reviewed charts of 41 patients (65 breasts) who had staged breast reconstruction with acellular cadaveric dermis to report postoperative complication rates. Rates for wound infection, expander removal, hematoma, and seroma were 3.1%, 1.5%, 1.5%, and 4.6%, respectively. The authors concluded that based on low rates of complications and good cosmetic outcomes, the technology should be in the repertoire of plastic surgeons, and that follow-up is required to evaluate long-term outcomes.
**Bio-Engineered Skin and Soft Tissue Substitutes**

**AlloDerm Versus DermaMatrix or FlexHD**

A 2014 retrospective review by Liu et al compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts). Eighty-one percent of the sample were immediate reconstructions; 165 used AlloDerm, and 97 used FlexHD. Mean follow-up was 6.4 months. Compared with breast reconstruction without use of AlloDerm or FlexHD, ADM had a higher rate of delayed healing (20.2% vs 10.3%), although this finding might be related to differences in fill volumes. In univariate analysis, there were no significant differences in complications (return to the operating room, surgical site infection, seroma, hematoma, delayed healing, or implant loss) between AlloDerm and FlexHD. In multivariate analysis, there were no significant differences between AlloDerm and FlexHD for the return to the operating room, surgical site infection, seroma, or delayed healing. Independent risk factors for implant loss included the use of FlexHD, single-stage reconstruction, and smoking.

Another retrospective review from 2013 compared complication rates following use of AlloDerm (n=136) or FlexHD (n=233) in a consecutive series of 255 patients (369 breasts). Total complication rates for the 2 products were similar (19.1% for AlloDerm, 19.3% for FlexHD). Analysis by type of complication showed no significant difference between the 2, and regression analysis controlling for differences in baseline measures found that the type of ADM was not a risk factor for any complication.

Brooke et al conducted a retrospective review of complication rates when AlloDerm (n=49), DermaMatrix (n=110), or FlexHD (n=62) was used for tissue expander breast reconstruction. Clinically significant complications were defined as cellulitis, abscess, seroma, expander leak or puncture, skin necrosis, wound dehiscence, or hematoma. The total clinically significant complication rate was 22% with AlloDerm, 15% with DermaMatrix, and 16% with FlexHD (not significantly different). Infectious complication rates for the 3 products were the same at 10%. When compared with breast reconstruction without an ADM (n=64), there was no significant difference in the total complication rate (17% vs 11%), but there was a trend toward a higher incidence of infectious complications (10% vs 2%, p=0.09).

This small amount of evidence from retrospective comparative studies does not show any difference in outcomes among different types of ADM products.

**SurgiMend (Fetal Bovine ADM) Versus AlloDerm (Human ADM)**

Butterfield reported a retrospective comparison of 281 patients who underwent breast reconstruction with SurgiMend (79.0%) or AlloDerm (21.0%). AlloDerm was used at the beginning of the study while SurgiMend was used predominantly in the latter period due to ease of use and lower cost; the 2 groups were comparable on patient demographics, risk factors, and concurrent therapy. The rate of seroma-, the most prevalent complication, was significantly lower for SurgiMend (8.3%) compared with AlloDerm (15.7%, p=0.044); however the necrosis rate was higher for SurgiMend (11.1% vs 3.4%, p=0.027), due entirely to a higher minor necrosis rate for SurgiMend (8.8% vs 1.1%). There were no significant differences in complication rates for hematoma, infection, major skin necrosis, or breast implant removal. SurgiMend is currently being studied in a randomized clinical trial compared to AlloDerm (NCT01781299) and in a non-randomized comparative trial of breast reconstruction with and without the use of SurgiMend (NCT01959867).
Section Summary: Breast Reconstruction

The extensive data from controlled cohorts and case series about the usefulness of this procedure in providing inferolateral support for breast reconstruction supports the use of acellular dermal matrix (ADM) allograft (ie, AlloDerm, AlloMax, DermaMatrix, FlexHD, Graftjacket) in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis; or when the inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Interpositional Graft Aafter Parotidectomy

AlloDerm

In 2003, Sinha et al. reported the use of AlloDerm acellular human dermal matrix as an interpositional physical barrier to prevent the development of Frey syndrome (gustatory sweating) after parotidectomy. Thirty patients were divided into 3 groups; it was not described if the assignments were randomized. One group underwent superficial parotidectomy with reconstruction of the defect with AlloDerm, a second group had superficial parotidectomy without placement of an interpositional barrier, and the third group underwent deep-plane rhytidectomy without disruption of the parotid fascia. At minimum 1-year follow-up, there was a subjective incidence of Frey syndrome in 1 patient treated with AlloDerm and 5 patients in group 2. The objective incidence of Frey syndrome, measured with the Minor starch-iodine test, was 2 patients treated with AlloDerm and 8 patients in group 2. None of the patients in group 3 who underwent deep-plane rhytidectomy without disruption of the parotid fascia had subjective or objective Frey syndrome. There were no AE adverse effects.

A 2008 publication from Asia compared use of allogeneic acellular dermal matrix (RENOV) in 168 patients who had superficial or partial parotidectomy. Sixty-four patients received an acellular dermal matrix ADM and 104 patients had superficial or partial parotidectomy alone. The size of the graft depended on the amount of tissue required to restore the normal facial contour. The method of assignment to the 2 groups was not described. At a median follow-up of 16 months (range, 11-27), the subjective incidence of Frey syndrome was 2% in the acellular dermal matrix ADM group compared with 61% in controls. Objective assessment, performed in 30 patients randomly selected from each group, found an incidence of Frey syndrome in 2 patients (7%) treated with acellular dermal matrix ADM and 24 patients (80%) in the control group. One patient in the acellular dermal matrix ADM group and 18 patients in the control group developed a parotid fistula.

DermaMatrix

DermaMatrix is an acellular dermal matrix ADM that differs from AlloDerm in several ways: it can be stored at room temperature (vs. refrigerated), it has a shelf-life of 3 years (vs. 2 years), and it can be rehydrated in 3 minutes (vs. 30 minutes).

Athavale et al. evaluated complications of AlloDerm and DermaMatrix in a retrospective review of 100 patients treated between 2001 and 2009 at a single U.S. institution. Exclusion criteria for the study included presence of malignancy on final surgical pathology report, incomplete medical
records, previous history of radiation therapy to the head and neck region, and additional procedures to the region of the parotid gland. Initially, only AlloDerm was used; this changed to a 20/80 ratio of AlloDerm/DermaMatrix due to more readily available stock of DermaMatrix.

Complications were defined as any outcome that required procedural intervention for resolution (seroma/sialocele formation, infected fluid collection, and/or serosanguinous fluid collection). The authors identified 8 complications in 31 DermaMatrix implants (26%) compared with 5 complications in 69 AlloDerm implants (7%). The complication rate did not differ for total parotidectomies but was higher for DermaMatrix compared to AlloDerm for subtotal parotidectomies (37% vs 8%). Nearly half of all complications were seroma/sialocele formation.

Randomized, double-blind, controlled trials RCTs with longer follow-up are needed to evaluate this procedure.

**Tendon Repair**

**Graftjacket**

In 2012, Barber et al reported an industry-sponsored multicenter RCT of augmentation with Graftjacket acellular human dermal matrix for arthroscopic repair of large (>3 cm) rotator cuff tears involving 2 tendons. Twenty-two patients were randomized to Graftjacket augmentation, and 20 patients were randomized to no augmentation. At a mean follow-up of 24 months (range, 12-38) the American Shoulder and Elbow Surgeons score improved from 48.5 to 98.9 in the Graftjacket group and from 46.0 to 94.8 in the control group (p=0.035). The Constant score improved from 41 to 91.9 in the Graftjacket group and from 45.8 to 85.3 in the control group (p=0.008). The University of California, Los Angeles score was not significantly different between the groups. Gadolinium-enhanced magnetic resonance imaging (MRI) scans showed intact cuffs in 85% of repairs in the Graftjacket group and 40% of repairs in the control group. However, no correlation was found between MRI findings and clinical outcomes. Rotator cuff retears occurred in 3 patients (14%) in the Graftjacket group and 9 patients (45%) in the control group. Although these results are promising, additional study with a larger number of patients is needed.

