Introduction

Bioengineered skin and soft tissue substitutes are artificial alternatives to live skin grafts for wound care and tissue reconstruction. The products are made from various sources including human tissue (from the patient or others), nonhuman tissue (cows, pigs, horses), synthetic materials (man-made) or a combination of these materials. Some skin substitutes are labeled for specific uses such as for healing severe diabetic foot sores or during surgery for severe burns or breast reconstruction; other uses are being researched. This policy outlines when specific bioengineered skin and soft tissue substitutes might be medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Products</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allogeneic Acellular Dermal Matrix Products,</td>
<td>Breast reconstructive surgery using the banked human tissue products listed in the left column may be considered medically</td>
</tr>
</tbody>
</table>
### Products

including but not limited to:

- AlloDerm®*
- AlloMend®
- Cortiva® [AlloMax™]
- DermACELL®
- DermaMatrix™*
- FlexHD®*
- FlexHD® Pliable™
- Graftjacket®*

#### Medical Necessity

**necessary when:**

- there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required

**OR**

- there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis

**OR**

- the inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed

- AlloPatch®*
- Apligraft®**
- Dermagraft®**
- Integra® Flowable Wound Matrix
- Integra® Omnigraft™ Dermal Regeneration Matrix (also known as Omnigraft™)

#### Treatment of chronic, non-infected, full-thickness diabetic lower-extremity ulcers using the tissue-engineered skin substitute products listed in the left column may be considered medically necessary.

**Note:** Criteria for using human amniotic membrane products are in a separate medical policy (see Related Policies).

- Apligraft®**
- Oasis™ Wound Matrix***

#### Treatment of chronic, non-infected, partial or full-thickness lower-extremity skin ulcers due to venous insufficiency using the tissue-engineered skin substitute products listed in the left column may be considered medically necessary when:

- A 1-month period of conventional ulcer therapy has failed to promote healing

- OrCel™****

#### Treatment of dystrophic epidermolysis bullosa using the tissue-engineered skin substitute product listed in the left column may be considered medically necessary when:

- Standard wound therapy has failed for the treatment of mitten-hand deformity

**AND**

- When provided in accordance with the humanitarian device exemption (HDE) specifications of the U.S. Food and Drug Administration (FDA)****

- Epicel ®****
- Integra Dermal Regeneration Template™**

#### Treatment of second- and third-degree burns using the tissue-engineered skin substitute products listed in the left column may be considered medically necessary when:
### Products

<table>
<thead>
<tr>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epicel® only:</strong> It is used for the treatment of deep dermal or full-thickness burns covering a total body surface area ≥30% when provided in accordance with the HDE specifications of the FDA)****</td>
</tr>
<tr>
<td>**Integra Dermal Regeneration Template™****: No additional criteria required</td>
</tr>
</tbody>
</table>

All other uses of the bioengineered skin and soft tissue substitutes listed above are considered investigational.

*Banked human tissue; **FDA premarket approval; ***FDA 510(k) cleared; ****FDA-approved under an HDE

**Note:** Amniotic membrane and amniotic fluid products are reviewed in a Related Policy.

### Investigational

Bioengineered and other skin and soft tissue substitute products considered investigational include, but are not limited to, those listed below.

