MEDICAL POLICY

MEDICAL POLICY

Skin and Tissue Substitutes

Effective Date: 1/1/2020

Section: MED
Policy No: 378

Technology Assessment Committee Approved Date: 3/09; 10/14; 1/16
Medical Policy Committee Approved Date: 4/02; 4/03; 9/04; 11/05; 5/07; 1/09; 11/09; 12/10; 4/2011; 3/12; 1/13; 1/14; 3/14; 9/14; 11/15; 12/15; 12/16; 3/18; 10/18; 12/18; 8/19; 9/19; 12/19

1/1/2020

Medical Officer

Date

See Policy CPT/HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:

All lines of business

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

DOCUMENTATION REQUIREMENTS

Medical records documentation must clearly support the medical necessity of bioengineered skin and tissue substitutes. This would include the following:

- Characteristics of the wound/ulcer
- Wound/ulcer measurement
- Evidence of prior ineffective standard care, including the duration of this treatment
- The presence of qualifying or disqualifying conditions (i.e., HbA1C levels, ankle-brachial index [ABI])
### POLICY CRITERIA

**Medically Necessary Skin and Tissue Substitutes by Indication**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Products</th>
<th>Product HCPCS Codes</th>
<th>Medical Necessity Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast reconstruction</td>
<td>AlloDerm®</td>
<td>Q4116</td>
<td>I. These products may be considered <strong>medically necessary and covered</strong> when used for a medically necessary breast reconstruction surgery. (See policies Cosmetic and Reconstructive Surgery, SUR193, or Breast Reconstruction, SUR162, for more information)</td>
</tr>
<tr>
<td></td>
<td>Dermacell™</td>
<td>Q4122</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FlexHD® Acellular Hydrated Dermis</td>
<td>Q4128</td>
<td></td>
</tr>
<tr>
<td>Burn wound</td>
<td>Biobrane®/Biobrane®-L</td>
<td>Q4100 C9399</td>
<td>II. This product may be considered <strong>medically necessary and covered</strong> as a treatment of burn wounds when all of the following (A.-B.) criteria are met:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A. The skin substitute is used as a temporary covering of a partial-thickness burn (See description section for definition); <strong>and</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>B. Applied to freshly debrided or excised wounds, or meshed autografts containing less than 105 bacteria/g tissue.</td>
</tr>
<tr>
<td></td>
<td>Epicel</td>
<td>Q4100 C9399</td>
<td>III. This product may be considered <strong>medically necessary and covered</strong> when used in accordance with the U.S. Food and Drug Administration Humanitarian Device Exemption for adult and pediatric patients who have deep dermal or full thickness</td>
</tr>
</tbody>
</table>
burns comprising a total body surface area greater than or equal to 30%.

IV. These products may be considered medically necessary and covered as a treatment of burn wounds when all of the following (A.-B.) criteria are met:

A. To be used for the post-excisional treatment of life-threatening full thickness or deep partial-thickness thermal injuries (See description section for definition); and

B. Sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient.

V. This product may be considered medically necessary and covered when used as a temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft placement.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Products</th>
<th>Medical Necessity Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetic foot ulcer</strong></td>
<td>Apligraf® Q4101</td>
<td>VI. These products may be considered medically necessary and covered for the treatment of diabetic foot ulcers when all of the following (A.-H.) criteria are met:</td>
</tr>
<tr>
<td></td>
<td>Dermagraft® Q4106</td>
<td>A. The skin substitute is used in conjunction with standard diabetic ulcer care; and</td>
</tr>
<tr>
<td></td>
<td>EpiFix®</td>
<td>B. The ulcer extends through the dermis but without tendon, muscle, joint, or bone exposure; and</td>
</tr>
<tr>
<td></td>
<td>Amniotic Membrane Q4186</td>
<td>C. The ulcer is at least 1cm² but no more than 25cm²; and</td>
</tr>
<tr>
<td></td>
<td>Grafix® Core/Grafix® Prime Q4132</td>
<td>D. The ulcer is free of infection; and</td>
</tr>
<tr>
<td></td>
<td>Grafix® PL Prime Q4133</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GraftJacket® Regenerative Tissue Matrix Q4107</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Integra® Dermal Q4105</td>
<td></td>
</tr>
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### Indication

<table>
<thead>
<tr>
<th>Medical Necessity Criteria</th>
<th>Products</th>
<th>Product HCPCS Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous stasis ulcer</td>
<td>Apligraf®</td>
<td>Q4101</td>
</tr>
<tr>
<td></td>
<td>EpiFix® Amniotic Membrane</td>
<td>Q4186</td>
</tr>
<tr>
<td></td>
<td>Oasis® Wound Matrix</td>
<td>Q4102, Q4124</td>
</tr>
<tr>
<td></td>
<td>TheraSkin®</td>
<td>Q4121</td>
</tr>
</tbody>
</table>

#### Medical Necessity Criteria

- **A.** The skin substitute is used in conjunction with standard venous stasis ulcer care; **and**
- **B.** The ulcer extends through the dermis but **without** tendon, muscle, joint, or bone exposure; **and**
- **C.** The ulcer is at least 2cm² but no more than 20cm²; **and**
- **D.** The ulcer is free of infection; **and**
- **E.** Failure of at least 4 weeks of standard venous stasis ulcer therapy (e.g., compression therapy); **and**
- **F.** The leg to be treated has adequate blood supply as defined by **at least one** of the following (1.-2.) criteria:
  1. Ankle-brachial index (ABI) of ≥ 0.70; **and/or**
  2. The presence of a palpable pedal pulse; **and**
- **G.** The foot to be treated has adequate blood supply as defined by **at least one** of the following (1.-2.) criteria:
  1. Ankle-brachial index (ABI) of ≥ 0.70; **and/or**
  2. The presence of a palpable pedal pulse; **and**
- **H.** The skin substitute is limited to no more than 5 applications, at a minimum of 1 week between applications, over the course of 12 weeks. (Except GraftJacket® Regenerative Tissue Matrix [Q4107] which is limited to only 1 initial application.)

### Regeneration Template
- Integra™ Omnigraft Dermal Regeneration Matrix

### Products
- Oasis® Wound Matrix/Oasis® Ultra Tri-Layer Matrix
- TheraSkin®

### Medical Necessity Criteria

- The patients A1c (HbA1C) level is less than 12%; **and**
- Failure of at least 4 weeks of standard diabetic foot ulcer therapy (e.g., surgical debridement, dressing changes); **and**
- The foot to be treated has adequate blood supply as defined by **at least one** of the following (1.-2.) criteria:
  1. Ankle-brachial index (ABI) of ≥ 0.70; **and/or**
  2. The presence of a palpable pedal pulse; **and**
- The skin substitute is limited to no more than 5 applications, at a minimum of 1 week between applications, over the course of 12 weeks. (Except GraftJacket® Regenerative Tissue Matrix [Q4107] which is limited to only 1 initial application.)
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2. The presence of a palpable pedal pulse; and
G. The skin substitute is limited to no more than 5 applications, at a minimum of 1 week between applications.

Traumatic Wounds

VIII. The use of the following skin and tissue substitute products may be considered medically necessary and covered for the treatment of traumatic wounds when autografting is not possible:

- Biobrane®/Biobrane®-L (Q4100, C9399)
- Epicel (Q4100, C9399)
- Integra Products (Q4104, Q4105, C9363):
  o Integra® Dermal Regeneration Template
  o Integra® Omnigraft Dermal Regeneration Matrix
  o Integra® Bilayer Matrix Wound Dressing
  o Integra® Meshed Bilayer Wound Matrix
- TransCyte® (Q4182)

Skin and Tissue Substitutes as a Component of Genital Surgery

IX. The use of a skin substitute as a component of a genital surgery may be medically necessary and covered for surgical wound coverage prior to skin grafting. Please see medical policy, Gender Affirming Surgical Interventions, for additional criteria and codes.