**Fistula Repair**

**Acellular Dermal Matrix**

A study from Asia compared a xenogeneic ADM (J-I type; J.Y. Life Tissue Engineering, China) with endorectal advancement flap (ERAF) for the treatment of complex anorectal fistula in a randomized study with 90 consecutive patients. Follow-up was performed at 2 days, 2, 4, 6, and 12 weeks, and 5 months after surgery. Success was defined as closure of all external opening, absence of drainage without further intervention, and absence of abscess formation. Success was observed in 82.2% of the ADM group. Fistula recurred in 2 (4.45%) patients in the ADM group compared with 13 (28.89%) patients in the ERAF group. Healing time was reduced (7.5 days vs 24.5 days), and quality of life was rated higher in the ADM group (85.9 vs 65.3). No significant difference was observed in the incontinence and anal deformity rate between the 2 groups. This product is not cleared for marketing in the United States, although the manufacturing process was reported to be similar to Surgisis® AFPTM (Cook Surgical).

**Surgical Repair of Hernias**

A 2011 systematic review included 30 level III and level IV articles on ADM for abdominal wall reconstruction. No RCTs or high-quality comparative studies (level I or II) were identified.
Examples of the level III studies are described next.

**AlloDerm**

Gupta et al. compared the efficacy and complications associated with the use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair in 2006. The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine sub-mucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7 to 10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in 8 hernia recurrences (24%). Fifteen of the AlloDerm patients (45%) developed a diastasis or bulging at the repair site. Seroma formation was only a problem in two patients.

In 2007, Espinosa-de-las-Monteros and colleagues retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases. They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery. From 2005 to 2007, AlloDerm was used to repair large (>200 cm²) symptomatic complicated ventral hernias that resulted from trauma or emergency surgery (N=55). From 2008 to 2010, FlexHD was used to repair large complicated ventral hernias in patients meeting the same criteria (n=40). The 2 groups were comparable at baseline. At one-year follow-up, all of the AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, or true recurrence) requiring a second repair. Eleven patients (31%) in the FlexHD group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

**Reconstructive Tissue Matrix**

The PRISM Study Group reported a multicenter double-blinded, randomized trial of porcine acellular dermal matrix for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies. Patients were randomly assigned to undergo standard stoma construction with no reinforcement (n=58) or stoma construction with Reconstructive Dermal Matrix as parastomal reinforcement (n=55). At 24-months of follow-up (n=75), the incidence of parastomal hernias was similar for the 2 groups (13.2% of controls, and 12.2% of the study group).

The limited evidence available at this time does not support the use of AlloDerm in hernia repair or prevention of parastomal hernia.

**Oral Surgery**

In 2008, Novaes and de Barros described 3 randomized trials from their research group that examined use of ADM in root coverage therapy and alveolar ridge augmentation. Two trials used...
ADM in both the study and control groups and are not described here. A third trial compared ADM with subepithelial connective tissue graft in 30 gingival recessions (9 patients). At 6 months postsurgery, the ADM showed recession reduction of 1.83 mm while subepithelial connective tissue graft showed recession reduction of 2.10 mm; these were not significantly different.

A nonrandomized cohort study compared AlloDerm with the criterion standard of split-thickness skin grafts in 34 patients who underwent oral cavity reconstruction following surgical removal of tumors. Patients were enrolled after surgical treatment for evaluation at a tertiary care center and divided into 2 cohorts according to the reconstruction method used, which was based on surgeon preference. Twenty-two patients had been treated with AlloDerm, and 12 had been treated with split-thickness skin grafts. The location of the grafts (AlloDerm vs autograft) were on the tongue (54% vs 25%), floor of mouth (9% vs 50%), tongue and floor of mouth (23% vs 8%), buccal (9% vs 0%), or other (5% vs 17%). More patients in the AlloDerm group were treated with radiotherapy (45% vs 17%), and the graft failure rate was higher (14% vs 0%). Radiotherapy had a significantly negative impact for both groups. Histology on a subset of the patients showed increased inflammation, fibrosis, and elastic fibers with split-thickness skin grafts. Functional status and quality of life were generally similar in the 2 groups. Interpretation of these results is limited by the differences between the groups at baseline.

Laryngoplasty
There are several reports with short-term follow-up of micronized AlloDerm (Cymetra) injection for laryngoplasty. In 2005, Milstein et al. reported mean 11.2 month follow-up (range, 1 to 35 months) of Cymetra injection in 20 patients with unilateral vocal-fold paralysis. Pre- and post-operative digital voice samples and video stroboscopy were rated on a 4-point scale by a panel of 3 voice experts who were blinded to the pre- or postoperative status. Compared with preoperative measures, Cymetra improved voice quality (from 3.23 to 1.65), glottal closure (from 3.21 to 1.42), and degree of vocal-fold bowing (from 2.38 to 1.36). Quality-of-life measures and patients’ self-perceptions of vocal quality were also improved. In 5 patients (25%), the effect was temporary, and in 8 patients (40%) who had follow-up of 1 year or longer, the improvement was maintained. Longer-term study in a larger number of patients is needed to determine the durability of this procedure and to evaluate the safety of repeat injections.

Tympanoplasty
Vos et al. reported a retrospective non-randomized comparison of AlloDerm versus native tissue grafts for type I tympanoplasty in 2005. Included in the study were 108 patients (25 AlloDerm, 53 fascia reconstruction, and 30 fascia plus cartilage reconstruction) treated between 2001 and 2004. One surgeon had performed 96% of the AlloDerm tympanoplasties. Operative time was reduced in the AlloDerm group (82 minutes for AlloDerm, 114 minutes for fascial cases, and 140 minutes for fascia plus cartilage). There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia). There was no significant difference in hearing between the groups at follow-up (time not specified). Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure.

Diabetic Lower Extremity Ulcers
Apligraf
In 2001, Veves and colleagues et al. reported on a randomized prospective study on the
effectiveness of Apligraf (previously called Graftskin (Apligraf), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers. The study involved 24 centers in the United States, 208 patients were randomly assigned to ulcer treatment either with Graftskin-Apligraf (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical débridement and adequate foot off-loading, was provided in both groups. Apligraf Graftskin was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of five applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Apligraf Graftskin-treated patients achieved complete wound healing compared with 36 (38%) in the control group (p=0.0042). The Kaplan-Meier median time to complete closure was 65 days for Apligraf Graftskin, significantly lower than the 90 days observed in the control group (p=0.0026). The rate of adverse reactions was similar between the two groups with the exception of osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf Graftskin group. The authors concluded that application of Apligraf Graftskin for a maximum of 4 weeks resulted in a higher healing rate when compared with state-of-the-art treatment and was not associated with any significant side effects AEs. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (Graftskin), in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.

In 2010, Steinberg and colleagues et al reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of non-infected diabetic foot ulcers. The design and patient population of this study were similar to the 208-subject U.S. study (previously described above) which led to FDA approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with a non-infected neuropathic diabetic foot ulcer present for at least two weeks were enrolled in these prospective, multicenter, randomized, controlled, open-label RCTs studies that compared Apligraf use in conjunction with standard therapy (sharp débridement, standard wound care, and off-loading) against standard therapy alone. Pooling of data was performed because of the similarity and consistency of the two studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration that was significantly longer in the European study (21 months, compared to 10 months in the U.S. study). Reported adverse events AEs by 12 weeks were comparable across treatment groups in the two studies. Efficacy measures demonstrated superiority of Apligraf treatment over control treated groups in both studies. Combining the data from both studies, 55.2% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared to 34.3% (46/134) of control subjects (p<0.001=0.0005), and Apligraf subjects had a significantly shorter time to complete wound closure (p<0.001=0.0004). The authors concluded that both the EU and U.S. studies exhibited superior efficacy and comparable safety for subjects treated with Apligraf compared to control subjects, and the studies provide evidence of the benefit of Apligraf in treating diabetic foot ulcer DFU.