<table>
<thead>
<tr>
<th>ACell® UBM Hydrated Wound Dressing</th>
<th>Durepair Regeneration Matrix®</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACell® UBM Lyophilized Wound Dressing</td>
<td>Endoform Dermal Template™</td>
</tr>
<tr>
<td>AlloSkin™</td>
<td>ENDURAGen™</td>
</tr>
<tr>
<td>AlloSkin™ RT</td>
<td>Excellagen</td>
</tr>
<tr>
<td>Aongen™ Collagen Matrix</td>
<td>ExpressGraft™</td>
</tr>
<tr>
<td>Architect® ECM, PX, FX</td>
<td>E-Z Derm™</td>
</tr>
<tr>
<td>ArthroFlex™ (Flex Graft)</td>
<td>FlexiGraft®</td>
</tr>
<tr>
<td>Atlas Wound Matrix</td>
<td>GammaGraft</td>
</tr>
<tr>
<td>Avagen Wound Dressing</td>
<td>Graftjacket® Xpress, injectable</td>
</tr>
<tr>
<td>AxoGuard® Nerve Protector (AxoGen)</td>
<td>Helicoll™</td>
</tr>
<tr>
<td>Biobrane®/Biobrane-L</td>
<td>Hyalomatrix®</td>
</tr>
<tr>
<td>CollaCare®</td>
<td>Hyalomatrix® PA</td>
</tr>
<tr>
<td>CollaCare® Dental</td>
<td>hMatrix®</td>
</tr>
<tr>
<td>Collagen Wound Dressing (Oasis Research)</td>
<td>Integra™ Bilayer Wound Matrix</td>
</tr>
<tr>
<td>CollaGUARD®</td>
<td>Keramatrix®</td>
</tr>
<tr>
<td>CollaMend™</td>
<td>Kerecis™</td>
</tr>
<tr>
<td>CollaWound™</td>
<td>MariGen™/Kerecis™ Omega3™</td>
</tr>
<tr>
<td>Colllexa®</td>
<td>MatriDerm®</td>
</tr>
<tr>
<td>Collieva®</td>
<td>Oasis® Ultra</td>
</tr>
</tbody>
</table>

- Pelvicol®/PelviSoft®
- Permacol™
- PriMatrix™
- PriMatrix™ Dermal Repair Scaffold
- PuraPly™ Wound Matrix (previously FortaDerm™)
- PuraPly™ AM (Antimicrobial Wound Matrix)
- Puros® Dermis
- RegenePro™
- Repliform®
- Repriza™
- Suprathel®
- SurgiMend®
- StrataGraft®
- Strattice™ (xenograft)
- Talymed®
- TenoGlide™
- TenSIX™ Acellular Dermal Matrix
- TissueMend
## Investigational

- Conexa™
- Coreleader Colla-Pad
- CorMatrix®
- Cymetra™ (Micronized (AlloDerm™))
- Cytal™ (previously MatriStem®)
- Dermadapt™ Wound Dressing
- DermaPure™
- DermaSpan™
- DressSkin

- Matrix HD™
- Mediskin®
- MemoDerm™
- MicroDerm® biologic wound matrix
- NeoForm™
- NuCel
- Oasis® Burn Matrix

- TheraForm™ Standard/Sheet
- TheraSkin®
- TransCyte™
- TruSkin™
- Veritas® Collagen Matrix
- XCM Biologic® Tissue Matrix
- XenMatrix™ AB

## Documentation Requirements

For wound care, detailed history and physical with: The record should include the following:

- Associated medical comorbidities

- Description of wound (eg, full-thickness [affecting all layers of the skin], deep dermal [deeper than a superficial wound but not a full thickness wound])

- Standard wound therapy treatment provided, including duration and effectiveness or failure of treatment

## Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>Q4100</td>
<td>Skin substitute, not otherwise specified</td>
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### Medically Necessary (Eligible for Coverage)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>Q4101</td>
<td>Apligraf, per square centimeter</td>
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<tr>
<td>Q4104</td>
<td>Integra Bilayer Matrix Wound Dressing (BMWD), 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>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Q4107</td>
<td>Graftjacket, per square centimeter</td>
</tr>
<tr>
<td>Q4108</td>
<td>Integra Matrix, 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>Q4128</td>
<td>FlexHD, Allopatch HD or Matrix HD, per square centimeter</td>
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</table>