Repeat Treatment

X. Repeat treatment of diabetic foot ulcers or venous stasis ulcers using skin and tissue substitutes may be considered medically necessary and covered when the ulcer continues to improve on the basis of wound documentation. Wound documentation must include all of the following (A.-C.):

A. The number and position of ulcers; and
B. Wound measurements for each ulcer, including all of the following (1.-3.):
   1. Length; and
   2. Width; and
   3. Depth; and
C. Descriptions of wound edge parameters, wound base quality, drainage, and infection.
Non-Covered Indications

XI. The use of skin and tissue substitutes is considered investigational and is not covered when the medically necessary indication and/or product and/or criteria above are not met, including, but not limited to:

- Hernia repair
- Rotator cuff tear repair
- Repair of non-traumatic surgical excision of skin/soft tissue mass/lesion (e.g., Mohs surgery for squamous or basal cell carcinomas)

Investigational Skin Substitutes

XII. Skin and tissue substitute products not listed in the tables above are considered investigational and are not covered, including, but not limited to, the following:

<table>
<thead>
<tr>
<th>Products</th>
<th>Indication</th>
<th>Product HCPCS Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affinity</td>
<td>Wound care</td>
<td>Q4159</td>
</tr>
<tr>
<td>Allogen</td>
<td>Wound care</td>
<td>Q4212</td>
</tr>
<tr>
<td>Allopatch HD™</td>
<td>Tendon augmentation</td>
<td>Q4128</td>
</tr>
<tr>
<td>Alloskin™ AC</td>
<td>Wound care</td>
<td>Q4115, Q4141</td>
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<td>Alloskin™ RT</td>
<td>Wound care</td>
<td>Q4123</td>
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<td>Alowrap™</td>
<td>Wound care</td>
<td>Q4150</td>
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<td>AmnioArmor</td>
<td>Wound care</td>
<td>Q4188</td>
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<td>AmnioBand/Guardian</td>
<td>Wound care</td>
<td>Q4151</td>
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<tr>
<td>AmnioBand® Particulate</td>
<td>Wound care</td>
<td>Q4168</td>
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<tr>
<td>Amnion Bio/Axobiomembrane</td>
<td>Wound care</td>
<td>Q4211</td>
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<tr>
<td>AmnioEXCEL™/BiodExcel™</td>
<td>Wound care, Soft tissue repair</td>
<td>Q4137</td>
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<tr>
<td>AmnioFix®</td>
<td>Tendon/nerve repair</td>
<td>Q4100, C9399</td>
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<tr>
<td>AmnioMatrix®/BioMatrix®</td>
<td>Wound care, Soft tissue repair</td>
<td>Q4139</td>
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<tr>
<td>AmnioPro-A</td>
<td>Wound care, Soft tissue repair</td>
<td>Q4100</td>
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<td>Amnio Wound</td>
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<td>Q4181</td>
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<td>Q4221</td>
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<td>Architect™/Architect™ PX/Architect™ FX/Architect™ Extracellular Matrix</td>
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<td>Artacent™ AC Powder</td>
<td>Surgical barrier</td>
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<td>Artacent™ AC Graft</td>
<td>Wound care, Soft tissue repair</td>
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<td>Artracent™ Cord</td>
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<td>ArthroFlex™</td>
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<td>Achilles tendon repair</td>
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<td>Axolotl Graft/Axolotl Dualgraft</td>
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<td>Axolotl Ambient/Axolotl Cryo</td>
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<td>BellaCell HD</td>
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<td>Bio-conneKt™ Wound Matrix</td>
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<td>BioDfactor™</td>
<td>Wound care</td>
<td>Soft tissue repair</td>
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<td>BioDfence™</td>
<td>Surgical barrier</td>
<td>Tendon repair</td>
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<td>BioDfence™ Dryflex</td>
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<td>BioVance®</td>
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<td>BioWound/Bio Wound Plus/BioWound Xplus</td>
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<td>Cellesta™ Amniotic Membrane</td>
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<td>Cellesta™ Cord</td>
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<td>Cellesta™ Flowable Amnion</td>
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<td>Clarix® Flo</td>
<td>Integumental tissue repair</td>
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<td>Coll-e-Derm</td>
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<td>Conexa™</td>
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<td>CorMatrix</td>
<td>Cardiac/vascular tissue repair</td>
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<td>Cygnus™</td>
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<td>Cymetra™</td>
<td>Integumental tissue repair</td>
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<td>Note: Medically necessary and covered for the treatment of vocal cord paralysis.</td>
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<tr>
<td>Cytal®</td>
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<td>Dermacell™</td>
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<td>Excellagen®</td>
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<td>E-Z Derm™</td>
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<td>FloGraft™</td>
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<td>Soft tissue trauma</td>
<td>Q4100, Q9399</td>
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<td>Flowerannnio™ Flo</td>
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<td>Hyalomatrix®</td>
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<td>Note: Medically necessary and covered for the treatment of vocal cord paralysis.</td>
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<td>NEOX® 100 Quick-Peel Wound Matrix</td>
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<td>NuShield™</td>
<td>Tendon repair</td>
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<td>Oasis® Burn Matrix</td>
<td>Burn wounds</td>
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<tr>
<td>PalinGen®/Promatrx®</td>
<td>Soft tissue repair</td>
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<td>PalinGen® Xplus</td>
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<td>Permacol™</td>
<td>Soft tissue repair</td>
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<tr>
<td>PriMatrix™</td>
<td>Wound care</td>
<td>Q4110</td>
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</table>
## MEDICAL POLICY

### Skin and Tissue Substitutes

<table>
<thead>
<tr>
<th>Product</th>
<th>Category</th>
<th>Code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progenamatrix</td>
<td>Wound care</td>
<td>Q4222</td>
</tr>
<tr>
<td>PuraPly™/PuraPly™ AM</td>
<td>Wound care</td>
<td>Q4195, Q4196, Q4197</td>
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<tr>
<td>Repriza®</td>
<td>Reconstructive surgery</td>
<td>Q4143</td>
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<td></td>
<td>Abdominal wall repair</td>
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<tr>
<td>Restorigin™ Membrane</td>
<td>Wound care</td>
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<td>Injury healing</td>
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<td>Restorigin™ Fluid</td>
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<td>Injury healing</td>
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<td>Revitalon™</td>
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<td>TenSIX™</td>
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<td>WoundEx/Bioskin</td>
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<td>Q4163</td>
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<td>WoundEx Flow/Bioskin Flow</td>
<td>Integumental tissue repair</td>
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<td>Woundfix/Woundfix Plus/Woundfix Xplus</td>
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<tr>
<td>XWRAP®</td>
<td>Soft tissue repair</td>
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</table>

Link to [Policy Summary](#)

## BILLING GUIDELINES

Codes billed in association with the primary product code may also be denied if the product is not covered per the policy criteria above.