In 2010, Kirsner and colleagues et al reported on analysis of 2,517 patients with diabetic neuropathic foot ulcers who were treated between 2001 and 2004. The study was a retrospective analysis using a wound-care database; the patients received advanced biological therapy, specifically i.e., Apligraf (446 patients), Regranex, or Procuren. In this study, advanced biological therapy was used, on average, within 28 days from the first wound clinic visit and was associated
with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biological therapy were 31.2% more likely to heal than wounds first treated with topical recombinant growth factor (p<0.001), and 40.0% more likely to heal than those first treated with platelet releasate (p=0.01). Wound size, wound grade, duration of wound, and time to initiation of advanced biological therapy affected the time to healing.

Dermagraft
A pivotal multi-center FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft or control. Over the course of the 12-week study patients received up to 8 applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91% compared to 78% for the control group. Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious AEs were attributed to Dermagraft. Ulcer infections developed in 10.4% of the Dermagraft patients compared to 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group (19% vs. 32.5%).

Retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft (5.5% vs 12.6%, p=0.031). Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

TheraSkin vs Dermagraft
Sanders et al reported a small (n=23) industry-funded randomized comparison of TheraSkin (human skin allograft with living fibroblasts and keratinocytes) versus Dermagraft (human-derived fibroblasts cultured on mesh) for diabetic foot ulcers. Wound size at baseline ranged from 0.5 to 18.02 cm^2; the average wound size was about 5 cm^2 and was similar for the 2 groups (p=0.51). Grafts were applied according to manufacturer’s instructions over the first 12 weeks of the study until healing, with an average of 4.4 TheraSkin grafts (every 2 weeks) compared with 8.9 Dermagraft applications (every week). At week 12, complete wound healing was observed in 63.6% of ulcers treated with TheraSkin and 33.3% of ulcers treated with Dermagraft (p=0.0498). At 20 weeks, complete wound healing was observed in 90.9% of the TheraSkin-treated ulcers compared with 66.67% of the Dermagraft group (p=0.428). Additional study in a larger number of subjects is needed.

EpiFix Amniotic Membrane
EpiFix is an amniotic membrane extracellular collagen allograft comprised of an epithelial layer and two fibrous connective tissue layers. Amniotic membrane is banked human tissue regulated by the AATB and FDA. Four growth factors are present in EpiFix including epidermal growth factor (EGF), transforming growth factor – β (TGF-β), fibroblast growth factor (FGF) and platelet derived growth factor A & B (PDGF A & B). It 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. EpiFix comes in a wide-variety of sizes eliminating waste and reducing cost.

Clinical trials reported ninety percent of wounds treated exhibited 100% uptake of the amniotic-membrane graft without rejection after 1 week. An average of 50 percent reduction of wound-
volume and size was proven by weekly measurements. Clinical pain, signs of infection, and drainage post-application was noticeably less among amniotic membrane graft patients.

Postoperative course and maintenance is simple and direct, which allowed for better compliance. A single-site industry-sponsored prospective, randomized comparative parallel study of amniotic membrane vs. standard management in the treatment of diabetic ulcers was published by Zelen C. in 2012. It was terminated early due to dramatic and significant improved outcomes in the Epifix group. At 6 weeks the Epifix arm had a 92% wound healing rate compared to only 8% for the conventional treatment arm. Though the authors conclude that further expanded studies should be considered, they point out that the dramatic improvement in outcomes coupled with the cost-effective characteristic of the product already make it a viable clinical option for diabetic ulcers.

**GraftJacket Regenerative Tissue Matrix**

Brigido et al. reported a small (N=40) randomized pilot study of GraftJacket compared with conventional treatment for chronic non-healing diabetic foot ulcers in 2004. Control patients received conventional therapy with débridement, wound gel with gauze dressing, and off-loading. GraftJacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the GraftJacket group. Preliminary 1 month results showed that after a single treatment, ulcers treated with GraftJacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs. 15%), width (50% vs. 23%), area (73% vs. 34%) and depth (89% vs. 25%). All of the grafts incorporated into the host tissue.

In 2009, Reyzelman et al. reported an industry-sponsored multicenter randomized study that compared a single application of GraftJacket versus standard of care (SOC) in 86 patients with diabetic foot ulcers. Offloading was performed using a removable cast walker. Ulcer size at presentation was 3.6 cm² in the GraftJacket group and 5.1 cm² in the control group. Eight patients, 6 in the study group and 2 in the control group, did not complete the trial. At 12 weeks, complete healing was observed in 69.6% of the GraftJacket group and 46.2% of controls. After adjusting for ulcer size at presentation, a statistically significant difference in non-healing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks versus 6.8 weeks for the control group. The authors did not report if this difference was statistically significant. The median time to healing was 4.5 weeks for GraftJacket (range, 1—12) and 7.0 weeks for control (range 2—12). Kaplan-Meier survivorship analysis for time to complete healing at 12 weeks showed a significantly lower non-healing rate for the study group (30.4%) compared with the control group (53.9%). The authors commented that a single application of GraftJacket, as used in this study, is often sufficient for complete healing. This study is limited by the small study population, differences in ulcer size at baseline, and the difference in the percentage of patients censored in each group. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant. Additional trials with a larger number of subjects are needed to evaluate if GraftJacket Regenerative Tissue Matrix improves health outcomes in this population.

**Integra Dermal Regeneration Template**

Integra Dermal Regeneration Template is a biosynthetic skin substitute that is FDA approved for
life-threatening thermal injury. The Foot Ulcer New Dermal Replacement Study (FOUNDER) multicenter study (32 sites) on Integra Template for chronic nonhealing diabetic foot ulcers was conducted under an FDA-regulated investigational device exemption. A total of 307 patients with at least 1 chronic diabetic foot ulcer were randomized to treatment with Integra Template or a control condition of 0.9% sodium chloride gel. Treatment was given for 16 weeks or until wound closure. There was a modest increase in wound closure with Integra Template (51% vs 32%, \( p = 0.001 \)) and a shorter median time to closure (43 days vs 78 days, \( p = 0.001 \)). There was a strong correlation between investigator-assessed and computerized planimetry assessment of wound healing (\( r = 0.97 \)). Kaplan-Meier analysis showed the greatest difference between groups in wound closure up to 10 weeks, with diminishing differences after 10 weeks. Strengths of the study include adequate power to detect an increase in wound healing of 18%, which was considered to be clinically significant, secondary outcomes of wound closure and time to wound closure by computerized planimetry, and intention-to-treat (ITT) analysis.

Dehydrated Amniotic Membrane

In 2013, Zelen et al reported an industry-sponsored, non-blinded, RCT comparing use of EpiFix dehydrated amniotic membrane (\( n = 13 \)) with SOC (moist wound therapy, \( n = 12 \)) for diabetic foot ulcers of at least 4 weeks in duration. EpiFix was applied every 2 weeks if the wound had not healed, with weekly dressing changes comprised of nonadherent dressing, moisture retentive dressing, and a compression dressing. Standard moist wound dressing was changed daily. After 4 weeks of treatment, EpiFix-treated wounds had reduced in size by a mean of 97.1% compared with 32.0% for the SOC group. Healing rate, defined as complete epithelialization of the open area of the wound, was 77% for EpiFix compared with 0% for SOC. After 6 weeks of treatment, wounds were reduced by 98.4% with EpiFix treatment compared with -1.8% for SOC. The healing rate was 92% with EpiFix compared with 8% with SOC alone. At the conclusion of the trial, unhealed wounds from the control group were treated with EpiFix. The mean duration of foot ulcers at the beginning of treatment was 19.4 weeks (range, 6.0-54 weeks) for the combined group. Follow-up was available at 9 to 12 months after primary healing in 18 of 22 eligible patients. Examination of these 18 patients found that 17 (94.4%) wounds remained fully healed.

