Bio-Engineered Skin and Soft Tissue Substitutes

Policy Number: 7.01.113  Last Review: 8/2017
Origination: 4/2008  Next Review: 2/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for bio-engineered skin and soft tissue substitutes when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Breast reconstructive surgery using allogeneic acellular dermal matrix products* (i.e., AlloDerm®, AlloMax™, Cortiva™, AlloMend®, DermaMatrix™, FlexHD®, GraftJacket®, See Considerations) may be considered medically necessary,
- when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required,
- when there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis, or
- the infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.

Treatment of chronic, non-infected, full-thickness diabetic lower extremity ulcers using the following tissue-engineered skin substitutes may be considered medically necessary.
- AlloPatch®*
- Apligraf®**
- Dermagraft®**
- Integra® Dermal Regeneration Template

Please see policy 7.01.149 for human amniotic membrane products (AmnioBand® Membrane, Biovance®, Epifix®, Grafix™)

Treatment of chronic, non-infected, partial or full-thickness lower extremity skin ulcers due to venous insufficiency which have not adequately responded following a one month period of conventional ulcer therapy, using the following tissue-engineered skin substitutes may be considered medically necessary.
- Apligraf®**
- Oasis™ Wound Matrix***
Treatment of dystrophic epidermolysis bullosa using the following tissue-engineered skin substitutes may be considered **medically necessary**.
- OrCel™ (for the treatment of mitten-hand deformity when standard wound therapy has failed and when provided in accordance with the Humanitarian Device Exemption (HDE) specifications of the FDA)****

Treatment of second and third degree burns using the following tissue-engineered skin substitutes may be considered **medically necessary**.
- Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30% when provided in accordance with the HDE specifications of the FDA)****
- Integra Dermal Regeneration Template™**

The use of AlloDerm® graft as an interpositional barrier following parotidectomy to reduce the incidence of Frey syndrome is considered **medically necessary**.

The use of AlloDerm® graft as an implant for reconstruction following removal of a malignant neoplasm is considered **medically necessary**.

*Banked Human Tissue  
** FDA PMA approved  
*** FDA 510(k) cleared  
**** FDA-approved under a humanitarian device exemption (HDE)

**When Policy Topic is not covered**

All other uses of the bio-engineered skin and soft tissue substitutes not listed above are considered **investigational**.

All other skin substitutes not listed above are considered **investigational**, including, but not limited to:

- ACell® UBM Hydated Wound Dressing
- ACell® UBM Lyophilized Wound Dressing
- AlloSkin™
- AlloSkin™ RT
- Aongen™ Collagen Matrix
- Architect® ECM, PX, FX
- ArthroFlex™ (FlexGraft)
- Atlas Wound Matrix
- Avagen Wound Dressing
- AxoGuard® Nerve Protector (AxoGen)
- CellerateRX®
- CollaCare®
- CollaCare® Dental
- Collagen Wound Dressing (Oasis Research)
- Collaguard®
- CollaMend™
- CollaWound™
- Collexa®
- Collieva®
- Conexa™
- Coreleader Colla-Pad
- CorMatrix®
- Cymetra®
- CytaL™ (previously MatriStem®)
- Dermadapt™ Wound Dressing
- DermACELL™
- Dermapure™
- DermaSpan™
- DressSkin
- Durepair Regeneration Matrix®
- Endoform Dermal Template™
- ENDURagen™
- Excellagen
- ExpressGraft™
- E-Z Derm™
- FlexiGraft®
- GammaGraft
- GraftJacket® Xpress, injectable
- Hyalomatrix®
- Hyalomatrix® PA
- hMatrix®
- Integra™ Flowable Wound Matrix
- Integra™ Bilayer Wound Matrix
- Integra™ Omnigraft
- MariGen™/Kerecis™ Omega3™
- MatriDerm®
- Matrix HD™
- Mediskin®
- MemoDerm™
- Microderm® biologic wound matrix
- NeoForm™
- NuCel
- Oasis® Burn Matrix
- Oasis® Wound Matrix
- Oasis® Ultra
- Pelvicol®/PelviSoft®
- Permacol™
- PriMatrix™
- Primatrix™ Dermal Repair Scaffold
- PuraPly™ Wound Matrix (previously FortaDerm™)
- PuraPly™ AM (Antimicrobial Wound Matrix)
- Puros® Dermis
- RegenePre™
- Repliform®
- Repriza™
- StrataGraft
- Strattice™ (xenograft)
- Supratheral®
- SurgiMend®
- Talymed®
- TenGlide™
- TenSIX™ Acellular Dermal Matrix
- TissueMend
- TheraForm™ Standard/Sheet
- TheraSkin®
- TruSkin™
- Veritas® Collagen Matrix
- XCM Biologic® Tissue Matrix
- XenMatrix™ AB.

**Considerations**

Note: Amniotic membrane and amniotic fluid products are reviewed in evidence review in a separate policy.

Clinical input 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.

Application of skin replacements and skin substitutes is reported with CPT codes 15040-15278. Codes 15040-15261 are specific to autografts and tissue-cultured autografts, codes 15271-15278 are specific to skin substitute grafts.

Effective in 2012, there is a specific add-on CPT code for the use of these materials as an implant:
- 15777: Implantation of biologic implant (e.g., acellular dermal matrix) for soft tissue reinforcement (e.g., breast, trunk) (List separately in addition to code for primary procedure)

The HCPCS codes for these products that are used in outpatient and office settings are listed in the code table. There are also HCPC modifiers to indicate whether the skin substitute is or is not used as a graft (i.e., surface use vs. use as an implant):
- JC: Skin substitute used as a graft
- JD: Skin substitute not used as a graft

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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 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.

**Breast Reconstruction**
For individuals who are undergoing breast reconstruction who receive allogeneic ADM products, the evidence includes a randomized controlled trial (RCT) and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. A recent 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, including but not limited to when the use of ADM allows a single-stage reconstruction, the available evidence may be considered sufficient to permit conclusions about health outcomes that 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, the evidence includes 1 RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. One 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 Dermal Regeneration Template, 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 Dermal Regeneration Template (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 other ADM products other than AlloPatch, Apligraf, Dermagraft, or Integra Dermal Regeneration Template, cryopreserved skin allograft, or xenogenic skin substitutes, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Additional study with a larger number of subjects is needed to compare the effect of other human ADM products, cryopreserved skin allograft (TheraSkin) and xenogenic skin substitutes (eg, Oasis Wound Matrix, PriMatrix) to the standard of care. 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 disease-specific survival, 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 symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, there are few skin substitutes 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.