The following products are considered medically necessary and covered when billed for vocal cord paralysis treatment:
## MEDICAL POLICY

### Skin and Tissue Substitutes

**Products**

- Q4112 (Cymetra)
- Q4114 (Integra flowable wound matrix)

**Diagnosis codes**

- J38.02 Paralysis of vocal cords and larynx, bilateral
- J38.00 Paralysis of vocal cords and larynx, unspecified
- J38.01 Paralysis of vocal cords and larynx, unilateral

### CPT/HCPCS CODES

#### All Lines of Business

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>15271</td>
<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area</td>
</tr>
<tr>
<td>15272</td>
<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)</td>
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<tr>
<td>15273</td>
<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children</td>
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<tr>
<td>15274</td>
<td>Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)</td>
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<tr>
<td>15275</td>
<td>Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area</td>
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<tr>
<td>15276</td>
<td>Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)</td>
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<td>15277</td>
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<tr>
<td>15278</td>
<td>Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)</td>
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<td>Code</td>
<td>Description</td>
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<tr>
<td>15777</td>
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<td>Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (tenoglide tendon protector sheet), per square centimeter</td>
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<td>C9363</td>
<td>Skin substitute, integra meshed bilayer wound matrix, per square centimeter</td>
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<tr>
<td>Q4101</td>
<td>Apligraf, per square centimeter</td>
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<tr>
<td>Q4102</td>
<td>Oasis wound 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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<tr>
<td>Q4105</td>
<td>Integra dermal regeneration template (drt) or integra omnigraft dermal regeneration matrix, per square centimeter</td>
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<td>Dermagraft, per square centimeter</td>
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<tr>
<td>Q4107</td>
<td>Graftjacket, per square centimeter</td>
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<td>Q4108</td>
<td>Integra matrix, per square centimeter</td>
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<td>Q4116</td>
<td>Alloderm, per square centimeter</td>
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<td>Q4121</td>
<td>Theraskin, per square centimeter</td>
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<td>Q4122</td>
<td>Dermacell, per square centimeter</td>
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<td>Oasis ultra tri-layer wound matrix, per square centimeter</td>
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<td>Q4128</td>
<td>Flex hd, allopatch hd, or matrix hd, per square centimeter</td>
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<tr>
<td>Q4131</td>
<td>TERMED 12/31/18 Epifix or epicord, per square centimeter</td>
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<td>Q4132</td>
<td>Grafix core, per square centimeter</td>
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<td>Q4133</td>
<td>Grafix prime, per square centimeter</td>
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<td>Membrane graft or membrane wrap, per square centimeter</td>
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<tr>
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<td>Q4111</td>
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<td>Graftjacket xpress, injectable, 1 cc</td>
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<td>Alloskin, per square centimeter</td>
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<td>Q4117</td>
<td>Hyalomatrix, per square centimeter</td>
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<td>Q4118</td>
<td>Matristem micromatrix, 1 mg</td>
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<td>Q4123</td>
<td>Alloskin rt, per square centimeter</td>
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<td>Q4125</td>
<td>Arthrolex, per square centimeter</td>
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<tr>
<td>Q4126</td>
<td>Memoderm, dermaspan, tranzgraft or integuply, per square centimeter</td>
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<td>Talymed, per square centimeter</td>
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<td>Strattice tm, per square centimeter</td>
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<td>Q4134</td>
<td>Hmatrix, per square centimeter</td>
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<tr>
<td>Q4135</td>
<td>Mediskin, per square centimeter</td>
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<tr>
<td>Q4136</td>
<td>Ez-derm, per square centimeter</td>
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<td>Q4137</td>
<td>Amnioexcel or biodexcel, per square centimeter</td>
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**Not Covered**

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<td>Repriza, per square centimeter</td>
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<td>Dermapure, per square centimeter</td>
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<td>Dermavest and plurivest, per square centimeter</td>
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<td>Q4177</td>
<td>Neopatch, per square centimeter</td>
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<td>Q4183</td>
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<td>Code</td>
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<td>Cellesta flowable amnion (25 mg per cc); per 0.5 cc</td>
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<td>Q4187</td>
<td>Epicord, per square centimeter</td>
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<td>Q4188</td>
<td>Amnioarmor, per square centimeter</td>
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<tr>
<td>Q4189</td>
<td>Artacent ac, 1 mg</td>
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<td>Q4190</td>
<td>Artacent ac, per square centimeter</td>
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<tr>
<td>Q4191</td>
<td>Restorigin, per square centimeter</td>
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<tr>
<td>Q4192</td>
<td>Restorigin, 1 cc</td>
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<tr>
<td>Q4193</td>
<td>Coll-e-derm, per square centimeter</td>
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<tr>
<td>Q4194</td>
<td>Novachor, per square centimeter</td>
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<td>Q4195</td>
<td>Puraply, per square centimeter</td>
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<tr>
<td>Q4196</td>
<td>Puraply am, per square centimeter</td>
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<tr>
<td>Q4197</td>
<td>Puraply xt, per square centimeter</td>
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<tr>
<td>Q4198</td>
<td>Genesis amniotic membrane, per square centimeter</td>
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<tr>
<td>Q4200</td>
<td>Skin te, per square centimeter</td>
</tr>
<tr>
<td>Q4201</td>
<td>Matrion, per square centimeter</td>
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<tr>
<td>Q4202</td>
<td>Kerox (2.5g/cc), 1cc</td>
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<td>Q4203</td>
<td>Derma-gide, per square centimeter</td>
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<td>Q4204</td>
<td>Xwrap, per square centimeter</td>
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<td>Q4205</td>
<td>Novafix, per square centimeter</td>
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<tr>
<td>Q4206</td>
<td>Surgraft, per square centimeter</td>
</tr>
<tr>
<td>Q4207</td>
<td>Axolotl graft or axolotl dualgraft, per square centimeter</td>
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<tr>
<td>Q4208</td>
<td>Amnion bio or Axobiomembrane, per square centimeter</td>
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<tr>
<td>Q4209</td>
<td>Allogen, per cc</td>
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<tr>
<td>Q4210</td>
<td>Ascent, 0.5 mg</td>
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<tr>
<td>Q4211</td>
<td>Cellesta cord, per square centimeter</td>
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<tr>
<td>Q4212</td>
<td>Axolotl ambient or axolotl cryo, 0.1 mg</td>
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<tr>
<td>Q4213</td>
<td>Artacent cord, per square centimeter</td>
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<tr>
<td>Q4214</td>
<td>Woundfix, BioWound, Woundfix Plus, BioWound Plus, Woundfix Xplus or BioWound Xplus, per square centimeter</td>
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<tr>
<td>Q4215</td>
<td>Surgicord, per square centimeter</td>
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<tr>
<td>Q4216</td>
<td>Surgigraft-dual, per square centimeter</td>
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<td>Q4217</td>
<td>BellaCell HD or Surederm, per square centimeter</td>
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<td>Q4218</td>
<td>Amniowrap2, per square centimeter</td>
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<tr>
<td>Q4219</td>
<td>Progenamatrix, per square centimeter</td>
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<tr>
<td>Q4220</td>
<td>MyOwn skin, includes harvesting and preparation procedures, per square centimeter</td>
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**No Prior Authorization Required**

<table>
<thead>
<tr>
<th>Code</th>
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<tbody>
<tr>
<td>Q4112</td>
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<tr>
<td>Q4114</td>
<td>Integra flowable wound matrix, injectable, 1 cc</td>
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**Unlisted Codes**

All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then **prior-authorization is required.**

<table>
<thead>
<tr>
<th>Code</th>
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<tbody>
<tr>
<td>C9399</td>
<td>Unclassified drugs or biologicals</td>
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</table>
Q4100  Skin substitute, not otherwise specified

DESCRIPTION

Burn Wounds

Burn injuries are classified by the depth of the wound.\(^1\)

- First-degree burns involve only the epidermal layer (the outermost layer of skin). These burns heal completely within several days.
- Second-degree (partial-thickness) burns involve the epidermis and only part of the dermis (the thick layer of living tissue below the epidermis that forms the true skin, containing blood capillaries, nerve endings, sweat glands, hair follicles, and other structures). These burns may heal spontaneously, although healing usually requires reepithelialization from adjacent unburned skin or skin substitutes.
- Third-degree (full-thickness) burns involve all of the epidermal and dermal layers, with varying amounts of the sub-cutaneous layer. These burns cannot heal spontaneously and thus require excision and grafting.
- Fourth-degree burns involve deep structures such as tendon, muscle, and bone.