In 2015, Smiell et al reported an industry-sponsored multicenter registry study of Biovance dehydrated amniotic membrane for the treatment of various chronic wound types, including 47 diabetic foot wounds, 20 pressure ulcers, and 89 venous ulcers. This study shows effectiveness of dehydrated amniotic membrane in a real-world setting. The size of the wounds at baseline ranged from less than 2 cm\(^2\) (35.4% of wounds) to over 25 cm\(^2\) (9.0% of wounds). Ninety-eight percent were on the lower extremities. Twenty-eight ulcers had failed prior treatment with advanced biological therapies. For all wound types, 41.6% closed with a mean time to closure of 8 weeks and a mean of 2.4 amniotic membrane applications. In the subgroup of 112 patients who practiced good wound care, including offloading or compression therapy as indicated, 49.6% of wounds achieved closure at a mean of 7.4 weeks. Wounds that had not closed during the observation period decreased in size by a mean of 46.6%.

Dehydrated Amniotic Membrane Versus Apligraf

EpiFix (dehydrated amniotic allograft) was compared with Apligraf (living cell therapy) in a multicenter RCT published by Zelen et al in 2015. Sixty patients were randomized to treatment with Epifix, Apligraf, or standard wound care. Although the patient and site investigator could
not be blinded due to differences in products, wound healing was verified by 3 independent physicians who evaluated photographic images. The median wound size was 2.0 cm² (range, 1.0-9.0) and the median duration of the index ulcer was 11 weeks (range, 5-54). After 6 weekly treatments, the mean percent wound area healed was 97.1% for EpiFix, 80.9% for Apligraf, and 27.7% for standard care; 95% of wounds had healed in the EpiFix group compared with 45% treated with Apligraf and 35% who received standard wound care (p≤0.003). The estimated median time to wound closure, based on Kaplan-Meier analysis, was 13 days for EpiFix compared with 49 days for both Apligraf and SOC (p≤0.001).

In 2015, Kirsner et al reported an industry-sponsored observational study comparing the effectiveness of Apligraf versus EpiFix in a real-world setting. Data was obtained from a wound care-specific database from 3000 wound care facilities. The database included 1458 diabetic ulcers treated for the first time in 2014 with either Apligraf (n=994) or EpiFix (464). Using the same criteria used in the 2015 study by Zelen et al (described above), data were included on the treatment of 226 diabetic foot ulcers from 99 wound care centers. Foot wounds were included with size between 1 and 25 cm², duration of 1 year or less, and wound reduction of 20% or less in the 14 days prior to treatment. Although wounds for the 2 groups were comparable at baseline, the rationale for using a particular product was not reported. There were 163 wounds treated with Apligraf (mean, 2.5 applications) and 63 treated with EpiFix (mean, 3.5 applications, p=0.003). By week 24, 72% of wounds treated with Apligraf and 47% of wounds treated with EpiFix had closed (p=0.01). The median time to closure was 13.3 weeks for Apligraf and 26.0 weeks for EpiFix (p=0.01). This study is limited by the possibility of selection bias in determining treatment assignment.

Cryopreserved Amniotic Membrane
Grafix cryopreserved amniotic membrane was compared with standard wound care in a multicenter RCT. Strengths of this well-designed study include power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and ITT analysis. Ninety-seven patients with chronic diabetic foot ulcers were randomized to treatment with Grafix or to standard wound therapy, both administered once a week for up to 12 weeks. Power analysis indicated that 94 patients per arm would be needed for adequate power. However, after prespecified interim analysis at 50% enrollment, the blinded review committee recommended that the trial be stopped due to efficacy of the treatment. ITT analysis from the blinded evaluation phase showed a significant increase in the proportion of patients achieving the primary outcome of wound closure by 12 weeks (62.0% vs 21.3%, p<0.001) and a decrease in the median time to complete wound closure (42.0 days vs 69.5 days, p=0.019). Safety evaluation found that fewer Grafix-treated patients experienced at least 1 AE (44.0% vs 66.0%, p=0.031) and had wound-related infections (18.0% vs 36.2%, p=0.044), with a trend toward reduced hospitalization related to infections (6% vs 15%, p=0.15).

Oasis Wound Matrix
Niezgoda and colleagues et al compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix, an acellular wound care product, versus Regranex Gel. This was an industry-sponsored randomized controlled multicenter trial RCT conducted at 9 outpatient wound care clinics and involved 73 patients with at least 1 diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix (n=37) or Regranex Gel (n=36) and a
secondary dressing. Wounds were cleansed and débrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks of treatment, 18 (49%) Oasis-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients. Oasis treatment met the noninferiority margin, but did not demonstrate that healing in the Oasis group was statistically superior (p=0.055). Post-hoc subgroup analysis showed no significant difference in incidence of healing in patients with type 1 diabetes (33% vs. 25%) but showed a significant improvement in patients with type 2 diabetes (63% vs. 29%). There was also an increased healing of plantar ulcers in the Oasis group (52% vs. 14%). These post-hoc findings are considered hypothesis-generating. Additional study with a larger number of subjects is needed to evaluate the effect of Oasis treatment in comparison with the current SOC.

**PriMatrix**

In 2014, Kavros et al reported a prospective multicenter study of PriMatrix (a xenograft fetal bovine dermal collagen matrix) for the treatment of chronic diabetic foot ulcers in 55 patients. The average duration of ulcers prior to treatment was 286 ±353 days and the average area was 4.34 cm². Of the 46 patients who completed the study, 76% healed by 12 weeks with an average of 2 applications of PriMatrix. For the intention-to-treat (ITT) population, 64% of wounds healed by 12 weeks.

In 2011, Karr published a retrospective comparison of PriMatrix (a xenograft fetal bovine dermal collagen matrix) and Apligraf in 40 diabetic foot ulcers. The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. Included were diabetic foot ulcers of 4 weeks’ duration; ulcer to at least 1 sq. cm² in diameter and to the depth of subcutaneous tissue; healthy tissue at the ulcer; adequate arterial perfusion to heal; and ability to off-load the diabetic ulcer. The products were placed on the wound with clean technique, overlapping the edges of the wound, and secured with sutures or staples. The time to complete healing for PriMatrix was 38 days with 1.5 applications compared to 87 days with 2 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care (SOC).

**Section Summary: Diabetic Lower-Extremity Ulcers**

RCTs have demonstrated the efficacy of Apligraf, Dermagraft, and Integra Dermal Regeneration Template over the SOC. Several amniotic membrane products have also been shown to improve healing. Additional study with a larger number of subjects is needed to evaluate the effect of Oasis Wound Matrix and PriMatrix treatment in comparison with the current SOC.

**Lower Extremity Ulcers due to Venous Insufficiency**

**Apligraf**

Apligraf is a living cell therapy composed of living human keratinocytes and fibroblasts. Falanga and colleagues reported a multicenter randomized trial of Apligraf (human skin equivalent) in 1998. A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or compression therapy and treatment with Apligraf. Apligraf was applied up to a maximum of 5 (mean 3.3) times per patient during the initial 3 weeks. The primary end points were the percentage of patients with complete healing by 6 months after initiation of treatment and the time required for complete healing. At 6-months’ follow-up, the
percentage of patients healed was increased with Apligraf (63% vs. 49%) and the median time to complete wound closure was reduced (61 days vs. 181 days). Treatment with Apligraf was found to be superior to compression therapy in healing larger (>1000 mm²) and deeper ulcers and ulcers of more than 6 months' in duration. There were no symptoms or signs of rejection and the occurrence of adverse events AEs were similar in both groups. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (Graftskin), in conjunction with good local wound care, met the TEC criteria for the treatment of venous ulcers that fail to respond to conservative management.