**Clinical Input**
Clinical input has been obtained on several occasions. The input considered ADM products to be medically necessary for breast reconstruction under select conditions and for the various products to be similar in efficacy. Input was mixed on the efficacy of xenogenic products for other indications.

It was concluded that, based on the extensive data from case series and clinical input on the usefulness of this procedure in providing inferolateral support for breast reconstruction, this procedure was medically necessary for breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis; or when the inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed.

**Background**
Bio-engineered 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. The various ADM products can differ in a number of ways, including as 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. Tissue-engineered skin substitutes can be used as either temporary or permanent wound coverings.

There are a large number of potential applications for artificial skin and soft tissue products. One large category is non-healing 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, non-healing lower extremity wounds represent an ongoing risk for infection, sepsis, limb amputation and death. Bio-engineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

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

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

**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**
Allograft acellular dermal matrix products derived from donated human skin tissue are supplied by U.S. AATB-compliant tissue banks using the standards of the American Association of Tissue Banks (AATB) and U.S. Food and Drug Administration’s (FDA) guidelines. The processing removes the cellular components (i.e., epidermis and all viable dermal cells) that can lead to rejection and infection. Acellular dermal matrix products from human skin tissue are regarded as minimally processed and not significantly changed in structure from the natural material; the FDA classifies it as banked human tissue and therefore does not require FDA approval.

- **AlloDerm®** (LifeCell Corporation) is an acellular dermal matrix (allograft) tissue-replacement product that is created from native human skin and processed so that the basement membrane and cellular matrix remain intact. An injectable micronized form of AlloDerm (Cymetra) is also available.
- **AlloMax™ Surgical Graft** (Bard Davol), **Cortiva™ Allograft Dermis** (RTI Biologics) is an acellular non-cross-linked human dermis allograft. (Cortiva™ was previously marketed as AlloMax and NeoForm).
- **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®** (Ethicon) is an acellular hydrated dermis derived from donated human allograft skin. The Musculoskeletal Transplant Foundation acquires and processes the tissue.
- **DermaCell™** (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL® and PRESERVON®.
- **DermaMatrix** (Synthes) is an acellular dermal matrix (allograft) derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation® (MTF®).
- **DermaPure™** (Tissue Regenix Wound Care Inc.) is a single layer decellularized human dermal allograft for the treatment of acute and chronic wounds.
- **GraftJacket® Regenerative Tissue Matrix** (KCI) is an acellular regenerative tissue matrix that has been processed from screened donated human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells, while preserving dermal structure.

**Xenogenic Products**

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 exudating partial and full-thickness wounds:
pressure (stage I-IV) and venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, donor sites, and grafts.

Helicoll (Encol) is an acellular collagen matrix 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.

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.

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.

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

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

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

**Living Cell Therapy**

Apligraf® (Organogenesis) is a bi-layered 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. It was FDA-approved in 1998 for use in conjunction with compression therapy for the treatment of non-infected, partial- and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower extremity ulcers nonresponsive to standard wound therapy.
Dermagraft® (Shire Regenerative Medicine) is composed of cryopreserved human-derived fibroblasts and collagen applied to a bioabsorbable polyglactin mesh scaffold. Dermagraft has been approved by the FDA for repair of diabetic foot ulcers. FDA product code: PFC

Theraskin® (Soluble Systems) is a cryopreserved 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 in compliance with the AATB and FDA guidelines. It is considered a minimally processed human cell, tissue, and cellular- and tissue-based product (HCT/P) by the FDA.

Epicel® (Genzyme Biosurgery) is a cultured epithelial autograft 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 greater than or equal to 30%. It may be used in conjunction with split-thickness autografts, or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns.

OrCel™ (Forticell Bioscience) (formerly called Composite Cultured Skin) is an absorbable allogeneic bi-layered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. It was approved by the FDA premarket approval (PMA) 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.

**Biosynthetic**

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

Integra® Dermal Regeneration Template (Integra LifeSciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It is FDA-approved for use in postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable because of the physiologic condition of the patient.

Integra™ Matrix Wound Dressing and Integra™ meshed Bilayer Wound Matrix are substantially equivalent skin substitutes that are FDA- 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.

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

**Synthetic 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.

**Rationale**
This evidence review was originally created in December 2007 for use of an allogeneic bioengineered skin substitutes in breast reconstructive surgery and expanded in 2011 to address additional indications. This evidence review has been updated on a periodic basis with searches of the MEDLINE database. The most recent literature update was performed through November 7, 2016. Where available, this evidence review focuses on randomized controlled trials (RCTs), registries, and systematic reviews. Following is a summary of key literature to date.

**Breast Reconstruction**
A variety of breast reconstruction techniques are used postmastectomy, including implant-based (immediate or delayed following use of a tissue expander) and those using autologous tissue flaps. Some of these techniques have been used with acellular dermal matrix (ADM) to provide additional support or tissue coverage. The literature on ADM for breast reconstruction consists primarily of retrospective, uncontrolled series and systematic reviews of these studies.

A 2013 study used data from the American College of Surgeon’s National Surgical Quality Improvement Program to compare ADM-assisted tissue-expander breast reconstruction (n=1717) to submuscular tissue-expander breast reconstruction (n=7442) after mastectomy.\(^4\) Complication rates did not differ significantly between the ADM-assisted (5.5%) and the submuscular tissue-expander groups (5.3%; \(p=0.68\)). Rates of reconstruction-related complications, major complications, and 30-day reoperation did not differ significantly between cohorts.

**Systematic Reviews**
A 2016 meta-analysis by Lee and Mun included 23 studies (total N=6199 cases) on implant-based breast reconstruction that were published between February 2011 and December 2014.\(^5\) The analysis included 1 RCT and 3 prospective comparative cohort studies; the remainder were retrospective comparative cohort studies. Use of ADM did not affect the total complication rate (see Table 1). ADM significantly increased the risk of major infection, seroma, and flap necrosis, but reduced risks of capsular contracture and implant malposition. Use of ADM allowed for significantly greater intraoperative expansion (mean difference [MD], 79.63; 95% confidence interval [CI], 41.99 to 117.26; \(p<0.001\)) and percentage of
intraoperative filling (MD=13.30; 95% CI, 9.95 to 16.65; p<0.001), and reduced the frequency of injection to complete expansion (MD = -1.56; 95% CI, -2.77 to -0.35; p=0.01).