**Investigational (Not Eligible for Coverage)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Q4102</td>
<td>Oasis Wound Matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4103</td>
<td>Oasis Burn Matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4110</td>
<td>PriMatrix, per square centimeter</td>
</tr>
<tr>
<td>Q4111</td>
<td>GammaGraft, per square centimeter</td>
</tr>
<tr>
<td>Q4112</td>
<td>Cymetra, injectable, 1 cc</td>
</tr>
<tr>
<td>Q4113</td>
<td>Graftjacket Xpress, injectable, 1 cc</td>
</tr>
<tr>
<td>Q4114</td>
<td>Integra Flowable Wound Matrix, injectable, 1 cc</td>
</tr>
<tr>
<td>Q4115</td>
<td>AlloSkin, per square centimeter</td>
</tr>
<tr>
<td>Q4117</td>
<td>Hyalomatrix, per square centimeter</td>
</tr>
<tr>
<td>Q4118</td>
<td>MatriStem micromatrix, 1 mg</td>
</tr>
<tr>
<td>Q4121</td>
<td>TheraSkin, per square centimeter</td>
</tr>
<tr>
<td>Q4123</td>
<td>AlloSkin RT, per square centimeter</td>
</tr>
<tr>
<td>Q4124</td>
<td>Oasis Ultra Tri-Layer Wound Matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4125</td>
<td>Arthroflex, per square centimeter</td>
</tr>
<tr>
<td>Q4126</td>
<td>Memoderm, Dermapan, Transgraft or Integuply, per square centimeter</td>
</tr>
<tr>
<td>Q4127</td>
<td>Talymed, per square centimeter</td>
</tr>
<tr>
<td>Q4130</td>
<td>Strattice TM, per square centimeter</td>
</tr>
<tr>
<td>Q4134</td>
<td>hMatrix, per square centimeter</td>
</tr>
<tr>
<td>Q4135</td>
<td>Mediskin, per square centimeter</td>
</tr>
<tr>
<td>Q4136</td>
<td>EZ-derm, per square centimeter</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Q4138</td>
<td>Biodfence Dryflex, per square centimeter</td>
</tr>
<tr>
<td>Q4140</td>
<td>Biodfence, per square centimeter</td>
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<tr>
<td>Q4141</td>
<td>Alloskin AC, per square centimeter</td>
</tr>
<tr>
<td>Q4142</td>
<td>Xcm biologic tissue matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4143</td>
<td>Repriza, per square centimeter</td>
</tr>
<tr>
<td>Q4146</td>
<td>TenSIX, per square centimeter</td>
</tr>
<tr>
<td>Q4147</td>
<td>Architect, Architect PX, or Architect FX, extracellular matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4149</td>
<td>Excellagen, 0.1 cc</td>
</tr>
<tr>
<td>Q4150</td>
<td>AlloWrap DS or dry, per square centimeter</td>
</tr>
<tr>
<td>Q4152</td>
<td>DermaPure per square centimeter</td>
</tr>
<tr>
<td>Q4153</td>
<td>Dermavest and Plurivest, per square centimeter</td>
</tr>
<tr>
<td>Q4157</td>
<td>Revitalon, per square centimeter</td>
</tr>
<tr>
<td>Q4158</td>
<td>Kerecis Omega3, per sq cm (updated 1/1/18)</td>
</tr>
<tr>
<td>Q4159</td>
<td>Affinity, per square centimeter</td>
</tr>
<tr>
<td>Q4160</td>
<td>NuShield, per square centimeter</td>
</tr>
<tr>
<td>Q4161</td>
<td>Bio-ConneKt Wound Matrix, per square centimeter</td>
</tr>
<tr>
<td>Q4164</td>
<td>Helicoll, per square centimeter</td>
</tr>
<tr>
<td>Q4165</td>
<td>Keramatrix, per square centimeter</td>
</tr>
<tr>
<td>Q4166</td>
<td>Cytal, per square centimeter</td>
</tr>
<tr>
<td>Q4167</td>
<td>Truskin, per square centimeter</td>
</tr>
<tr>
<td>Q4169</td>
<td>Artacent wound, per square centimeter</td>
</tr>
<tr>
<td>Q4170</td>
<td>Cygnus, per square centimeter</td>
</tr>
<tr>
<td>Q4171</td>
<td>Interfyl, 1 mg</td>
</tr>
<tr>
<td>Q4172</td>
<td>Puraply or puraply am, per square centimeter</td>
</tr>
<tr>
<td>Q4173</td>
<td>Palingen or palingen xplus, per square centimeter</td>
</tr>
<tr>
<td>Q4174</td>
<td>Palingen or promatrix, 0.36 mg per 0.25 cc</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Q4175</td>
<td>Miroderm, per square centimeter</td>
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</tbody>
</table>