**Dermagraft**

Dermagraft is a living cell therapy composed of cryopreserved human fibroblasts cultured on a bioabsorbable mesh. Dermagraft has been approved by the FDA for repair of diabetic foot ulcers. Use of Dermagraft for venous ulcers is an off-label indication. In 2013, Harding et al. reported an open-label multi-center randomized controlled trial RCT that compared Dermagraft plus compression therapy (n=186) versus compression therapy alone (n=180). The study had numerous inclusion/exclusion criteria that restricted the study population to patients who had nonhealing ulcers with compression therapy but had capacity to heal. Intent-to-treat ITT analysis revealed no significant difference between the 2 groups in the primary outcome measure, the proportion of patients with completely healed ulcers by 12 weeks (34% Dermagraft vs. 31% control). Pre-specified subgroup analysis revealed a significant improvement in the percent of ulcers healed for ulcers of 12 months or less in duration (52% vs. 37%) and for ulcers of 10 cm or less (47% vs. 39%). There were no significant differences in the secondary outcomes of time to healing, complete healing by week 24, and percent reduction in ulcer area.

**Oasis Wound Matrix**

Oasis Wound Matrix is a xenogeneic collagen scaffold derived from porcine small intestinal mucosa. In 2005, Mostow et al. reported an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment with Oasis Wound Matrix versus standard of care SOC in 120 patients with chronic ulcers due to venous insufficiency that were not adequately responding to conventional therapy. Healing was assessed weekly for up to 12 weeks, with follow-up performed after 6 months to assess recurrence. After 12 weeks of treatment, there was a significant improvement in the percentage of wounds healed in the Oasis group (55% vs. 34%). After adjusting for baseline ulcer size, patients in the Oasis group were 3 times more likely to achieve healing than those in the standard care group receiving SOC. Patients in the standard care SOC group whose wounds did not heal by the 12th week were given the option to cross over to Oasis treatment. None of the healed patients treated with Oasis wound matrix and who were seen for the 6-month follow-up experienced ulcer recurrence.

A research group in Europe has described two comparative studies of the Oasis matrix for mixed arterial/venous and venous ulcers. In a 2007 quasi-randomized study, Romanelli et al. compared the efficacy of two extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid). A total of 54 patients with mixed arterial/venous leg ulcers were assigned to the two arms based on order of entry into the study; 50 patients completed the study. Patients were followed up twice a week and the dressings were changed more than once a week only if necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis-treated ulcers compared with 46.2% of Hyaloskin-treated ulcers. Oasis treatment
significantly increased the time to dressing change (mean of 6.4 days vs. 2.4 days), reduced pain on a 10-point scale (3.7 vs. 6.2) and improved patient comfort (2.5 vs. 6.7).

In a 2010 trial, Romanelli et al. compared Oasis with a moist wound dressing (SOC) in 23 patients with mixed arterial/venous ulcers and 27 patients with venous ulcers. The study was described as randomized, but the method of randomization was not described. After the 8-week study period, patients were followed up monthly for 6 months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis-treated ulcers at 8 weeks, compared to 65% of the standard-of-care SOC group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks as compared with 8.3 weeks for the standard-of-care SOC group. Treatment with Oasis also increased the time to dressing change (5.2 days vs. 2.1 days) and the percentage of granulation tissue formed (65% vs. 38%).

**PriMatrix**

*PriMatrix is a xenogeneic ADM.* In 2011, Karr published a retrospective comparison of PriMatrix and Apligraf in 28 venous stasis ulcers. The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Included Criteria were venous stasis ulcers of 4 weeks’ duration, at least 1 sq. cm² in diameter and to a depth of subcutaneous tissue, with healthy tissue at the ulcer edge, adequate arterial perfusion to heal, and able to tolerate compression therapy. The products were placed on the wound with clean technique, overlapping the edges of the wound, and secured with sutures or staples. The time to complete healing for PriMatrix was 32 days with 1.3 applications compared to 63 days with 1.7 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care SOC.

**Dehydrated Amniotic Membrane**

In 2014, Serena et al reported an industry-sponsored multicenter open-label RCT that compared Epifix dehydrated amniotic membrane combined with compression therapy to compression therapy alone for the treatment of venous leg ulcers. Ulcers were included if they were chronic (>1 month in duration); extended through the full thickness of the skin but not down to muscle, tendon, or bone; and had been treated with compression therapy for at least 14 days. A total of 84 participants were enrolled and assigned to a single Epifix allograft (n=26), 2 allografts (n=27), or compression therapy alone (n=31). The primary outcome, the proportion of patients achieving 40% wound closure at 4 weeks, was 62% in the combined Epifix groups and 32% in the control group (p=0.005). During the 4-week study period, 6 patients (11.3%) in the combined Epifix group and 4 (12.9%) in the control group achieved complete wound closure. Secondary outcomes, which evaluated the use of 1 versus 2 applications of amniotic membrane, showed no significant difference in outcomes (62% vs 63%). Strengths of this study include adequate power and ITT analysis with last observation carried forward. Limitations include the lack of blinding for wound evaluation and use of 40% closure rather than complete closure. A report was published subsequently in 2015 on 44 patients from this RCT (31 had been treated with amniotic membrane) found that wounds with at least 40% wound closure at 4 weeks (n=20) had a rate of closure of 80% by 24 weeks; however, this was a retrospective study and didn’t take into account additional treatments after the 4-week randomized trial period.

Section Summary: Lower-Extremity Ulcers due to Venous Insufficiency.
Randomized controlled trials RCTs have demonstrated the efficacy of Apligraf and Oasis Wound Matrix and Epifix over the standard of care SOC. Use of these products may be considered medically necessary for lower-extremity ulcers due to venous insufficiency. In a moderately large randomized controlled trial RCT, Dermagraft was not shown to be more effective than controls in the primary or secondary end points for the entire population and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or size of 10 cm or less. Given the lack of difference between 1 or 2 applications of Epifix and the lack of difference between the experimental and control groups in complete wound closure at 4 weeks, additional study is needed. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care SOC.

**Dystrophic Epidermolysis Bullosa**

Dermagraft had been FDA approved by a Humanitarian Device Exemption (HDE) for the treatment of dystrophic epidermolysis bullosa. The manufacturer has since withdrawn Dermagraft from HDE status.

OrCel is approved by an HDE for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites.

As this is a rare disorder, it is unlikely that there will be randomized controlled trials RCTs to evaluate if whether OrCel improves health outcomes for this condition. Dermagraft is no longer considered medically necessary for this indication, due to the withdrawal of HDE status.

In 2003, Fivenson et al reported the off-label use of Apligraf in 5 patients with recessive dystrophic epidermolysis bullosa who underwent syndactyly release.

Dermagraft, OrCel, and Apligraf are all living cell therapies. Apligraf is a bilayered cell therapy composed of living human keratinocytes and fibroblasts, while OrCel is a bilayered cellular matrix made of bovine collagen in which human dermal cells (fibroblasts and keratinocytes) have been cultured. Dermagraft is composed of cryopreserved human-derived fibroblasts and collagen on a bioabsorbable mesh.