**Table 1. Meta-Analysis of Breast Reconstruction Outcomes With and Without ADM**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>1.42</td>
<td>1.02 to 1.99</td>
<td>0.04</td>
</tr>
<tr>
<td>Seroma</td>
<td>1.41</td>
<td>1.12 to 1.78</td>
<td>0.004</td>
</tr>
<tr>
<td>Mastectomy flap necrosis</td>
<td>1.44</td>
<td>1.11 to 1.87</td>
<td>0.006</td>
</tr>
<tr>
<td>Unplanned return to the operating room</td>
<td>1.09</td>
<td>0.63 to 1.90</td>
<td>NS</td>
</tr>
<tr>
<td>Implant loss</td>
<td>1.00</td>
<td>0.68 to 1.48</td>
<td>NS</td>
</tr>
<tr>
<td>Total complications</td>
<td>1.08</td>
<td>0.87 to 1.34</td>
<td>NS</td>
</tr>
<tr>
<td>Capsular contracture</td>
<td>0.26</td>
<td>0.15 to 0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Implant malposition</td>
<td>0.21</td>
<td>0.07 to 0.59</td>
<td>0.003</td>
</tr>
</tbody>
</table>

ADM: acellular dermal matrix.

**AlloDerm**

**Randomized Controlled Trials**

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

**Comparisons Between Products**

**AlloDerm vs DermaMatrix or FlexHD**

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

Brooke et al (2012) retrospectively reviewed complication rates when AlloDerm (n=49), DermaMatrix (n=110), or FlexHD (n=62) were used for tissue expander breast reconstruction. Clinically significant complications were defined as cellulitis, abscess, seroma, expander leak or puncture, skin necrosis, wound dehiscence, or hematoma. Total clinically significant complication rates were 22% with AlloDerm, 15% with DermaMatrix, and 16% with FlexHD (p=NS). Infectious complication rates for the 3 products were the same (10%). When compared to breast reconstruction without an ADM (n=64), there were no significant differences in the total complication rates (17% vs 11%), but there was a trend toward a higher incidence of infectious complications (10% vs 2%, p=0.09)

Section Summary: Breast Reconstruction

Results of 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, rates of capsular contracture and malposition of implants may be reduced. Thus, in cases where there is limited tissue coverage, including but not limited to when the use of ADM allows a single-stage reconstruction, the available studies may be considered sufficient to permit conclusions about health outcomes.

Tendon Repair

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

Section Summary: Tendon Repair
One small RCT was identified that found improved outcomes with Graftjacket ADM allograft for rotator cuff repair. Although results of this trial were positive, additional study with a larger number of patients is needed to evaluate consistency of findings and determine the effects of this technology with greater certainty.

**Surgical Repair of Hernias or Parastomal Reinforcement**
A 2013 systematic review evaluated the clinical effectiveness of acellular collagen-based scaffolds for the repair of incisional hernias.\(^\text{10}\) The bioprosthetic materials could be harvested from bovine pericardium, human cadaveric dermis, porcine small intestine mucosa, porcine dermal collagen, or bovine dermal collagen. Products included in the search were Surgisis, Tutomesh, Veritas, AlloDerm, FlexHD, AlloMax, CollaMend, Permacol, Strattice, FortaGen, ACell, DermaMatrix, XenMatrix, and SurgiMend. Sixty publications with 1212 repairs were identified and included in the review, although meta-analysis could not be performed. There were 4 level III studies (2 AlloDerm, 2 Permacol); the remainder was level IV or V. The largest number of publications were on AlloDerm (n=27) and Permacol (n=18). No publications on incisional hernia repair were identified for AlloMax, FortaGen, DermaMatrix, or ACell. The overall incidence of a surgical site occurrence (eg, postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, mechanical failure) was 82.6% for porcine small intestine mucosa, 50.7% for xenogenic dermis, 48.3% for human dermis, and 6.3% for xenogenic pericardium. No comparative data were identified that could establish superiority to permanent synthetic meshes.

A 2011 systematic review included 30 level III and IV articles on ADM for abdominal wall reconstruction.\(^\text{11}\) No RCTs or high-quality comparative studies (level I or II) were identified. Examples of the level III studies are described next.

**AlloDerm as an Overlay**
In 2007, Espinosa-de-los-Monteros et al retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases.\(^\text{12}\) They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

**Comparisons Between Products**

**AlloDerm vs Surgisis Gold**
Gupta et al compared the efficacy and complications associated with use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair in 2006.\(^\text{13}\) The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine submucosa and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7 to 10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection,
diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in 8 (24%) hernia recurrences. Fifteen (45%) of the AlloDerm patients developed a diastasis or bulging at the repair site. Seroma formation was only a problem in 2 patients.

**AlloDerm vs FlexHD**
A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery. From 2005 to 2007, AlloDerm was used to repair large (>200 cm²) symptomatic complicated ventral hernias that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD was used to repair large complicated ventral hernias in patients meeting the same criteria (n=40). The 2 groups were comparable at baseline. At 1-year follow-up, all AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, true recurrence) requiring a second repair. Eleven (31%) patients in the FlexHD group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

**Strattice vs Synthetic Mesh**
In 2014, Bellows et al reported early results of an industry-sponsored multicenter RCT that compared Strattice (non-cross-linked porcine ADM, n=84) to a standard synthetic mesh (n=88) for the repair of inguinal hernias. The trial was designed by the surgeons and was patient- and assessor-blinded to reduce risk of bias. Allocation concealment continued through 2 years of follow-up. The primary outcome was resumption of activities of daily living at 1 year. Secondary outcomes included complications, recurrences, or chronic pain (ie, pain that did not disappear by 3 months postsurgery). At 3-month follow-up, there were no significant differences in either the occurrence or type of wound events (relative risk [RR], 0.98; 95% CI, 0.52 to 1.86). Pain was reduced from 1 to 3 days postoperative in the group treated with Strattice, but at 3 month follow-up pain scores did not differ significantly between groups.

**Strattice vs No Reinforcement**
Also in 2014, the PRISM Study Group reported a multicenter, double-blinded, randomized trial of Strattice for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies. Patients were randomly assigned to standard stoma construction with no reinforcement (n=58) or stoma construction with Strattice as parastomal reinforcement (n=55). At 24-month follow-up (n=75), the incidence of parastomal hernias was similar for the 2 groups (13.2% of controls, 12.2% of study group).