The successful treatment of burn wounds requires timely restoration of the skin’s protective function. “Conventionally, autologous split or full-thickness skin grafts have been recognized as the best definitive burn wound coverage, but it is constrained by the limited available sources, especially in major burns. Donor site morbidities in terms of additional wounds and scarring are also of concern of the autograft application.”\(^2\) Skin substitutes are necessary for both acute burn wounds and in patients requiring extensive reconstruction post-burn.

Diabetic Foot Ulcer

Chronic foot ulcers are common in hyperglycemia or undiagnosed poorly controlled diabetes due to damage of nerves (neuropathy), blood vessels (poor blood flow), and other body systems. “Approximately 85% of lower limb amputations among people with diabetes are preceded by a foot ulcer.”\(^3\) Diabetes-related foot ulcers are diagnosed by clinical evaluation and are classified based on the ulcer size, depth, and presence of an infection. The Wagner Ulcer Classification System is the most commonly used:

- Grade 0: No open lesions; may have deformity of cellulitis
- Grade 1: Superficial diabetic ulcer (partial- or full-thickness)
- Grade 2: Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis
- Grade 3: Deep ulcer with abscess, osteomyelitis, or joint sepsis
- Grade 4: Gangrene localized to portion of forefoot or heel
- Grade 5: Extensive gangrenous involvement of the entire foot\(^3\)

Treatment includes vascular and wound assessment, infection control, debridement, dressing changes, and offloading. “Offloading is the use of devices to reduce pressure on the wound, such as casts,
removable cast walkers, and special shoes.” Amputation is required when diabetic foot ulcers do not respond to treatment or become infected.

**Venous Stasis Ulcer**

Venous stasis ulcers, also known as venous leg ulcers or varicose ulcers, “are partial or full-thickness defects of an area of the skin in the lower leg, usually between the knee and the ankle, due to valvular incompetence and venous reflux causing venous hypertension.” These ulcers are common in older patients, women, and patients with conditions causing chronic venous insufficiency (e.g., congestive heart failure) and/or venous damage (e.g., injection drug use). Longer wound duration and larger wound surface area are associated with poor ulcer healing. “Standard care for venous leg ulcers typically includes wound care and compression therapy. Wound care may include cleansing, debridement, infection control, dressing, and bandaging.” In patients whose venous stasis ulcers do not heal despite standard care, venous surgery to correct underlying venous pressure may be required.

**Skin Substitutes**

Skin substitutes, also known as bioengineered, tissue-engineered, or artificial skin, are intended to protect wounds and reconstruct defective, ulcerated tissue. They function by physically covering wounds and providing structure to induce tissue regeneration and subsequent wound healing. They are generally classified into three main types:

1. Cellular—composed of living cells; or
2. Acellular—composed of synthetic materials or tissue from which living cells have been removed; or
3. A combination of cellular and acellular components.

Cellular skin substitutes are further categorized as follows:

- **Autograft**: A sample of the patient’s own healthy skin is harvested and placed in the ulcer
- **Allografts**: Skin or tissue harvested from another human (e.g., cadaver)
- **Xenograft**: Skin or tissue is harvested from an animal with similar skin structure (e.g., pigs).

Although there are many different types of skin substitutes, they are all similarly used as an adjunct to standard wound care. Application of a skin substitute requires that no infection be present, the wound bed is properly prepared, and the wound has achieved hemostasis.

**REVIEW OF EVIDENCE**

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of skin substitutes for breast reconstruction, burn wounds, diabetic foot ulcers, or venous stasis ulcers. Below is a summary of the available evidence identified through December of 2017.

**Systematic Reviews**

- In 2017, Hayes conducted a comparative effectiveness review to evaluate skin substitutes for chronic foot ulcers in adults with diabetes mellitus. The evidence review identified 7 studies as
eligible for inclusion, including 1 systematic review, 4 randomized controlled trials (RCTs), and 2 observational studies. Sample sizes ranged from 222 to 5,530 patients and follow-up times varied from 6 to 28 weeks. Outcomes of interest included, complete ulcer healing, amputation, quality of life (QOL), and complications.

In regards to amputation, the data suggests that using skin substitutes to treat diabetes-related foot ulcers may prevent amputation for some patients. However, the Hayes reviewers noted that the evidence base may be underpowered to accurately characterize differences between groups. When evaluating complete ulcer healing, “the achievement of complete ulcer closure was significantly higher overall among 13 RCTs with 1472 patients when assessed in terms of the Mantel-Haenszel Risk Ratio (RR), random effects model (13 studies; n=1472; RR=1.55 [95% CI, 1.30-1.85]).” Therefore, the reviewers concluded that for complete ulcer healing the overall evidence suggests that more patients achieve wound closure when skin substitutes are used in addition to standard wound therapy. The evidence was insufficient to make reliable conclusion regarding the impact of skin substitutes on quality of life. Lastly, the evidence indicates that skin substitutes do not present treatment-related safety issues, and treatment-related harms are similar to that of standard wound therapy.

Strengths of these studies included the randomized controlled design, large sample sizes, masked outcome assessors, and using computer programs to assess wound size and/or closure. Limitations are present in the short follow-up duration of some studies and inadequate number of patients to attain adequate power. Ultimately, Hayes concluded the following rating:

- C—“For use of skin substitutes as an adjunct to standard wound care to treat chronic, uninfected diabetes-associated foot ulcers that have not healed with standard wound care in adults with good glucose control and adequate blood flow to the extremities.”

In 2017, Hayes conducted a comparative effectiveness review to evaluate skin substitutes for chronic venous leg ulcers in adults. The evidence review identified 4 studies as eligible for inclusion, encompassing 1 systematic review, 2 randomized controlled trials (RCTs), and 1 retrospective nonrandomized study. Sample sizes ranged from 448 patients in the RCTs, 1,034 patients in the systematic review, and 1,489 patients in the retrospective nonrandomized study. Length of follow-up varied from 6 weeks to 12 months and the outcomes included complete ulcer healing, time to ulcer healing, and complications.

The evidence suggested that more patients achieve complete ulcer healing when a bilayer human skin equivalent of allograft is used in addition to standard care. The RCTs did not demonstrate benefit with other products. In directly comparing types of skin substitutes, 5 RCTs found no significant differences in the proportion of patients who healed when different products were used. There was an insufficient amount of evidence to make meaningful conclusions regarding time to complete ulcer healing. In regards to safety, the evidence does not indicate skin substitutes are associated with serious adverse events or greater safety risks than standard care alone.

Strengths of the included studies included the randomized controlled design and large sample sizes. Limitations were present due to a lack of statistical power, lack of blinding, and lack of intention to treat analysis. Ultimately, Hayes concluded the following ratings:
MEDICAL POLICY

Skin and Tissue Substitutes

- C—“For use of a bilayer human skin equivalent or an allograft skin substitute as an adjunct to standard wound care in adults with chronic venous leg ulcers that have not healed with standard care alone.”
- D—“For use of other types of skin substitutes (e.g., autografts, single-layer dermal skin, growth-arrested human keratinocytes and fibroblasts, poly-N-acetyl glucosamine matrix) as adjuncts to standard wound care in adults with chronic venous leg ulcers that have not healed with standard care alone.”

In 2016, Santema et al. conducted a Cochrane systematic review and meta-analysis of skin substitutes in the treatment of diabetic foot ulcers. Following the Cochrane Collaboration methodology, independent reviewers systematically identified relevant literature, assessed quality and extracted data. The outcomes of interest included proportion of ulcers completely healed, time to complete ulcer healing, and incidence of lower limb amputations.