**Ocular Burns**

A 2012 Cochrane review evaluated the evidence on amniotic membrane transplantation (AMT) for acute ocular burns. Included in the review was a single RCT from India of 68 patients with acute ocular burns who were randomized to treatment with AMT and medical therapy or medical therapy alone. In the subset of 36 patients with moderate ocular burns who were treated within 7 days, 13 of 20 (65.0%) of control eyes and 14 of 16 (87.5%) of AMT-treated eyes had complete epithelialization by 21 days. There was a trend (p=0.09) toward a reduced risk ratio of failure of epithelization in the treatment group. Mean LogMAR (logarithm of the minimum angle of resolution) final visual acuities were 0.06 in the treatment group and 0.38 in the control group. In the subset of patients with severe ocular burns treated within 7 days, 1 of 17 (5.9%) of AMT-treated eyes and 1 of 15 (6.7%) control eyes were epithelialized by day 21. Final visual acuity was 1.77 logMAR in the treated eyes and 1.64 in the control group (not significantly different). The risk of bias was considered to be high because of differences between the groups at baseline and
because outcome assessors could not be masked to treatment. The review determined that conclusive evidence supporting the treatment of acute ocular surface burns with AMT is lacking. It should also be noted that the amniotic membrane used in this study was fresh frozen and is not commercially available.

Nonocular Burns

Biomembrane
A small (N=46) quasirandomized trial compared treatment with amniotic membrane (Biomembrane) versus polyurethane membrane (Tegaderm) for patients with second- or third-degree burns covering less than 50% total body surface area (BSA). Treatment with amniotic membrane significantly reduced occurrence of infection (4.3%) compared with treatment with polyurethane (13.0%). Pain during dressing was reduced in the group treated with amniotic membrane (43.5% vs 60.9%), while the frequency of healing within the 11- to 20-day follow-up was greater (47.8% vs 39.1%). It was not reported if the evaluators in this quasirandomized study were blinded to treatment condition. In addition, this study did not have a control group treated with medical therapy alone.

Epigel
Epigel is FDA approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a total BSA of 30% or more. It is unlikely that there will be RCTs to evaluate whether Epigel will improve health outcomes for this condition. One case series described the treatment of 30 severely burned patients with Epigel. The cultured epithelial autografts were applied to a mean of 37% of total BSA. Epigel achieved permanent coverage of a mean of 26% of total BSA, an area greater than that covered by conventional autografts (mean, 25%). Survival was 90% in these severely burned patients.

Epifix
Although several small trials from the Middle East and Asia have evaluated locally harvested and processed amniotic membrane, no RCTs were identified with the commercially available Epifix amniotic membrane.

Integra Dermal Regeneration Template
A 2013 study compared Integra versus split-thickness skin graft or viscose cellulose sponge (Cellonex), using 3 test sites of 10x5 cm on each of 10 burn patients. The surrounding burn area was covered with meshed autograft. Biopsies were taken from each site on days 3, 7, 14, and 21, and at 3 months and 12 months. The tissue samples were stained and examined for markers of inflammation and proliferation. The Vancouver Scar Scale was used for scar assessment. At 12-month follow-up, the 3 methods resulted in similar clinical appearance, along with similar histologic and immunohistochemical findings.

In 2007, Branski et al reported a randomized trial of Integra compared with a standard autograft-allograft technique in 20 children with an average burn size of 73% total BSA (71% full-thickness burns). Once vascularized (about 14-21 days), the Silastic epidermis was stripped and replaced with thin (0.05-0.13 mm) epidermal autograft. There were no significant differences between the Integra group and controls in burn size (70% vs 74% total BSA), mortality (40% vs 30%), and length of stay (41 vs 39 days, all respectively). Long-term follow-up revealed a significant increase in bone mineral content and density (24 months) and improved scarring in terms of height,
thickness, vascularity, and pigmentation (12 months and 18-24 months) in the Integra group. No differences were observed between the groups in the time to first reconstructive procedure, cumulative reconstructive procedures required during 2 years, and the cumulative operating room time required for these procedures. The authors concluded that Integra can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

In 2003, Heimbach et al reported a multicenter (13 U.S. burn care facilities) postapproval study involving 222 burn injury patients (36.5% total BSA; range, 1%-95%) who were treated with Integra Dermal Regeneration Template. Within 2 to 3 weeks, the dermal layer regenerated, and a thin epidermal autograft was placed over the wound. The incidence of infection was 16.3%. Mean take rate (absence of graft failure) of Integra was 76.2%; the median take rate was 98%. The mean take rate of epidermal autograft placed over Integra was 87.7%; the median take rate was 95%.

OrCel
There is limited evidence to support the efficacy of OrCel compared with the SOC for the treatment of split-thickness donor sites. In 2003, Still et al examined the safety and efficacy of bilayered OrCel to facilitate wound closure of split-thickness donor sites in 82 severely burned patients. Each patient had 2 designated donor sites that were randomized to receive a single treatment of either OrCel or the standard dressing (Biobrane-L). The healing time for OrCel sites was significantly shorter than for sites treated with a standard dressing, enabling earlier recropping. OrCel sites also exhibited a nonsignificant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

TransCyte
In 2001, Lukish et al compared 20 consecutive cases of pediatric burns greater than 7% total BSA that underwent wound closure with TransCyte with the previous 20 consecutive burn cases greater than 7% total BSA that received standard therapy. Standard therapy consisted of application of antimicrobial ointments and hydrodébridement. Only 1 child in the TransCyte group required autografting (5%) compared with 7 children in the standard therapy group (35%). Children treated with TransCyte had a statistically significant decreased length of stay compared with those receiving standard therapy (5.9 days vs 13.8 days, respectively).

In 2006, Amani et al compared results from 110 consecutive patients with deep partial-thickness burns who were treated with TransCyte with data from the American Burn Association Patient Registry. Significant differences were found in patients who were treated with dermabrasion and TransCyte compared with the population in the Registry. Patients with 0% to 19.9% total BSA burn treated with dermabrasion and TransCyte had length of stay of 6.1 days versus 9.0 days (p<0.001). Those with 20% to 39.9% total BSA burn had length of stay of 17.5 days versus 25.5 days. Patients who had 40% to 59.9% total BSA burn had length of stay of 31 versus 44.6 days. The authors found this new method of managing patients with partial-thickness burns to be more efficacious and to significantly reduce length of stay compared with traditional management.

Traumatic and Surgical Wounds
A 2013 RCT examined the efficacy of Keramatrix keratin dressing on partial-thickness skin graft
donor sites. Keramatrix was placed side by side with standard dressing in this within-subject RCT of 26 patients. Split-skin graft donor sites were chosen for the study because they provide uniform thickness wounds for comparisons. Wound healing was assessed as a percent epithelialization, rather than the preferred outcome of percentage of wounds healed and time to complete healing. In patients more than 50 years of age, blinded evaluation found median wound healing of 5% with standard dressing and 10% with Keramatrix (range, 0-100; p=0.023). In patients ages 50 years or younger, median epithelialization was 80% at 7 days (range, 0-100) and there was no significant difference in percent healed between the treatment and control portions of the wound. Study in a larger number of patients/wounds with complicating factors is needed.

Use of Integra Dermal Regeneration Template has been reported in small case series (<20 patients) for the treatment of severe wounds with exposed bone, joint and/or tendon. No controlled trials were identified.