**Section Summary: Surgical Repair of Hernias or Parastomal Reinforcement**
Acknowledging that the 2014 Bellows trial has not reached its primary end point, the limited evidence available at this time does not support a benefit of ADMs in hernia repair or prevention of parastomal hernia.
Diabetic Lower-Extremity Ulcers

A 2016 Cochrane review evaluated skin substitutes for the treatment of diabetic foot ulcers. Seventeen trials (total N=1655 participants) were included in the meta-analysis. Most trials identified were industry-sponsored, and an asymmetric funnel plot indicated publication bias. Pooled results of published trials found that skin substitutes increased the likelihood of achieving complete ulcer closure compared with standard of care (SOC) alone (RR=1.55; 95% CI, 1.30 to 1.85). Use of skin substitutes also led to a statistically significant reduction in amputations, (RR=0.43; 95% CI, 0.23 to 0.81), although the absolute risk difference was small. Analysis by individual products found a statistically significant benefit on ulcer closure for Apligraf, Epifix, and Hyalograft-3D. The products that did not show a statistically significant benefit for ulcer closure were Dermagraft, Graftjacket, Kaloderm, and OrCel. Individual RCTs are described next.

Martinson and Martinson (2016) conducted an industry-sponsored analysis of Medicare claims data (13,193 treatment episodes) to compare efficacy and cost of skin substitutes for the management of diabetic foot ulcers. Included in the analysis were treatment episodes with Apligraf (37%), Dermagraft (42%), Oasis (19%), and Cytal (MatriStem, 2%). The mean number of applications was 3.24 for Apligraf, 4.48 for Oasis, 5.53 for Cytal, and 5.96 for Dermagraft. All comparisons were statistically significant. Healing at 90 days was modestly but statistically higher for Oasis (63%) and Cytal (62%) than for Apligraf (58%) or Dermagraft (58%). Amputation rates were similar after treatment with the 4 products, ranging from 1.3% for Oasis to 2.1% for Cytal.

Apligraf

In 2001, Veves et al reported on a randomized prospective study on the effectiveness of Apligraf (previously called Graftskin), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers. The study involved 24 centers in the United States; 208 patients were randomly assigned to ulcer treatment with Apligraf (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical débridement and adequate foot off-loading, was provided in both groups. Apligraf was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of 5 applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Apligraf-treated patients achieved complete wound healing compared with 36 (38%) in the control group (p=0.004). The Kaplan-Meier method median time to complete closure was 65 days for Apligraf, significantly lower than the 90 days observed in the control group (p=0.003). The rates of adverse reactions were similar between groups, with the exception of osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf group. The study concluded that application of Apligraf for a maximum of 4 weeks resulted in a higher healing rates compared with state-of-the-art treatment and was not associated with any significant AEs. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf, in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.
In 2010, Steinberg et al reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of noninfected diabetic foot ulcers.\textsuperscript{21} Study design and patient population were similar to the 208-subject U.S. study (previously described), which led to Food and Drug Administration (FDA) approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with noninfected neuropathic diabetic foot ulcers present for at least 2 weeks were enrolled in prospective, multicenter, open-label RCTs that compared Apligraf use in conjunction with standard therapy (sharp débridement, standard wound care, off-loading) to standard therapy alone. Pooling of data was performed because of the similarity and consistency of the 2 studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration, which was significantly longer in the European study (21 months vs 10 months in the U.S. study). Reported AEs by 12 weeks were comparable across treatment groups in the 2 studies. Efficacy measures demonstrated superior of Apligraf treatment over control-treated groups in both studies. Combining the data from both studies, 55.2\% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared with 34.3\% (46/134) of control subjects (p<0.001), and Apligraf subjects had a significantly shorter time to complete wound closure (p<0.001). The authors concluded that both the EU and U.S. studies exhibited superior efficacy and comparable safety for subjects treated with Apligraf compared with control subjects, and that the studies provided evidence of the benefit of Apligraf in treating diabetic foot ulcer.

In 2010, Kirsner et al analyzed 2517 patients with diabetic neuropathic foot ulcers treated between 2001 and 2004.\textsuperscript{22} This retrospective analysis used a wound care database; the patients received advanced biological therapy, specifically, Apligraf (446 patients), Regranex, or Procuren. Analysis found that advanced biological therapy was used, on average, within 28 days from the first wound clinic visit and was associated with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biological therapy were 31\% more likely to heal than wounds first treated with topical recombinant growth factor (p<0.001) and 40\% more likely to heal than those first treated with platelet releasate (p=0.01). Wound size, wound grade, duration of wound, and time to initiation of advanced biological therapy affected the time to healing.

**Dermagraft**

A 2003 pivotal multicenter FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft (human-derived fibroblasts cultured on mesh) or control.\textsuperscript{23} Over the 12-week study, patients received up to 8 applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91\% compared with 78\% for the control group. Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious AEs were attributed to Dermagraft. Ulcer infections developed in 10.4\% of the Dermagraft patients compared with 17.9\% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group.
(19% vs 32.5%). Retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft (5.5% vs 12.6%, p=0.031). Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

**Cytal (MatriStem) vs Dermagraft**
Frykberg et al (2016) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cytal, a porcine urinary bladder–derived extracellular matrix) versus Dermagraft in 56 patients with diabetic foot ulcers. The mean duration of ulcers before treatment was 263 days (range, 30-1095 days). The primary outcome was the percent wound closure with up to 8 weeks of treatment using blinded evaluation of photographs. Intention-to-treat (ITT) analysis found complete wound closure in 5 (18.5%) wounds treated with Cytal compared to 2 (6.9%) wounds treated with Dermagraft (p=NS). Quality of life, measured by the Diabetic Foot Ulcer Scale, improved from 181.56 to 151.11 in the Cytal group and from 184.46 to 195.73 in the Dermagraft group (p=0.074). It should be noted that this scale is a subjective measure and patients were not blinded to treatment. Power analysis indicated that 92 patients would be required; further recruitment is ongoing for completion of the study.