The authors identified 17 randomized controlled trials as eligible for inclusion, encompassing 1,655 patients with diabetic foot ulcerations. Of these trials, 13 compared a skin substitute to standard care and 4 compared two types of skin substitutes. "When including all randomized participants, the proportion of completely healed ulcers ranged between 7.7% and 56.3% in the standard care group and 21.1% and 92.3% in the intervention group. The pooled risk ratio (RR) for complete ulcer healing was 1.55 in favor of the intervention group (95% CI 1.30–1.85; RD 0.25, 95% CI 0.14–0.37; NNT 4, 95% CI 3–8). The reporting was very heterogeneous for the outcome of time to complete ulcer healing; therefore, it was not possible to make clinical relevant comparisons. When pooling the studies that evaluated the incidence of lower limb amputations, the authors found a statistically significant lower amputation rate for the skin substitute group at 12 weeks.

This Cochrane systematic review was of good quality and had several strengths, including:

1. the systematic gathering of evidence, assessment of quality, and extraction of data by several independent reviewers following a pre-defined protocol
2. contacting authors of selected studies for additional information or data
3. assessment of heterogeneity, reporting bias, and publication bias
4. meta-analyses only being conducted when studies were determined to be homogeneous
5. sensitivity analyses to evaluate the influence of studies with a high risk of bias or high losses to follow-up

Limitations of this systematic review were the inclusion of studies with a high risk of bias and the potential for publication bias. Ultimately, the authors concluded "(t)his systematic review provides evidence that skin substitutes can, in addition to standard care, increase the likelihood of achieving complete ulcer closure compared with standard care alone in the treatment of diabetic foot ulcers.”

Evidence Tables

Medically Necessary Skin Substitutes

The following evidence tables are intended to succinctly list the peer-reviewed literature which supports medical necessity for the respective products. An evidence review was not performed for products.
which are included in the systematic reviews described above. Due to the large body of evidence, only the most recent peer-reviewed medical literature is included in the citations.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Products</th>
<th>Evidence</th>
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<tbody>
<tr>
<td><strong>Breast reconstruction</strong></td>
<td>AlloDerm®</td>
<td>Both AlloDerm® and FlexHD® Acellular Hydrated Dermis are established products for breast reconstruction and are supported in the peer-reviewed medical literature.6-12</td>
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<tr>
<td></td>
<td>FlexHD® Acellular Hydrated Dermis</td>
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<thead>
<tr>
<th>Indication</th>
<th>Products</th>
<th>Evidence</th>
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</thead>
<tbody>
<tr>
<td><strong>Burn wound</strong></td>
<td>Biobrane®/Biobrane®-L</td>
<td>The peer-reviewed medical literature supports the use of Biobrane as temporary skin substitute in acute burn wounds.13-15 In general, Biobrane performed better than the standard of care for wound healing rates, length of hospital stay, and pain.</td>
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<tr>
<td></td>
<td>Epicel</td>
<td>Epigel received FDA approval under a Humanitarian Device Exemption (HDE); therefore, this product is exempt from the effectiveness requirements necessary for FDA approval. The evidence review did identify two nonrandomized studies which evaluated Epigel for burn wounds.16,17 The most recent study (Carsin et al.) found that Epigel provided extensive and permanent burn coverage and improved the survival rate in severely burned patients.</td>
</tr>
<tr>
<td></td>
<td>– Integra® Dermal Regeneration Template</td>
<td>The Integra dermal regeneration and bilayer products are well-established in the peer-reviewed medical literature as safe and effective treatments for burn wounds.18-24</td>
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<tr>
<td></td>
<td>– Integra® Omnigraft Dermal Regeneration Matrix</td>
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<td></td>
<td>– Integra® Bilayer Matrix Wound Dressing</td>
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<td>– Integra® Meshed Bilayer Wound Matrix</td>
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<tr>
<td></td>
<td>TransCyte®</td>
<td>The peer-reviewed medical literature supports TransCyte as a safe and effective treatment for burn wounds.25-29 Results of these clinical trials indicated that TransCyte promoted faster healing, less scarring, and shorter hospital stays.</td>
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<tr>
<th>Indication</th>
<th>Products</th>
<th>Evidence</th>
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<tbody>
<tr>
<td><strong>Diabetic foot ulcer</strong></td>
<td>Apligraf®</td>
<td>This product was included in the Hayes comparative effectiveness review and Cochrane systematic review described above.</td>
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<tr>
<td></td>
<td>Dermagraft®</td>
<td>This product was included in the Hayes comparative effectiveness review and Cochrane systematic review described above.</td>
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### Skin and Tissue Substitutes

<table>
<thead>
<tr>
<th>Product</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>EpiFix® Amniotic Membrane</td>
<td>This product was included in the Hayes comparative effectiveness review and Cochrane systematic review described above.</td>
</tr>
<tr>
<td>Grafix® Core/Grafix® Prime</td>
<td>Recent randomized controlled trials support the efficacy of Grafix products for the treatment of diabetic foot ulcers (DFU). Both studies showed that treatment of DFU with Grafix significantly improved healing, reduced DFU-related complications, and shortened healing times. The evidence review also identified one additional nonrandomized study evaluating Grafix for DFU.</td>
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<tr>
<td>GraftJacket® Regenerative Tissue Matrix</td>
<td>This product was included in the Hayes comparative effectiveness review and Cochrane systematic review described above.</td>
</tr>
<tr>
<td>- Integra® Dermal Regeneration Template</td>
<td>The use of Integra products for the treatment of diabetic foot ulcers (DFU) is supported in the peer-reviewed literature by randomized controlled trials (RCT). A good-quality RCT by Driver et al. (2015) was conducted at 32 sites and randomized 307 patients to treatment with Integra or standard of care. Patients were treated for 16 weeks or until complete wound closure and followed-up for an additional 12 weeks. The results showed a statistically significant increase in the rate of complete wound closure for Integra patients compared to the standard of care (51% vs. 32%; p=0.001). In addition, patients treated with Integra had increased healing times and less adverse events.</td>
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<tr>
<td>- Integra™ Omnigraft Dermal Regeneration Matrix</td>
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<tr>
<td>Oasis® Wound Matrix/Oasis® Ultra Tri-Layer Matrix</td>
<td>This product was included in the Hayes comparative effectiveness review described above.</td>
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<tr>
<td>TheraSkin®</td>
<td>This product was included in the Hayes comparative effectiveness review described above.</td>
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### Indication

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<tr>
<th>Indication</th>
<th>Products</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>Venous stasis ulcer</td>
<td>Apligraf®</td>
<td>This product was included in the Hayes comparative effectiveness review described above.</td>
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<tr>
<td></td>
<td>EpiFix® Amniotic Membrane</td>
<td>The use of EpiFix for the treatment of venous stasis ulcers is supported in the peer-reviewed literature by randomized controlled trials (RCT). Most recently, Bianchi et al. (2017) conducted a multicenter RCT evaluating 109 patients with venous leg ulcers. Patients were recruited from 15 centers around the U.S. and followed-up for 16 weeks. The results indicated that patients receiving EpiFix in conjunction with compression therapy were statistically significantly more likely to experience complete wound healing than patients receiving standard wound care alone (60% vs. 35% at 12 weeks, p=0.0128; 71% vs. 44% at 16 weeks, p=0.0065). The older RCT by Serena et al. (2014) also showed a statistically significant difference in wound closure.</td>
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rates in favor of the Epifix group at 4 weeks follow-up (62% vs. 32%, p=0.005).