Other
In addition to indications previously reviewed, off-label uses of bio-engineered skin substitutes have included pressure ulcers, inflammatory ulcers such as pyoderma gangrenosum and vasculitis, scleroderma digital ulcers, postkeloid removal wounds, genetic conditions, and variety of other conditions. In addition, products that have been FDA approved/cleared for 1 indication (eg, lower-extremity ulcers) have been used off-label in place of other FDA approved/cleared products (eg, for burns). No controlled trials were identified for these indications. Therefore, they are considered investigational.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02120755</td>
<td>A Randomized Comparison of AmnioClear™ Human Allograft Amniotic Membrane vs. Moist Wound Dressing in the Treatment of Diabetic Wounds</td>
<td>60</td>
<td>Unknown</td>
</tr>
<tr>
<td>NCT02399826</td>
<td>A Prospective, Randomized, Comparative Parallel Study of Amniotic Membrane Graft in the Management of Diabetic Foot Ulcers</td>
<td>40</td>
<td>Jan 2016</td>
</tr>
<tr>
<td>NCT02609594</td>
<td>A Multi-center Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Amnioband Dehydrated Human Amniotic Membrane and Standard of Care vs. Standard of Care Alone in the Treatment of Venous Leg Ulcers</td>
<td>240</td>
<td>Dec 2016</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.
within the different categories (eg, ADM, living cell therapy, xenogeneic collagen scaffold, and amniotic membrane). Five reviewers addressed the use of ADM products for breast reconstruction, and most considered the various ADM products (AlloDerm, AlloMax, DermaMatrix, FlexHD, GraftJacket) to have similar outcomes when used for breast reconstructive surgery, although differences in firmness and stretch of the products were noted. Six reviewers addressed questions on bio-engineered skin and soft tissue substitutes for diabetic and venous lower extremity ulcers. Responses were mixed, although a majority of reviewers considered living cell therapies to be equivalent for these indications. A majority of reviewers did not consider xenogeneic ADM products (eg, PriMatrix) or amniotic membrane (eg, EpiFix) to be medically necessary for any indication.

Summary of Evidence

Surgical Repair

The evidence on bioengineered soft-tissue substitutes for individuals undergoing surgical repair includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, there are a limited number of soft-tissue substitutes, and the evidence is limited for any specific product. Following is a description of the evidence for specific indications.

Bio-engineered skin and soft tissue substitutes are being evaluated for a variety of conditions. Overall, the number of bio-engineered skin and soft tissue substitutes is large but the evidence is limited for any specific product. Relatively few products have been compared with the standard of care, and then only for some indications. A few comparative trials have been identified for use in lower extremity ulcers (diabetic or venous). In these trials, there is a roughly 15% to 20% increase in the rate of healing. Several other products/indications are supported by either clinical input or by an FDA HDE.

Breast Reconstruction

Given the extensive data from controlled cohorts and case series, as well as the clinical input obtained about the usefulness of this procedure in providing inferolateral support for breast reconstruction, supports the use of acellular dermal matrixes (ADM) allograft (ie, AlloDerm, AlloMax, DermaMatrix, FlexHD, Graftjacket) or Strattice may be considered medically necessary in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis, or when the infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Interpositional Graft After Parotidectomy

Two lower quality controlled trials were identified that demonstrated a reduction in the incidence of Frey syndrome with use of an interpositional acellular dermal matrix ADM allograft. Neither study described the method of group assignment or blinding of patients and assessors. In addition, clinical input regarding the use of an interpositional spacer after parotidectomy was not uniform. Therefore, bio-engineered skin and soft tissue substitutes are considered investigational to fill in contour defects and prevent Frey syndrome after parotidectomy. The evidence is insufficient to
determine the effects of the technology on health outcomes.

**Tendon Repair**
One small RCT was identified that found improved outcomes with Graftjacket ADM allograft for rotator cuff repair. Although these results are promising, additional study with a larger number of subjects is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Fistula Repair**
One randomized controlled trial RCT was identified that used an acellular dermal matrix ADM product allograft that has not been cleared for marketing in the United States. Therefore, the use of this product for fistula repair is not covered. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Surgical Repair of Hernias**
The limited evidence available does not support the efficacy of any tissue-engineered skin substitute for surgical repair of hernias. The evidence is sufficient to determine qualitatively that the technology is unlikely to improve the net health outcome. Therefore, this use is not covered.

**Oral Surgery**
Use of an ADM allograft (AlloDerm) has been reported for root coverage therapy and oral cavity reconstruction following surgical removal of tumors. Although AlloDerm may possibly result in less scar contracture, results to date have not shown an improvement over the standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Laryngoplasty**
The effect of micronized AlloDerm ADM (eg, Cymetra) in laryngoplasty has been reported in case series. Longer term controlled study in a larger number of patients is needed to determine the durability of this procedure and to evaluate the safety of repeat injections. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Tympanoplasty**
AlloDerm ADM has been compared with native tissue grafts in a non-RCT randomized controlled study. There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia), and there was no significant difference in hearing between the groups at follow-up. Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Chronic Wounds**
The evidence on bioengineered skin substitutes for individuals with chronic wounds includes RCTs. Relevant outcomes include disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Overall, the number of bio-engineered skin substitutes is large, but the evidence is limited for any specific product. Relatively few products have been compared with the standard of care, and then only for some indications. Some comparative trials have been identified for use in lower-extremity ulcers (diabetic or venous) and for treatment of burns.
In these trials, there is a roughly 15% to 20% increase in the rate of healing. Several other products/indications are supported by a U.S. Food and Drug Administration (FDA) humanitarian device exemption. Following is a description of the evidence for specific indications.

**Diabetic Lower-Extremity Ulcers**

- Randomized controlled or comparative trials (RCTs) have demonstrated the efficacy of Apligraf, Dermagraft (ADM), and Integra Dermal Regeneration Template (biosynthetic) Epifix over the standard of care and of Epifix in comparison to Apligraf. Use of these products may be considered medically necessary for the treatment of diabetic lower extremity ulcers. Several amniotic membrane products have also been shown to improve healing. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

- Additional study with a larger number of subjects is needed to evaluate the effect of xenogenic skin substitutes (eg Oasis Wound Matrix and PriMatrix) treatment in comparison with the current standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Lower-Extremity Ulcers due to Venous Insufficiency**

- Randomized controlled or comparative trials (RCTs) have demonstrated the efficacy of Apligraf ADM, Epifix and xenogenic Oasis Wound Matrix over the standard of care. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome. Use of these products may be considered medically necessary for lower extremity ulcers due to venous insufficiency.

- In a moderately large RCT, Dermagraft ADM was not shown to be more effective than controls in the primary or secondary end points for the entire population and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or size of 10 cm or less. The evidence is insufficient to determine the effects of the technology on health outcomes.

- In a randomized comparison of Epifix amniotic membrane versus standard of care that used a primary outcome measure of 40% wound healing, there was no difference between 1 or 2 applications of Epifix and no difference between the experimental and controls groups in complete wound closure at 4 weeks. Additional study is needed. Additional study with a larger number of subjects is also needed to evaluate the effect of the xenogenic PriMatrix skin substitute in comparison with the current standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

**Dystrophic Epidermolysis Bullosa**

OrCel (living cell therapy) has received approval via a Humanitarian Device Exemption (HDE). As this is a rare disorder and it is unlikely that there will be randomized controlled trials (RCTs), this product is considered medically necessary for this indication.

All other uses of the tissue-engineered skin substitutes do not meet payment determination criteria.

**Burns, Skin Grafts, and Traumatic Wounds**
The evidence on bio-engineered soft-tissue substitutes for individuals with burns, skin grafts, and traumatic wounds includes RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, there are a limited number of soft-tissue substitutes, and the evidence is limited for any specific product. Following is a description of the evidence for specific indications.

**Ocular Burns**
The evidence is insufficient to determine the effects of the technology on health outcomes.

**Nonocular Burns**
Epicel (living cell therapy) is FDA-approved under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. The evidence is insufficient to determine the effects of the technology on health outcomes.

Comparative studies have demonstrated improved outcomes for the biosynthetic skin substitutes Integra Dermal Regeneration Template and TransCyte for the treatment of burns. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

**Skin Grafts**
Keramatrix (xenogenic skin substitute) was compared with standard of care in a small RCT for healing of skin graft donor sites. Results overall are equivocal. Study in a larger number of patients/wounds is needed.