**TheraSkin vs Dermagraft**
Sanders et al (2014) reported a small (N=23) industry-funded randomized comparison of TheraSkin (cryopreserved human skin allograft with living fibroblasts and keratinocytes) and Dermagraft for diabetic foot ulcers. Wound size at baseline ranged from 0.5 to 18.02 cm²; the average wound size was about 5 cm² and was similar for the 2 groups (p=0.51). Grafts were applied according to manufacturers’ instructions over the first 12 weeks of the study until healing, with an average of 4.4 TheraSkin grafts (every 2 weeks) compared with 8.9 Dermagraft applications (every week). At week 12, complete wound healing was observed in 63.6% of ulcers treated with TheraSkin and 33.3% of ulcers treated with Dermagraft (p<0.049). At 20 weeks, complete wound healing was observed in 90.9% of the TheraSkin-treated ulcers compared with 66.7% of the Dermagraft group (p=0.428). Additional study in a larger number of subjects is needed.

**TheraSkin vs Apligraf**
DiDomenico et al (2011) compared TheraSkin to Apligraf for the treatment of diabetic foot ulcers in a small (N=29) RCT. The risk of bias in this study is uncertain, because reporting did not include a description of power analysis, statistical analysis, method of randomization, or blinding. The percentage of wounds closed at 12 weeks was 41.3% in the Apligraf group and 66.7% in the TheraSkin group. Results at 20 weeks were not substantially changed from those at 12 weeks, with 47.1% of wounds closed in the Apligraf group and 66.7% closed in the TheraSkin group. The percentage healed in the Apligraf group was lower than expected based on prior studies. The average number of grafts applied was similar for both groups at 1.53 for Apligraf and 1.38 for TheraSkin. The low number of dressing changes may have influenced results, with little change in the percentage of wounds closed between 12 and 20 weeks. An adequately powered
trial with blinded evaluation of wound healing and a standard treatment regimen would permit greater certainty on the efficacy of this product.

**AlloPatch**
AlloPatch Pliable human reticular acellular dermis was compared to SOC in a 2016 industry-sponsored multicenter trial by Zelen et al.\(^{28}\) The trial was powered to detect a 45% difference between groups in percent healing at 6 weeks with 20 patients per group. Evaluation of the outcome measures were not blinded. At 6 weeks, 65% (13/20) of wounds treated with AlloPatch had healed compared to 5% (1/20) in the SOC-alone group (p<0.001). After adjusting for wound area at baseline, the hazard ratio for healing was 168 (95% CI, 10 to 2704; p<0.001), indicating a lack of precision in the estimate. Per protocol, 10 patients in the SOC group and 1 in the AlloPatch group exited the study at 6 weeks because their wounds failed to reduce in area by at least 50%. According to ITT analysis with last observation carried forward, the percentage of wounds healed at 12 weeks was 80% in the AlloPatch group compared to 20% in the SOC group. However, because there was a high (50%) withdrawal rate in the SOC group, this result has a high risk of bias.

**Graftjacket Regenerative Tissue Matrix**
Brigido et al reported a small (N=40) randomized pilot study of Graftjacket compared with conventional treatment for chronic nonhealing diabetic foot ulcers in 2004.\(^{29}\) Control patients received conventional therapy with débridement, wound gel with gauze dressing, and off-loading. Graftjacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the Graftjacket group. Preliminary 1-month results showed that, after a single treatment, ulcers treated with Graftjacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs 15%), width (50% vs 23%), area (73% vs 34%), and depth (89% vs 25%). With follow-up to 4 weeks, no data were reported on the proportion with complete closure or the mean time to heal. All grafts were incorporated into the host tissue.

In 2009, Reyzelman et al reported an industry-sponsored multicenter randomized study that compared a single application of Graftjacket to SOC in 86 patients with diabetic foot ulcers.\(^{30}\) Eight patients, 6 in the study group and 2 in the control group, did not complete the trial. At 12 weeks, complete healing was observed in 69.6% of the Graftjacket group and 46.2% of controls. After adjusting for ulcer size at presentation, a statistically significant difference in nonhealing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks for the Graftjacket group versus 6.8 weeks for the control group. The authors did not report whether this difference was statistically significant. Median time to healing was 4.5 weeks for Graftjacket (range, 1-12 weeks) and 7.0 weeks for control (range, 2-12 weeks). Kaplan-Meier method survivorship analysis for time to complete healing at 12 weeks showed a significantly lower nonhealing rate for the study group (30.4%) compared with the control group (53.9%). The authors commented that a single application of
Graftjacket, as used in this study, was often sufficient for complete healing. Conclusions drawn from this study are limited by the small study population and differences in ulcer size at baseline. Questions also remain whether the difference in mean time to healing is statistically or clinically significant.

In 2015, Reyzelman and Bazarov\(^3\) reported an industry-sponsored meta-analysis of Graftjacket for diabetic foot ulcers that included the 2 studies described above and a third RCT by Brigido (2006)\(^4\) with 28 patients (total N=154 patients). The time to heal was estimated for the 2004 study by Brigido, based on the average wound reduction per week. The estimated difference in time to heal was considerably larger for Brigido’s 2004 study (-4.30 weeks) than for the other 2 studies that measured the difference in time to heal (-1.58 weeks and -1.10 weeks). Analysis of the proportion of wounds that healed included Brigido (2006) and Reyzelman (2009). The odds ratio (OR) in the smaller study by Brigido was considerably larger with a lack of precision in the estimate (OR=15.0; 95% CI, 2.26 to 99.64), and the combined odds ratio (3.75; 95% CI, 1.72 to 8.19) was not significant when analyzed using a random-effects model. Potential sources of bias, noted by Reyzelman and Bazarov, included publication and reporting biases, study selection biases, incomplete data selection, post hoc manipulation of data, and subjective choice of analytic methods. Overall, results of these studies do not provide convincing evidence that Graftjacket is more effective than SOC for healing diabetic foot ulcers. Additional trials with a larger number of subjects are needed to determine whether Graftjacket Regenerative Tissue Matrix improves health outcomes in this population.

**DermACELL vs Graftjacket Regenerative Tissue Matrix**

DermACELL and Graftjacket are both composed of human ADM. In 2016, Walters et al reported a multicenter randomized comparison of DermACELL, Graftjacket, or SOC (2:1:2 ratio) in 168 patients with diabetic foot ulcers.\(^3\) The study was sponsored by LifeNet Health, a nonprofit organ procurement association and processor for DermACELL. At 16 weeks, the proportion of completely healed ulcers was 67.9% for DermACELL, 47.8% for Graftjacket, and 48.1% for SOC. The 20% difference in completely healed ulcers was statistically significant for DermACELL versus SOC (p=0.039). The mean time to complete wound closure did not differ significantly for DermACELL (8.6 weeks), Graftjacket (8.6 weeks), and SOC (8.7 weeks).