**Modifiers**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>JC</td>
<td>Skin substitute used as a graft</td>
</tr>
<tr>
<td>JD</td>
<td>Skin substitute not used as a graft</td>
</tr>
</tbody>
</table>

**Related Information**

Clinical input has indicated that the various acellular dermal matrix (ADM) products used in breast reconstruction have similar efficacy. The products listed are those that have been identified for use in breast reconstruction. Additional ADM products may become available for this indication.

**Benefit Application**

Many states have mandates related to breast reconstruction that may impact the application of this policy.

**Evidence Review**

**Description**

Bioengineered 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. Bioengineered skin and soft tissue substitutes are being evaluated for use in a variety of conditions, including breast reconstruction and healing lower-extremity ulcers and severe burns. Acellular dermal matrix (ADM) products are also being evaluated for soft tissue repair.
Background

Skin and Soft Tissue Substitutes

Bioengineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (e.g., dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. Acellular dermal matrix (ADM) products can differ in a number of ways, including the species source (human, bovine, porcine), tissue source (e.g., dermis, pericardium, intestinal mucosa), additives (e.g., 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 (e.g., 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. Bioengineered skin substitutes can be used as either temporary or permanent wound coverings.

Applications

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. Bioengineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

Other situations in which bioengineered skin products might substitute for living skin grafts include certain postsurgical states (e.g., breast reconstruction) in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Second- and third-degree burns are another indication in which artificial skin products may substitute for auto- or allografts. Certain primary dermatologic conditions that involve large areas of skin breakdown (e.g., bullous diseases) may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. ADM products are also being evaluated in other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and other conditions.
Summary of Evidence

Breast Reconstruction

For individuals who are undergoing breast reconstruction who receive allogeneic acellular dermal matrix (ADM) products, the evidence includes randomized controlled trials (RCT) and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. A systematic review found no difference in overall complication rates with ADM allograft compared to standard procedures for breast reconstruction. Reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM. However, capsular contracture and malposition of implants may be reduced. Thus, in cases where there is limited tissue coverage, the available evidence may inform patient decision making about reconstruction options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Tendon Repair

For individuals who are undergoing tendon repair who receive Graftjacket ADM, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. The RCT identified found improved outcomes with Graftjacket ADM allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of patients is needed to evaluate consistency of the effect. The evidence is insufficient to determine the effects of the technology on health outcomes.

Surgical Repair of Hernias or Parastomal Reinforcement

For individuals who are undergoing surgical repair of hernias or parastomal reinforcement who receive acellular collagen-based scaffolds, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Several comparative studies including RCTs have shown no difference in outcomes between tissue-engineered skin substitutes and either standard synthetic mesh or no reinforcement. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.
Diabetic Lower-Extremity Ulcers

For individuals who have diabetic lower-extremity ulcers who receive AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. RCTs have demonstrated the efficacy of AlloPatch (reticular ADM), Apligraf and Dermagraft (living cell therapy), and Integra (biosynthetic) over the standard of care. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have diabetic lower-extremity ulcers who receive ADM products other than AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients who only required a single application of the ADM. Studies are needed to further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of Graftjacket, TheraSkin, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Lower-Extremity Ulcers Due to Venous Insufficiency

For individuals who have lower-extremity ulcers due to venous insufficiency who receive Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. RCTs have demonstrated the efficacy of Apligraf living cell therapy and xenogenic Oasis Wound Matrix over the standard of care. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have lower-extremity ulcers due to venous insufficiency who receive bioengineered skin substitutes other than Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. In a moderately large RCT, Dermagraft was not shown to be more effective than controls for the primary or secondary end points in the entire population and was only slightly more effective than controls (an 8%-15% increase in healing) in subgroups of patients with ulcer durations 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 the xenogenic PriMatrix skin substitute versus the current standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Dystrophic Epidermolysis Bullosa**

For individuals who have dystrophic epidermolysis bullosa who receive OrCel, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, morbid events, and quality of life. OrCel was approved under a humanitarian drug exemption 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. Outcomes have been reported in small series (eg, 5 patients). The evidence is insufficient to determine the effects of the technology on health outcomes.