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<tr>
<th>Skin and Tissue Substitutes</th>
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<tbody>
<tr>
<td>Oasis® Wound Matrix</td>
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<td>TheraSkin®</td>
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**Investigational Skin Substitutes**

The following skin substitutes are considered investigational due to at least one of the following:

- There is no peer-reviewed literature to support the safety and/or clinical utility of the product.
- The available peer-reviewed literature is inadequate to establish the product’s safety and/or clinical utility due to poor quality studies with a high risk of bias. These studies had small and heterogeneous patient populations, lack of randomized controlled design, lack of a control group, and/or short-term follow-up periods.
- The product requires, but has not yet received U.S. Food and Drug Administration (FDA) approval under the 510(k) premarket notification or premarket approval (PMA) process.

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<th>Products</th>
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<td>Affinity</td>
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<td>Allogen</td>
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<td>Allopatch HD™</td>
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<td>Alloskin™ AC</td>
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<td>Alloskin™ RT</td>
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<td>Allowrap™</td>
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<td>AmnioArmor</td>
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<td>AmnioBand/Guardian</td>
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<td>AmnioBand® Particulate</td>
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<td>Amnion bio/Axobiomembrane</td>
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<td>AmnioEXCEL™/BiodExcel™</td>
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<td>AmnioFix®</td>
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<td>AmnioMatrix®/BioMatrix®</td>
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<td>AmnioPro-A</td>
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<td>Amnio Wound</td>
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<td>Amniowrap 2</td>
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<tr>
<td>Architect™/Architect™ PX/Architect™ FX/Architect™ Extracellular Matrix</td>
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<td>Artacent™/Artacent™ Cord</td>
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<td>ArthroFlex™</td>
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<td>Ascent</td>
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<td>Axolotl Graft/Axolotl Dualgraft/Axolotl Ambient/Axolotl Cryo</td>
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<tr>
<td>BellaCell HD</td>
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<td>Bio-conneKt™ Wound Matrix</td>
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<td>BioDfactor™</td>
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### MEDICAL POLICY

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<tr>
<th>BioDfence™</th>
<th>NuCel™</th>
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<tr>
<td>BioDfence™ Dryflex</td>
<td>NuShield™</td>
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<td>BioVance®</td>
<td>Oasis® Burn Matrix</td>
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<tr>
<td>BioWound/BioWound Plus/BioWound Xplus</td>
<td>PalinGen®/Promatrx®</td>
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<tr>
<td>Cellesta™ Amniotic Membrane</td>
<td>PalinGen® Xplus</td>
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<td>Cellesta™ Cord</td>
<td>Permacol™</td>
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<td>Cellesta™ Flowable Amnion</td>
<td>PriMatrix™</td>
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<td>Clarix® Flo</td>
<td>Progenamatrix</td>
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<td>Coll-e-Derm</td>
<td>PuraPly™/PuraPly™ AM</td>
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<td>Conexa™</td>
<td>Repriza®</td>
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<td>CorMatrix</td>
<td>Restorigin™ Membrane</td>
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<td>Restorigin™ Fluid</td>
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<td>Revita®</td>
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<td>SkinTE™</td>
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<td>Derma-guide</td>
<td>Strattice™</td>
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<td>DermaMatrix Acellular Dermis</td>
<td>Surederm</td>
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<td>DermaPure™</td>
<td>Surgicord</td>
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<td>DermaSpan™</td>
<td>SURGlraft™/SURGlraft™ Dual</td>
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<td>Dermavest</td>
<td>Surgraft</td>
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<td>Durepair Regeneration Matrix®</td>
<td>Talymed™</td>
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<td>Endoform Dermal Template™</td>
<td>TenoGlide®</td>
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<tr>
<td>Epifix® Injectable</td>
<td>TenSIX™</td>
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<td>EpiCord™</td>
<td>TruSkin™</td>
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<tr>
<td>Excellagen®</td>
<td>Veritas Collagen Matrix</td>
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<td>E-Z Derm™</td>
<td>WoundEx/Bioskin</td>
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<tr>
<td>FloGraft™</td>
<td>WoundEx Flow/Bioskin Flow</td>
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<tr>
<td>Floweramnio™ Flo</td>
<td>XCM Biologic Tissue Matrix</td>
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<tr>
<td>Floweramnio™ Patch</td>
<td>XWRAP®</td>
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<tr>
<td>Flowerderm™</td>
<td>Woundfix/Woundfix Plus/Woundfix Xplus</td>
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<td>GammaGraft</td>
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### Investigational Indications for Skin Substitutes

#### Hernia Repair

**Systematic Reviews**

- In 2015, Antoniou et al. conducted a systematic review and meta-analysis to estimate the comparative risk of hernia recurrence following primary suture or biologic mesh repair.\(^{37}\) Independent authors systematically identified relevant literature, extracted data, and evaluated quality. The primary outcomes of interest were short-term and long-term recurrence rates.

The authors identified 5 studies (2 randomized controlled trials and 3 case-control studies) encompassing 295 patients as eligible for inclusion. “Short-term recurrence rates were 16.6% and 3.5% for suture repair and biologic mesh repair, respectively (OR 3.74, 95% CI 1.55–8.98, p = 0.003)."
Long-term recurrence based on data provided by one trial only was 51.3% and 42.4%, respectively (OR 1.43, 95% CI 0.56–3.63, p = 0.45). Sensitivity analysis of the two randomized trials at short-term follow up demonstrated no significant difference (OR 2.54, 95% CI 0.92–7.02, p = 0.07).

The strengths of this study include the systematic gathering of evidence, assessment of quality, and extraction of data by several independent reviewers following a pre-defined protocol, and the assessment of heterogeneity and sensitivity. Limitations are present in the small number of included studies, leading to possible publication bias, and the poor quality of included studies. The authors concluded, “(b)iologic mesh repair of large hiatal hernias may confer short-term benefits in terms of hernia recurrence; however, the limited available information does not allow us to make conclusions about the long-term efficacy of biologic mesh in this setting. Individual biologic mesh grafts require further clinical assessment.”

- In 2013, Slater and colleagues conducted a systematic review to evaluate the effectiveness and safety of biologic grafts for ventral hernia repair. Independent authors systematically identified relevant literature, extracted data, and evaluated quality. The primary outcomes of interest were recurrence, abdominal wall laxity, surgical morbidity, and adverse events.

The authors identified 25 retrospective studies as eligible for inclusion. A total of 17 studies encompassing 531 patients were included in the recurrence rate outcome analysis. Overall, the recurrence rate was 13.8%. “Postoperative infection ($r^2=.325$, $P =.011$) and total surgical morbidity ($r^2=.189$, $P=.038$) were revealed as significant explanatory variables for recurrent hernia.” Laxity was reported in 10.5% of patients, and all cases occurred with the AlloDerm product. The surgical morbidity rate was 46.3% (95% CI, 33.3–59.6), and infection occurred in 15.9% (95% CI, 9.8–23.2) of patients.

Strengths of this study include the systematic review of evidence and extraction of data by independent authors; however, the methodological quality of this study is limited due to the poor quality of the included studies (all nonrandomized retrospective studies). The authors concluded that because no randomized trials were available, the efficacy of biologic grafts for ventral hernia repair could not be properly evaluated.

**Randomized Controlled Trials (RCTs)**

The evidence review did not identify any RCTs evaluating skin substitutes for hernia repair that were not included in the systematic reviews described above.