**Integra Dermal Regeneration Template**

Integra Dermal Regeneration Template is a biosynthetic skin substitute that is FDA approved for life-threatening thermal injury. The Foot Ulcer New Dermal Replacement Study (FOUNDER) multicenter study (32 sites) on the Integra Template for chronic nonhealing diabetic foot ulcers was conducted under an FDA-regulated investigational device exemption.\(^3\) A total of 307 patients with at least 1 chronic diabetic foot ulcer were randomized to treatment with the Integra Template or a control condition (0.9% sodium chloride gel). Treatment was given for 16 weeks or until wound closure. There was a modest increase in wound closure with the Integra Template (51% vs 32%, p=0.001) and a shorter median time to closure (43 days vs 78 days, p=0.001). There was a strong correlation...
between investigator-assessed and computerized planimetry assessment of wound healing ($r=0.97$). Kaplan-Meier analysis showed the greatest difference between groups in wound closure up to 10 weeks, with diminishing differences after 10 weeks. Strengths of the study included adequate power to detect an increase in wound healing of 18%, which was considered to be clinically significant, secondary outcomes of wound closure and time to wound closure by computerized planimetry, and ITT analysis.

**Oasis Wound Matrix vs Regranex Gel**

Niezgoda et al (2005) compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix (an acellular wound care product) to Regranex Gel. This industry-sponsored, multicenter RCT was conducted at 9 outpatient wound care clinics and involved 73 patients with at least 1 diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix (n=37) or Regranex Gel (n=36) and a secondary dressing. Wounds were cleansed and débrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks, 18 (49%) Oasis-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients. Oasis treatment met the noninferiority margin, but did not demonstrate that healing in the Oasis group was statistically superior ($p=0.055$). Post hoc subgroup analysis showed no significant difference in incidence of healing in patients with type 1 diabetes (33% vs 25%) but showed a significant improvement in patients with type 2 diabetes (63% vs 29%). There was also an increased healing of plantar ulcers in the Oasis group (52% vs 14%). These post hoc findings are considered hypothesis-generating. Additional study with a larger number of subjects is needed to compare the effect of Oasis treatment to current SOC.

**PriMatrix**

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

In 2011, Karr published a retrospective comparison of PriMatrix and Apligraf in 40 diabetic foot ulcers. The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. The criteria were: diabetic foot ulcers of 4 weeks in duration; ulcer to at least 1 cm² in diameter and to the depth of subcutaneous tissue; healthy tissue at the ulcer; adequate arterial perfusion to heal; and ability to off-load the diabetic ulcer. The time to complete healing for PriMatrix was 38 days with 1.5 applications compared with 87 days with 2 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to compare the efficacy of PriMatrix to current SOC or advanced wound therapies.

**Section Summary: Diabetic Lower-Extremity Ulcers**
RCTs have demonstrated the efficacy of AlloPatch, Apligraf, Dermagraft, and Integra Dermal Regeneration Template over SOC. Additional study with a larger number of subjects is needed to evaluate the effect of Graftjacket, Cytal, Oasis Wound Matrix, PriMatrix, and TheraSkin compared to current SOC or other advanced wound therapies.

Lower-Extremity Ulcers due to Venous Insufficiency

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

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

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

A research group in Europe has described 2 comparative studies of the Oasis matrix for mixed arteriovenous ulcers. In a 2007 quasirandomized study, Romanelli et al compared the efficacy of 2 extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid).41 Fifty-four patients with mixed arteriovenous leg ulcers were assigned to the 2 arms based on order of entry into the study; 50 patients completed the study. Patients were followed twice weekly, and dressings changed more than once a week, only when necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis-treated ulcers compared with 46.2% of Hyaloskin-treated ulcers. Oasis treatment significantly increased the time to dressing change (mean, 6.4 days vs 2.4 days), reduced pain on a 10-point scale (3.7 vs 6.2), and improved patient comfort (2.5 vs 6.7).

In a 2010 trial, Romanelli et al compared Oasis to a moist wound dressing (SOC) in 23 patients with mixed arteriovenous ulcers and 27 patients with venous ulcers.42 The trial was described as randomized, but the method of randomization was not described. After the 8-week study period, patients were followed monthly for 6 months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis-treated ulcers at 8 weeks compared with 65% of the SOC group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks compared with 8.3 weeks for the SOC group. Treatment with Oasis also increased the time to dressing change (5.2 days vs 2.1 days) and the percentage of granulation tissue formed (65% vs 38%).

**PriMatrix**

In 2011, Karr published a retrospective comparison of PriMatrix (xenogenic ADM) and Apligraf in 28 venous stasis ulcers.37 The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Criteria were venous stasis ulcers of 4 weeks in duration, at least 1 cm² in diameter, and to a depth of subcutaneous tissue, with healthy tissue at the ulcer edge, adequate arterial perfusion to heal, and ability to tolerate compression therapy. The time to complete healing for PriMatrix was 32 days with 1.3 applications compared with 63 days with 1.7 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to assess the effect of PriMatrix treatment in compared with current SOC.

**Section Summary: Lower-Extremity Ulcers due to Venous Insufficiency**

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

**Dystrophic Epidermolysis Bullosa**

OrCel was approved under an HDE for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. Because this is a rare disorder, it is unlikely that RCTs will be conducted to evaluate whether OrCel improves health outcomes for this condition. HDE status has been withdrawn for Dermagraft for this indication. In 2003, Fivenson et al reported the off-label use of Apligraf in 5 patients with recessive dystrophic epidermolysis bullosa who underwent syndactyly release.43

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

**Deep Dermal Burns**

**Epicel**

Epicel is FDA approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a total body surface area (TBSA) of 30% or more. It is unlikely that RCTs will be conducted to evaluate whether Epicel improves health outcomes for this condition. One 2000 case series described the treatment of 30 severely burned patients with Epicel.44 The cultured epithelial autografts were applied to a mean of 37% of TBSA. Epicel achieved permanent coverage of a mean of 26% of TBSA, an area similar to that covered by conventional autografts (mean, 25%). Survival was 90% in these severely burned patients.