**Deep Dermal Burns**

For individuals who have deep dermal burns who receive bioengineered skin substitutes (ie, Epicel, Integra Dermal Regeneration Template), the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, few skin substitutes have been approved, and the evidence is limited for each product. Epicel (living cell therapy) has received Food and Drug Administration approval 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. Comparative studies have demonstrated improved outcomes for biosynthetic skin substitute Integra Dermal Regeneration Template for the treatment of burns. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**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><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>NCT01987700</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>120</td>
<td>Oct 2017 (ongoing)</td>
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<tr>
<td></td>
<td>A Randomized, Prospective, Double-blind, Multi-Center Study To Examine And Compare The Outcomes Associated With The Use Of Flex HD®, A Human Acellular Dermal Matrix, And Strattice™, A Porcine Acellular Dermal Matrix Allograft, When Used As A Reinforcing Material In The Repair Of Large Abdominal Wall Hernias By A Component Separation Technique</td>
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<tr>
<td></td>
<td><strong>NCT02587403</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>120</td>
<td>Oct 2019</td>
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<tr>
<td></td>
<td>A Randomized, Prospective Study Comparing Fortiva™ Porcine Dermis vs. Strattice™ Reconstructive Tissue Matrix in Patients Undergoing Complex Open Primary Ventral Hernia Repair</td>
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<td></td>
<td><strong>NCT02322554</strong></td>
<td>50,000</td>
<td>Jan 2020</td>
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<td></td>
<td>The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers</td>
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<tr>
<td><strong>Unpublished</strong></td>
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<td><strong>NCT01970163</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>202</td>
<td>Apr 2016 (completed)</td>
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<td></td>
<td>A Multicenter, Randomized, Controlled, Open Label Trial of DermACELL in Subjects With Chronic Wounds of the Lower Extremities</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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.
**2016 Input**

In response to requests, input was received from 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2016. Input was requested on the equivalency of products within the categories of amniotic membrane, living cell therapies, and biosynthetic skin substitutes for the treatment of diabetic foot ulcers and non-ocular burns (biosynthetic only). Input on the equivalency of products within these categories was mixed.

**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 bioengineered 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.

**2012 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 2012. Most reviewers supported the indications and products described in this policy. Input was requested on 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. Reviewers provided references for the additional indications; these were subsequently reviewed.
2009 Input

In response to requests, input was received from 1 physician specialty society (2 physicians) and 1 academic medical center while this policy was under review in 2009. All reviewers indicated that the use of AlloDerm should be available during breast reconstructive surgery.

Practice Guidelines and Position Statements

American Society of Plastic Surgeons and Wound Healing Society

A literature review for the 2013 guidelines from the American Society of Plastic Surgeons (ASPS) found that 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. ASPS noted 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 suggested that use of ADM is associated with increased postoperative complications, specifically related to infection and seroma. Overall, ASPS found that evidence on ADM products in postmastectomy expander/implant breast reconstruction was 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 ADM.

National Institute for Health and Care Excellence

In 2016, the National Institute for Health and Care Excellence (NICE) updated its guidance on the prevention and 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.”

Infectious Diseases Society of America

The 2012 guidelines from the Infectious Diseases Society of America state that, for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered 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 was emphasized that none of these measures had been shown to improve the resolution of infection and that they were expensive, not universally available, might require consultation with experts, and reports supporting their utility were mostly flawed.

Medicare National Coverage

Centers for Medicare & Medicaid Services (CMS) 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.

Since 2014, CMS has no longer distinguished between different skin substitutes and classifies them as either high cost or low cost. CMS packages 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.