**Traumatic Wounds**
Use of biosynthetic Integra Dermal Regeneration Template has been reported in small case series (<20 patients) for the treatment of severe wounds with exposed bone, joint, and/or tendon. Controlled trials are needed to evaluate this product/indication. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2014 Input
In response to requests, input was received from 3 physician specialty societies and 4 academic medical centers while this policy was under review in 2014. In addition to questions on medical necessity for different indications, input was specifically requested on the equivalency of products within the different categories (eg, acellular dermal matrix [ADM], living cell therapy, xenogeneic collagen scaffold, amniotic membrane). Five reviewers addressed the use of ADM products for breast reconstruction, and most considered the various ADM products (AlloDerm, AlloMax, DermaMatrix, FlexHD, Graftjacket) to have similar outcomes when used for breast reconstructive surgery, although differences in firmness and stretch of the products were noted. Six reviewers addressed questions on bio-engineered skin and soft tissue substitutes for diabetic and venous lower-extremity ulcers. Responses were mixed, although most reviewers considered
living cell therapies to be equivalent for these indications. Most reviewers did not consider xenogeneic ADM products (eg, PriMatrix) or amniotic membrane (eg, EpiFix) to be medically necessary for any indication.

2011 Input
In response to requests, input was received from 3 physician specialty societies and 2 academic medical centers while this policy was under review in 2011. Most reviewers supported the indications and products described in this policy. Clinical input was requested regarding the use of an interpositional spacer after parotidectomy. Support for this indication was mixed. Some reviewers suggested use of other products and/or additional indications; however, the input on these products/indications was not uniform. The reviewers provided references for the additional indications; these were subsequently reviewed.

2008 Input
In response to requests for input on use of AlloDerm in breast reconstruction surgery, input was received from 1 physician specialty society (2 physicians) and 1 academic medical center while this policy was under review in 2008. All reviewers indicated that this procedure should be available for use during breast reconstructive surgery.

Practice Guidelines and Position Statements

American Society of Plastic Surgeons and Wound Healing Society
Review of the literature for 2013 guidelines from the American Society of Plastic Surgeons (ASPS) found that evidence suggests that the use of acellular dermal matrix ADM, although increasingly common in postmastectomy expander/implant breast reconstruction, can result in increased risk of complications in the presence of certain risk factors. (59) The ASPS notes that cellular dermal matrix is currently used to increase soft tissue coverage, support the implant pocket, improve contour and reduce pain with expansion. However, evidence to support these improved surgical outcomes are limited. Some evidence suggests that use of acellular dermal matrix ADM is associated with increased postoperative complications, specifically related to infection and seroma. Overall, the ASPS found that evidence on acellular dermal matrix ADM products in postmastectomy expander/implant breast reconstruction is varied and conflicting, and gave a Grade C recommendation based on level III evidence that surgeons should evaluate each clinical case individually and objectively determine the use of acellular dermal matrix ADM.

In 2006, the American Society of Plastic Surgeons (ASPS) endorsed guidelines from the Wound Healing Society (WHS) on the treatment of arterial insufficiency ulcers. The guidelines state that extracellular matrix replacement therapy appears to be promising for mixed ulcers and may have a role as an adjuvant agent in arterial ulcers, but further study is required (Level IIIC). “Despite the existence of animal studies, case series, and a small number of random control trials to support biomaterial use for pressure ulcers, diabetic ulcers, and venous ulcers; there are no studies specifically on arterial ulcers. Therefore, studies in arterial ulcers must be conducted before the recommendation can be made.”

The ASPS endorsed guidelines from the Wound Healing Society (WHS) on the treatment of venous ulcers in 2006. The guidelines state that various skin substitutes or biologically active dressings are emerging that provide temporary wound closure and serve as a source of stimuli (e.g., growth
factors) for healing of venous ulcers. Guideline #7b.1 states that there is evidence that a bilayered artificial skin (biologically active dressing), used in conjunction with compression bandaging, increases the chance of healing a venous ulcer compared with compression and a simple dressing (Level I).

The ASPS also endorsed guidelines from the Wound Healing Society (WHS) on the treatment of diabetic ulcers in 2006. The guidelines state that healthy living skin cells assist in healing diabetic foot ulcers by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed. Guideline #7.2.2 states that living skin equivalents may be of benefit in healing diabetic foot ulcers (Level I).

The 2007 guidelines from the ASPS on chronic wounds of the lower extremity state that maintaining a moist environment, while simultaneously removing soluble factors detrimental to wound healing might logically provide optimal conditions for wound healing. Classic dressings include gauze, foam, hydrocolloid, and hydrogels. Fluid-handling mechanisms include absorption, gelling, retention and vapor transmission. Bioactive dressings include topical antimicrobials, bioengineered composite skin equivalent, bilaminar dermal regeneration template, and recombinant human growth factor.

National Institute for Health and Care Excellence
In 2015, Guidance from the United Kingdom’s National Institute for Health and Clinical Care Excellence (NICE) published clinical guidelines on the prevention and recommends not to use dermal or skin substitutes for the inpatient management of diabetic foot problems. NICE recommends that clinicians consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service, unless part of a clinical trial.

American College of Foot and Ankle Surgeons
The 2006 clinical consensus statement [previously called clinical practice guidelines] on diabetic foot disorders from the American College of Foot and Ankle Surgeons (ACFAS) states that bioengineered tissues have been shown to significantly increase complete wound closure in venous and diabetic foot ulcers. Tissue-engineered skin substitutes can function both as biologic dressings and as delivery systems for growth factors and extracellular matrix components through the activity of live human fibroblasts contained in their dermal elements. Currently, two bioengineered tissues have been approved to treat diabetic foot ulcers in the United States: Apligraf and Dermagraft; both have demonstrated efficacy in randomized, controlled trials (RCTs). Apligraf has been shown to significantly reduce the time to complete wound closure in venous and diabetic ulcers. Regenerative tissue matrix (GraftJacket) is a new therapy used in diabetic foot ulcers, although it had not undergone any randomized clinical trials (RCTs) at the time of this guideline. This allograft skin is minimally processed to remove epidermal and dermal cells while preserving the bioactive components and structure of dermis. This results in a framework that supports cellular repopulation and vascularization. Oasis, composed of structural cellular components and growth factors used to promote natural tissue remodeling, completed a randomized trial that showed noninferiority to becaplermin gel in the healing of diabetic foot ulcers. Integra Dermal Regeneration Template, a collagen-chondroitin sponge overlaid with silicone originally developed for burns, has been shown to be ideally suited to chronic and pathologic wounds.
Infectious Diseases Society of America
The 2012 guidelines from the Infectious Diseases Society of America (IDSA) state that for selected diabetic foot wounds that are slow to heal, clinicians might consider using bio-engineered skin equivalents (weak recommendation, moderate evidence) growth factors (weak, moderate), granulocyte colony stimulating factors (weak, moderate), hyperbaric oxygen therapy (strong, moderate), or negative pressure wound therapy (weak, low). It is emphasized that none of these measures have been shown to improve resolution of infection and that they are expensive, not universally available, may require consultation with experts, and reports supporting their utility are mostly flawed.

Agency for Healthcare Research and Quality
A 2012 Technology Assessment from the Agency for Healthcare Research and Quality (AHRQ) does not make a formal recommendation for bioengineered skin and soft tissue substitutes. The Assessment notes that autologous tissue grafting is an invasive and painful procedure and often the extent of damaged skin is too large to be covered by autologous tissue graft alone. A variety of skin substitutes and alternatives are designed to replace the damaged epithelial and dermal layers of skin, and many of the conditions and biological factors needed in the healing process may be provided by the substitute skin products.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
Centers for Medicare and Medicaid Services (CMS) has issued the following national coverage determination: Porcine (pig) skin dressings are covered, if reasonable and necessary for the individual patient as an occlusive dressing for burns, donor sites of a homograft, and decubiti and other ulcers.

Beginning in 2014, CMS will no longer distinguishes between different skin substitutes and will classify them as either high cost or low cost. CMS will package skin substitutes of the same class into the associated surgical procedures for hospital outpatient departments and ambulatory surgical centers. A separate payment might be made if the item is furnished on a different date of service as the primary service.

VII. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government
Bio-Engineered Skin and Soft Tissue Substitutes

approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References