**Integra Dermal Regeneration Template**

A 2013 study compared Integra to split-thickness skin graft and to viscose cellulose sponge (Cellonex), using three 10×5 cm test sites on each of 10 burn patients.45 The surrounding burn area was covered with meshed autograft. Biopsies were taken from each site on days 3, 7, 14, and 21, and at months 3 and 12. The tissue samples were stained and examined for markers of inflammation and proliferation. The Vancouver Scar Scale was used to assess scars. At 12-month follow-up, the 3 methods resulted in similar clinical appearance, along with similar histologic and immunohistochemical findings.

In 2007, Branski et al reported a randomized trial that compared Integra with a standard autograft-allograft technique in 20 children with an average burn size of
73% TBSA (71% full-thickness burns).\textsuperscript{46} Once vascularized (about 14-21 days), the Silastic epidermis was stripped and replaced with thin (0.05-0.13 mm) epidermal autograft. There were no significant differences between the Integra group and controls in burn size (70% vs 74% TBSA), mortality (40% vs 30%), and hospital length of stay (41 vs 39 days), all respectively. Long-term follow-up revealed a significant increase in bone mineral content and density (24 months) and improved scarring in terms of height, thickness, vascularity, and pigmentation (at 12 months and 18-24 months) in the Integra group. No differences were observed between groups in the time to first reconstructive procedure, cumulative reconstructive procedures required during 2 years, and cumulative operating room time required for these procedures. The authors concluded that Integra can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

In 2003, Heimbach et al reported a multicenter (13 U.S. burn care facilities) postapproval study involving 222 burn injury patients (36.5% TBSA; range, 1%-95%) who were treated with Integra Dermal Regeneration Template.\textsuperscript{47} Within 2 to 3 weeks, the dermal layer regenerated, and a thin epidermal autograft was placed over the wound. The incidence of infection was 16.3%. Mean take rate (absence of graft failure) of Integra was 76.2%; the median take rate was 98%. The mean take rate of epidermal autograft placed over Integra was 87.7%; the median take rate was 95%.

\textbf{OrCel}
There is limited evidence to support the efficacy of OrCel compared with SOC for the treatment of split-thickness donor sites. In 2003, Still et al examined the safety and efficacy of bilayered OrCel to facilitate wound closure of split-thickness donor sites in 82 severely burned patients.\textsuperscript{48} Each patient had 2 designated donor sites that were randomized to receive a single treatment of OrCel or standard dressing (Biobrane-L). The healing time for OrCel sites was significantly shorter than for sites treated with a standard dressing, enabling earlier recropping. OrCel sites also exhibited a nonsignificant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

\textbf{TransCyte}
In 2001, Lukish et al compared 20 consecutive cases of pediatric burns greater than 7% TBSA that underwent wound closure with TransCyte with the previous 20 consecutive burn cases greater than 7% TBSA that received standard therapy.\textsuperscript{49} Standard therapy consisted of application of antimicrobial ointments and hydrodébridement. Only 1 (5%) child in the TransCyte group required autografting compared with 7 (35%) children in the standard therapy group. Children treated with TransCyte had a statistically significant shorter hospital length of stay (5.9 days) compared with those receiving standard therapy (13.8 days).

In 2006, Amani et al compared results from 110 consecutive patients with deep partial-thickness burns who were treated with TransCyte to results from the American Burn Association Patient Registry for similar burns.\textsuperscript{50} Significant differences were found in patients who were treated with dermabrasion plus
TransCyte compared with the population in the Registry. Patients with 0% to 19.9% TBSA burns treated with dermabrasion plus TransCyte had shorter hospital length of stay (6.1 days vs 9.0 days; p<0.001) as did those with 20% to 39.9% TBSA burns (17.5 days vs 25.5 days) and those with 40% to 59.9% TBSA burns (31 days vs 44.6 days). The authors found that use of dermabrasion plus TransCyte for partial-thickness burns was more efficacious and significantly reduced length of stay than traditional management.

TransCyte is no longer commercially available.

Other
In addition to indications previously reviewed, off-label uses of bioengineered skin substitutes have included pressure ulcers, inflammatory ulcers (eg, pyoderma gangrenosum, vasculitis), scleroderma digital ulcers, postkeloid removal wounds, genetic conditions, and variety of other conditions. 

Products that have been FDA approved/cleared for 1 indication (eg, lower-extremity ulcers) have also been used off-label in place of other FDA approved/cleared products (eg, for burns). No controlled trials were identified for these indications.

Summary of Evidence
Acellular dermal matrix (ADM) products are also being evaluated for soft tissue repair.

Breast Reconstruction
For individuals who are undergoing breast reconstruction who receive allogeneic ADM products, the evidence includes a randomized controlled trial (RCT) and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. A recent 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, including but not limited to when the use of ADM allows a single-stage reconstruction, the available evidence may be considered sufficient to permit conclusions about health outcomes that 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 1 RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. One 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 Dermal Regeneration Template, 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 Dermal Regeneration Template (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 other ADM products, cryopreserved skin allograft, or xenogenic skin substitutes, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Additional study with a larger number of subjects is needed to compare the effect of other human ADM products, cryopreserved skin allograft (TheraSkin) and xenogenic skin substitutes (eg, Oasis Wound Matrix, PriMatrix) to the standard of care. 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.
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 disease-specific survival, 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 symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, there are few skin substitutes 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.

**Supplemental Information**

**Clinical Input 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 nonocular 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, Cortiva™, 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.

**2011 Input**
In response to requests, input was received from 3 physician specialty societies and 2 academic medical centers while this policy was under review in 2011. Most reviewers supported the indications and products described in this policy. Clinical input was requested 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. The reviewers provided references for the additional indications; these were subsequently reviewed.

**2008 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 2008. All reviewers indicated that use of AlloDerm in breast reconstruction surgery should be available for use 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 has 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.
In 2006, ASPS endorsed guidelines from the Wound Healing Society (WHS) on the treatment of arterial insufficiency ulcers. The guidelines stated that extracellular matrix replacement therapy appears to be promising for mixed ulcers and may have a role as an adjuvant agent in arterial ulcers, but further study is required (level IIIC): “Despite the existence of animal studies, case series, and a small number of random control trials to support biomaterial use for pressure ulcers, diabetic ulcers, and venous ulcers; there are no studies specifically on arterial ulcers. Therefore, studies in arterial ulcers must be conducted before the recommendation can be made.”