Regulatory Status

A large number of artificial skin products are commercially available or in development. The following summary of commercially available skin substitutes describes those products that have substantial relevant evidence on efficacy.

Acellular Dermal Matrix (ADM) Products

Allograft ADM products derived from donated human skin tissue are supplied by tissue banks compliant with standards of the American Association of Tissue Banks (AATB) and U.S. Food and Drug Administration (FDA) guidelines. The processing removes the cellular components (ie, epidermis, all viable dermal cells) that can lead to rejection and infection. ADM products from human skin tissue are regarded as minimally processed and not significantly changed in structure from the natural material; FDA classifies ADM products as banked human tissue and therefore, not requiring FDA approval.
• AlloDerm® (LifeCell Corp.) is an ADM (allograft) tissue-replacement product 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 stored at room temperature. An injectable micronized form of AlloDerm® (Cymetra) is available.

• Cortiva® (previously marketed as AlloMax™ Surgical Graft and before that NeoForm™) is an acellular non-cross-linked human dermis allograft.

• AlloPatch® (Musculoskeletal Transplant Foundation) is an acellular human dermis allograft derived from the reticular layer of the dermis and marketed for wound care. This product is also marketed as FlexHD® for postmastectomy breast reconstruction.

• FlexHD® and the newer formulation FlexHD® Pliable™ (Musculoskeletal Transplant Foundation) are acellular hydrated reticular dermis allograft derived from donated human skin.

• DermACELL™ (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL® and PRESERVON®.

• DermaMatrix™ (Synthes) is a freeze-dried ADM derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation.

• DermaPure™ (Tissue Regenix Wound Care) 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 human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells, while preserving dermal structure. Graftjacket Xpress® is an injectable product.

FDA product codes: FTM, OXF.

Xenogenic Products

• Cytal™ (previously called MatriStem®) Wound Matrix, Multilayer Wound Matrix, Pelvic Floor Matrix, MicroMatrix, and Burn Matrix (all manufactured by ACell) are composed of porcine-derived urinary bladder matrix.

• Helicoll (Encol) is an acellular collagen matrix derived 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.

- **Keramatrix®** (Keraplast Research) is an open-cell foam comprised of freeze-dried keratin that is derived from acellular animal protein. 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.

- **Kerecis™ Omega3 Wound** (Kerecis) is an ADM derived from fish skin. It has a high content of omega 3 fatty acids and is intended for use in burn wounds, chronic wounds, and other applications.

- **Oasis™ Wound Matrix** (Cook Biotech) is a collagen scaffold (extracellular matrix) 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. FDA Product code: KGN.

- **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™** (TEI Biosciences) is a xenogeneic ADM processed from fetal bovine dermis. It was cleared for marketing by FDA through the 510(k) process for partial- and full-thickness wounds; diabetic, pressure, and venous stasis ulcers; surgical wounds; and tunneling, draining, and traumatic wounds. FDA product code: KGN.

- **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.

- **SurgiMend® PRS** (TEI Biosciences) is a xenogeneic ADM processed from fetal bovine dermis.

### 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. Apligraf® is supplied as needed, in 1 size, with a shelf-life of 10 days. In 1998, it was approved by FDA for
use in conjunction with compression therapy for the treatment of noninfected, partial- and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower-extremity ulcers nonresponsive to standard wound therapy. FDA product code: FTM.

- Dermagraft® (Organogenesis) is composed of cryopreserved human-derived fibroblasts and collagen derived from newborn human foreskin and cultured on a bioabsorbable polyglactin mesh scaffold. Dermagraft has been approved by FDA for repair of diabetic foot ulcers. FDA product code: PFC.

- Epicel® (Genzyme Biosurgery) is a cultured epithelial autograft composed of a patient’s own keratinocytes cultured ex vivo and is FDA-approved under a humanitarian device exemption (HDE) for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. It may be used in conjunction with split-thickness autografts or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns. FDA product code: OCE.

- 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 FDA premarket approval for healing donor site wounds in burn victims and under a 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. FDA product code: ODS.