**Nonrandomized Studies**

The evidence review identified four additional recent nonrandomized studies evaluating allographic mesh for hernia repair. Meaningful conclusions cannot be drawn from the results of these studies due to methodological limitations; including, but not limited to, lack of randomized controlled design, lack of comparison group, small sample sizes, and short-term follow-up period.
Rotator Cuff Tear

In 2017, the ECRI Institute conducted a clinical comparison review of allografts for repairing rotator cuff tears.\(^{43}\) The authors identified two studies (1 small retrospective case series and 1 small prospective comparative trial) evaluating the AlloPatch HD and Arthroflex products for this indication. Overall, the evidence was inconclusive because of insufficient data. There was no published peer-reviewed literature that examined how well these products worked compared to the standard of care. The authors concluded by stating that randomized controlled trials comparing rotator cuff tear repair with and without these products, with a minimum of 2-year follow-up, are required to determine if there is an improvement in surgical outcomes.

Repair of Non-Traumatic Surgical Wounds

The evidence related to skin substitutes for the repair of non-traumatic surgical wounds (e.g., Mohs surgery for squamous or basal cell carcinomas) is limited to small case series and nonrandomized studies.\(^{44-53}\) Due to the poor methodological quality of these studies (lack of randomized design, lack of a control group, small sample sizes, short follow-up period, and lack of statistical analysis), there is insufficient evidence to establish the safety and medical necessity of skin substitutes for this indication. Further studies of good-methodological quality are required to support the effectiveness of skin substitutes for repair of non-traumatic surgical wounds, specifically Mohs surgery for squamous or basal cell carcinomas.

Parotidectomy

- In 2013, Li et al. conducted a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy and safety of different types of grafts for the prevention of Frey syndrome after parotidectomy.\(^{54}\) Independent reviewers systematically identified relevant literature, assessed quality, and extracted then pooled data. The outcomes of interest were the relative risk of Frey syndrome using skin substitute grafting or muscle flaps (another preventative measure) following parotidectomy.

The authors identified 14 randomized controlled trails encompassing 1,098 participants as eligible for inclusion. All studies had an unclear risk of bias. Although, the results of the meta-analysis indicated that the use of an acellular dermal matrix can reduce the risk of Frey syndrome up to 82%, the muscle flaps can also reduce the risk of Frey syndrome up to 81%. Additionally, there was no statistically significant difference was found between the acellular dermal matrix and muscle flap groups (RR 0.73, 95% CI 0.15 to 3.53, P = .70).

The strengths of this study include the systematic gathering of evidence, assessment of quality, and extraction of data by several independent reviewers following a pre-defined protocol, and the assessment of heterogeneity and sensitivity. Limitations are present in the heterogeneity of included studies and the poor quality of the RCTs (heterogenous patient populations, small sample sizes, and short follow-up periods). The authors concluded that “the evidence suggests grafts are effective in preventing Frey syndrome after peridectomy. More randomized clinical trials are needed to confirm our conclusions and prove the safety of the grafts.”\(^{54}\)
In 2012, Zeng and colleagues conducted a systematic review and meta-analysis to evaluate the AlloDerm skin substitute for the prevention of Frey syndrome after parotidectomy.\textsuperscript{55} Independent reviewers identified relevant studies, extracted and pooled data, and assessed quality. The primary outcome of interest was the relative risk reduction in objective and subjective incidence.

Following systematic review, the authors had identified 5 studies including 409 patients as eligible for inclusion. Results of the meta-analysis showed a relative risk reduction of 85% in the objective incidence and 68% in the subjective incidence of Frey syndrome with AlloDerm implants. There was also a 91% relative risk reduction in salivary fistula. However, there was no statistically significant reduction in the incidence of facial nerve paralysis or seroma/sialocele.

Strengths of this systematic review include the evaluation of evidence and extraction of data by independent authors following a pre-defined protocol and the inclusion of only randomized controlled trials. Limitations are present in the significant inter-study heterogeneity, the poor quality of the included studies (small sample sizes, short follow-up periods, lack of blinding, lack of intention to treat analysis), and the small number of included studies (possible publication bias). Ultimately, the authors concluded “(t)here is evidence that AlloDerm reduces the incidence of Frey syndrome effectively and safely, and also has the potential to improve facial contour and decrease salivary fistula. However, it is unclear whether AlloDerm implants improve facial contour and decrease other complications. Thus, further controlled evaluative studies incorporating more precise measures are required.”\textsuperscript{55}

**CLINICAL PRACTICE GUIDELINES**

**National Institute for Health and Care Excellence (NICE)**

The 2016 evidence-based NICE guideline for the prevention and management of diabetic foot problems recommended, “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.”\textsuperscript{56}

**Society for Vascular Surgery/American Venous Forum**

The 2014 evidence-based Society for Vascular Surgery/American Venous Forum guideline for the management of venous leg ulcers recommended the following:

- The Committee suggests against split-thickness skin grafting as primary therapy in treatment of venous leg ulcers. [Grade - 2; Level of Evidence - B] The Committee suggests split-thickness skin grafting with continued compression for selected large venous leg ulcers that have failed to show signs of healing with standard care for 4 to 6 weeks. [Grade - 2; Level of Evidence - B]
- The Committee suggests the use of cultured allogeneic bilayer skin replacements (with both epidermal and dermal layers) to increase the chances for healing in patients with difficult to heal venous leg ulcers in addition to compression therapy in patients who have failed to show signs of healing after standard therapy for 4 to 6 weeks. [Grade - 2; Level of Evidence - A]
- We recommend serial venous leg ulcer wound measurement and documentation. [BEST PRACTICE]. “Serial VLU wound measurement and documentation is important to determine baseline markers and effect of subsequent treatment measures on healing parameters. Documentation should
include number and position of ulcers on the leg. Wound measurements should be made for each VLU, including area, perimeter, and depth, with additional descriptors of wound edge parameters, wound base quality, drainage, and infection.\(^{57}\)

- We suggest reapplication of cellular therapy as long as the venous leg ulcer continues to respond on the basis of wound documentation. [GRADE - 2; LEVEL OF EVIDENCE - C]. “The optimal frequency and timing of reapplication of biologic skin substitutes to VLUs remain controversial with little consensus in published studies...With no comparative dosing studies published to determine clinical or economic outcomes, the frequency of application remains at the discretion of the clinician. Current clinical practice has included application of grafts followed by a period of 1 to 3 weeks of observation to determine effectiveness before reapplication is considered.”\(^{57}\)

**CENTERS FOR MEDICARE & MEDICAID**

As of January 2018, no Centers for Medicare & Medicaid (CMS) National Coverage Determinations (NCD)/Local Coverage Determinations (LCD)/Local Coverage Articles (LCA) were identified which addresses skin substitutes for any indication.

An MLN Matters\(^{\circ}\) (MLN# MM9923) was identified which addresses skin substitute procedure edits.\(^{58}\)

The MLN states, “(t)he fact that a drug, device, procedure or service is assigned a HCPCS code and a payment rate under the ASC payment system does not imply coverage by the Medicare program, but indicates only how the product, procedure, or service may be paid if covered by the program. Medicare Administrative Contractors (MACs) determine whether a drug, device, procedure, or other service meets all program requirements for coverage. For example, MACs determine that it is reasonable and necessary to treat the beneficiary’s condition and whether it is excluded from payment.”\(^{58}\)

**POLICY SUMMARY**

The evidence supports the efficacy and safety of select skin substitute products for the indications of breast reconstruction, burn wounds, diabetic foot ulcers, and venous stasis ulcers. The National Institute for Health and Care Excellence (NICE) recommends the use of skin substitutes as an adjunct to standard care when treating refractor diabetic foot ulcers. The Society for Vascular Surgery and the American Venous Forum also recommends skin substitutes in patients with refractory venous stasis ulcers.

The evidence is insufficient to establish the efficacy, safety, and medical necessity of several products due to a lack of high quality peer-reviewed literature or a lack of appropriate regulation. In addition, there is not enough evidence to support the use of skin substitutes for other indications, including hernia repair, repair of rotator cuff tears, repair of non-traumatic surgical wounds (e.g., Mohs surgery), and for the prevention of parotidectomy complications. Further studies of good methodological quality are required to establish the safety, effectiveness, and clinical utility of these products and indications.

**INSTRUCTIONS FOR USE**

Providence Health Plan (PHP) and Providence Health Assurance (PHA) Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. PHP and PHA Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are
available as of the last policy update. PHP and PHA reserve the right to determine the application of Medical Policies and make revisions to its Medical Policies at any time. Providers will be given at least 60-days’ notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and PHP and PHA Medical Policy will be resolved in favor of the coverage agreement.

**REGULATORY STATUS**

**U.S. Food and Drug Administration (FDA)**

Depending on the purpose or function of the skin substitute, FDA regulation is through the premarket approval (PMA) process or 510(k) premarket notification process. Products derived from donated human tissue are overseen by the FDA regulations for banked human tissue and the American Association of Tissue Banks (AATB) guidelines.

**PMA Process**

Skin substitutes that are classified by the FDA as an interactive wound and burn dressing are approved under the PMA process as a class III, high-risk device. These are considered interactive because they actively promote healing by interacting directly or indirectly with body tissues.

**510(k) Premarket Notification Process**

Skin substitutes approved under the 510(k) premarket notification processes are typically those whose primary purpose is to protect the wound and provide a foundation for proper healing. These skin substitutes may or may not interact with body tissues.

**FDA Regulations for Tissue and Tissue Products**

Donated skin or tissue “intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product or HCT/P.” The Center for Biologics Evaluation and Research (CBER) regulates HCT/Ps under 21 CFR Parts 1270 and 1271.

The following products are addressed in the policy criteria above as medically necessary for breast reconstruction, burn wounds, diabetic foot ulcers, or venous stasis ulcers.

**Humanitarian Device Exemption (HDE)**

HDE is a special FDA approval that allows a device to be marketed on a limited basis provided that:

1. The device is used to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year
2. The device would not be available to a person with such a disease or condition unless the exemption is granted
3. No comparable device is available to treat or diagnose the disease or condition; and
4. The device will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE applications are not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury. The labeling must also indicate that the effectiveness of the device for the specific indication has not been demonstrated.

Humanitarian use devices may only be used in facilities that have obtained an institutional review board (IRB) approval to oversee the usage of the device in the facility, and after an IRB has approved the use of the device to treat or diagnose the specific rare disease. The HDE holder (defined as the person who or entity that obtains the approval of an HDE from FDA) is responsible for ensuring that a device approved under an HDE is administered only in facilities having an IRB constituted and acting in accordance with the FDA’s regulation governing IRBs (21 CFR Part 56), including continuing review of use of the device.

### Products

<table>
<thead>
<tr>
<th>Products</th>
<th>Indications for Use</th>
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<tbody>
<tr>
<td>AlloDerm®</td>
<td>AlloDerm is to be used for repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument.</td>
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</table>
| Apligraf®        | • Apligraf is indicated for use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy.  
• Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule, or bone exposure. |
| Biobrane®/Biobrane®-L | • Temporary wound dressing for coverage of superficial burns, donor sites and meshed autographs.  
• Application should be to freshly debrided or excised wounds, or meshed autografts containing less than 105 bacteria/g tissue.  
• The debridement or excision must be done thoroughly to remove all coagulum or eschar. BIOBRANE/BIOBRANE-L will not adhere to dead tissue and any remaining necrotic tissue may cause infection.  
• Establish hemostatis prior to application of BIOBRANE/BIOBRANE-L.  
• Apply fabric (dull) side down, wrinkle-free against the wound surface with slight tension.  
• If less secondary adherence is desired (e.g. deeper donor sites or meshed autografts), BIOBRANE-L is recommended. |
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<tr>
<th><strong>Skin and Tissue Substitutes</strong></th>
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<tbody>
<tr>
<td><strong>Under slight tension immobilize BIOBRANE/BIOBRALE-L using staples, tape, sutures, or skin closure strips and wrap area with dry gauze dressing or other stenting device to hold the dressing firmly in contact with the wound surface for 24 to 36 hours.</strong></td>
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<tr>
<td><strong>Dermacell™</strong>&lt;sup&gt;65&lt;/sup&gt;</td>
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<td><strong>Dermagraft®</strong>&lt;sup&gt;66&lt;/sup&gt;</td>
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<tr>
<td><strong>Epigel</strong>&lt;sup&gt;67&lt;/sup&gt;</td>
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<tr>
<td><strong>EpiFix® Amniotic Membrane</strong>&lt;sup&gt;68&lt;/sup&gt;</td>
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<tr>
<td><strong>FlexHD® Acellular Hydrated Dermis</strong>&lt;sup&gt;69&lt;/sup&gt;</td>
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<tr>
<td><strong>GraftJacket™ Regenerative Tissue Matrix</strong>&lt;sup&gt;71&lt;/sup&gt;</td>
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<tr>
<td><strong>Integra® Dermal Regeneration Template/Omnigraft® Dermal Regeneration Matrix</strong>&lt;sup&gt;72&lt;/sup&gt;</td>
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### Skin and Tissue Substitutes

<table>
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<tr>
<th><strong>TheraSkin</strong></th>
<th>TheraSkin is a biologically active, cryopreserved real human skin allograft, composed of living cells, fibroblasts and keratinocytes, and a fully developed extra cellular matrix (ECM) in its epidermis and dermis layers. TheraSkin can be used on chronic wounds with exposed muscle, bone, tendon and joint capsule including, but not limited to, DFUs, VLUs, Arterial ulcers, dehisced surgical wounds, pressure sores and wounds that might otherwise require an autograft.</th>
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<tr>
<td><strong>TransCyte</strong></td>
<td>Indicated for use as a temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft placement; and for the treatment of mid-dermal to indeterminate depth burn wounds that typically require debridement and that may be expected to heal without autografting.</td>
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</tbody>
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| **Oasis® Wound Matrix** | The OASIS® Wound Matrix device's intended use is for the management of wounds including:  
- partial and full-thickness wounds,  
- pressure ulcers,  
- venous ulcers,  
- diabetic ulcers,  
- chronic vascular ulcers,  
- tunneled/undermined wounds,  
- surgical wounds (donor sites/grfts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence),  
- trauma wounds (abrasions, lacerations, second-degree burns, and skin tears),  
- draining wounds. |
| **Integra® Bilayer Matrix**  
- **Integra® Meshed Bilayer** | The Integra Bilayer Matrix Wound Dressing and the Integra Meshed Bilayer Wound Matrix Dressing are substantially equivalent to the Integra Dermal Regeneration Template. These products are indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grfts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use. |

**Mental Health Parity Statement**

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.
INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days’ notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

MEDICAL POLICY CROSS REFERENCES

- Cosmetic and Reconstructive Surgery, SUR193
- Breast Reconstruction, SUR162

REFERENCES

4. Hayes Medical Technology Directory: Skin Substitutes for Chronic Venous Leg Ulcers in Adults- A Review of Reviews. 2017; https://www.hayesinc.com/subscribers/displaySubscriberArticle.do?articleId=76006&searchStore=%24search_type%3Dal%24icd%3D%24keywords%3Dskin%2Csubstitute%24status%3Dal%24page%3D1%24from_date%3D%24to_date%3D%24report_type_options%3D%24technology_type_options%3D%24organ_system_options%3D%24specialty_options%3D%24order%3D%24%24 relevance. Accessed 1/12/2018.