- TheraSkin® (Soluble Systems) is a cryopreserved split-thickness human skin allograft composed of living fibroblasts and keratinocytes and an extracellular matrix in epidermal and dermal layers. TheraSkin® is derived from human skin allograft supplied by tissue banks compliant with the AATB and FDA guidelines. It is considered a minimally processed human cell, tissue, and cellular- and tissue-based product by FDA.

**Biosynthetic Products**

- 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 trifilament thread, which chemically binds collagen. Blood/sera clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs. FDA product code: FRO.
• Integra® Dermal Regeneration Template (also 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 and for certain diabetic foot ulcers.

• Integra® Matrix Wound Dressing and Integra® Meshed Bilayer Wound Matrix are substantially equivalent skin substitutes and were cleared for marketing 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 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 Products**

• 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.

### References


40. Karr JC. Retrospective comparison of diabetic foot ulcer and venous stasis ulcer healing outcome between a dermal repair scaffold (PriMatrix) and a bilayered living cell therapy (Apligraf), Adv Skin Wound Care. Mar 2011;24(3):119-125. PMID 21326023


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/01/16</td>
<td>New policy, approved August 9, 2016. Add to Surgery section. Some bioengineered skin and soft tissue substitutes may be considered medically necessary when criteria are met. The use of bioengineered skin and soft tissue substitutes is investigational when criteria are not met. The effective date of this policy is December 1, 2016.</td>
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<tr>
<td>01/06/17</td>
<td>Updated effective date. The effective date of this policy has been updated to March 1, 2017.</td>
</tr>
<tr>
<td>02/17/17</td>
<td>Coding update. Added new HCPCS codes Q4166-Q4167 and Q4169-Q4175 with effective date 01/01/17. Removed HCPCS codes Q4137, Q4139, Q4151, and Q4163.</td>
</tr>
<tr>
<td>04/01/17</td>
<td>Annual Review, approved March 14, 2017. Policy updated with literature review through November 7, 2016; references 6, 19, 26, and 28-29 added; rationale revised and some references removed. Investigational products list updated: Microderm, TruSkin products added; MatriStem renamed Cytal; FortaDerm renamed PuraPly; Unite Biomatrix deleted (no longer available). AlloMend added to medically necessary statement for breast reconstructive surgery. AlloPatch added to medically necessary statement for diabetic lower-extremity ulcers. Criteria for human amniotic membrane products for diabetic foot ulcers moved to policy 7.01.149. Section on laryngoplasty removed. Coding updated, removed HCPCS codes Q4119-Q4120 and Q4129 as they terminated as of 1/1/17. CPT code table removed.</td>
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<tr>
<td>06/20/17</td>
<td>Coding update, removed HCPCS codes Q4148, Q4155, and Q4156 as they are applicable to policy 7.01.149.</td>
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<tr>
<td>08/09/17</td>
<td>Coding update, removed HCPCS codes Q4131-Q4133, Q4145, and Q4154 from policy as they are addressed on a separate medical policy. Moved HCPCS codes Q4104 and Q4108 from investigational to medically necessary.</td>
</tr>
<tr>
<td>11/01/17</td>
<td>Interim Review, approved October 10, 2017. CellerateRX® (CRXα™) and Integra® Omnigraft™ Dermal Regeneration Matrix removed from the investigational policy statement, may be considered medically necessary if criteria are met. The Evidence Review section was reformatted.</td>
</tr>
<tr>
<td>12/01/17</td>
<td>Minor update; added DermACELL® which was inadvertently left off of policy.</td>
</tr>
</tbody>
</table>
Date | Comments
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05/01/18 | Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017; references 4-5, 7, 9, 15, 20, 29, 35, and 54 added; references 59 and 61 updated. DermACELL and FlexHD Pliable added to medically necessary statement on breast reconstructive surgery. Integra Flowable Wound Matrix added to medically necessary statement on use of Integra Dermal Regeneration Template for diabetic lower-extremity ulcers. Several products added to investigational list.

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