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

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

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

National Institute for Health and Care Excellence
In 2015, the U.K.’s National Institute for Health and Care Excellence (NICE) published guidance on the prevention and management of diabetic foot problems. NICE recommended 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.

American College of Foot and Ankle Surgeons
The 2006 clinical consensus statement on diabetic foot disorders from the American College of Foot and Ankle Surgeons (ACFAS) stated that bioengineered tissues have been shown to significantly increase complete wound closure in venous and diabetic foot ulcers. ACFAS stated that tissue-engineered skin substitutes can function both as biologic dressings and as delivery systems for
growth factors and extracellular matrix components through the activity of live human fibroblasts contained in their dermal elements, and that at the time of the statement, 2 bioengineered tissues had been approved to treat diabetic foot ulcers in the United States: Apligraf and Dermagraft; both had demonstrated efficacy in randomized controlled trials (RCTs). Apligraf has been shown to significantly reduce the time to complete wound closure in venous and diabetic ulcers. Regenerative tissue matrix (Graftjacket) was used in diabetic foot ulcers, although it had not undergone any RCTs at the time of this guideline. Oasis, composed of structural cellular components and growth factors used to promote natural tissue remodeling, showed noninferiority to becaplermin gel in the healing of diabetic foot ulcers. Integra Dermal Regeneration Template, a collagen-chondroitin sponge overlaid with silicone originally developed for burns, was shown to be ideally suited to chronic and pathologic wounds.

**Infectious Diseases Society of America**
The 2012 guidelines from the Infectious Diseases Society of America stated 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).\(^60\) It was emphasized that none of these measures had been shown to improve resolution of infection and that they were expensive, not universally available, might require consultation with experts, and reports supporting their utility were mostly flawed.

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

**Medicare National Coverage**
Centers for Medicare and 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.\(^61\)

Since 2014, CMS has no longer distinguished between different skin substitutes and classifies them as either high cost or low cost.\(^62\) 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.

**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**

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<td>Mar 2016 (completed)</td>
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NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

References


**Billing Coding/Physician Documentation Information**

Note: CPT 15777 would be correct coding when used for Frey’s syndrome and in reconstruction post neoplasm removal (other than skin cancers).

**15271** Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area

**15272** Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273  Application of skin substitute graft to trunk, arms, legs, total wound surface area 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)

15274  Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

15275  Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area

15276  Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area

15277  Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children

15278  Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

15777  Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk) (List separately in addition to code for primary procedure)

C9354  Acellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm

C9356  Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per sq cm

C9358  Dermal substitute, native, nonadenatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm

C9360  Dermal substitute, native, nonadenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm

C9363  Skin substitute (Integra Meshed Bilayer Wound Matrix), per square cm

C9364  Porcine implant, Permacol, per sq cm

Q4100  Skin substitute, not otherwise specified

Q4101  Apligraf®, per sq cm

Q4102  Oasis wound matrix, per sq cm

Q4103  Oasis burn matrix, per sq cm

Q4104  Integra bilayer matrix wound dressing (BMWD), per sq cm

Q4105  Integra dermal regeneration template (DRT), per sq cm

Q4106  Dermagraft®, per sq cm

Q4107  GRAFTJACKET, per sq cm
Q4108  Integra matrix, per sq cm
Q4110  PriMatrix, per sq cm
Q4111  GammaGraft, per sq cm
Q4112  Cymetra, injectable, 1 cc
Q4113  GraftJacket® xpress, injectable, 1cc
Q4114  Integra flowable wound matrix, injectable, 1 cc
Q4115  AlloSkin, per square centimeter
Q4116  AlloDerm®, per square centimeter
Q4117  Hyalomatrix, per square centimeter
Q4118  Matristem micromatrix, 1 mg
Q4121  Theraskin, per square centimeter
Q4122  DermACELL, per sq cm
Q4123  AlloSkin RT, per sq cm
Q4124  OASIS ultra tri-layer wound matrix, per sq cm
Q4125  Arthroflex, per sq cm
Q4126  MemoDerm, per sq cm
Q4127  Talymed, per sq cm
Q4128  FlexHD or AllopatchHD, per sq cm
Q4130  Strattice TM, per sq cm
Q4134  hMatrix, per sq cm
Q4135  Mediskin, per sq cm
Q4136  E-Z Derm, per sq cm
Q4141  Alloskin AC, per sq cm
Q4142  XCM biologic tissue matrix, per sq cm
Q4143  Repriza, per sq cm
Q4146  Tensix, per sq cm
Q4147  Architect extracellular matrix, per sq cm
Q4149  Excellagen, 0.1 cc
Q4152  Dermapure, per sq cm
Q4158  Marigen, per sq cm
Q4161  Bio-ConneKt wound matrix, per sq cm
Q4164  Helicoll, per sq cm
Q4165  Keramatrix, per sq cm
Q4166  Cytal, per sq cm (new code 1/1/2017)
Q4167  Truskin, per sq cm (new code 1/1/2017)
Q4172  PuraPly or PuraPly AM, per sq cm (new code 1/1/2017)
Q4175  Miroderm, per sq cm (new code 1/1/2017)

**ICD-10 Codes**

C50.01- Malignant neoplasm of breast code range (female codes only listed)
C50.01;
C50.111-
C50.119;
C50.211-
C50.219;
C50.311-
C50.319;
C50.411-
C50.419; C50.511- C50.519; C50.621- C50.619; C50.811- C50.819; C50.911- C50.919
E08.621- E08.622; E09.621- E09.622; E10.621- E10.622; E11.621- E11.622; E13.621- E13.622
I83.001- I83.029 Varicose veins with ulcer code range – code by site
I83.201- I83.229 Varicose veins with both ulcer and inflammation code range – code by site
Q81.2 Epidermolysis bullosa dystrophica
T20-T25 Burns code range – code by site and degree of burn
Z85.3 Personal history of malignant neoplasm breast
Z90.10 Acquired absence of breast and nipple

Effective 1/1/2017, CPT codes C9349, Q4119, Q4120, Q4129 were termed.

Effective January 1, 2012 CPT codes 15170, 15171, 15175, 15176, 15300, 15301, 15320, 15321, 15330, 15331, 15335, 15336, 15340, 15341, 15360, 15361, 15365, 15366, 15400, 15401, 15420, 15421, 15430 and 15431 were deleted and replaced with CPT codes 15271-15278.

**Additional Policy Key Words**
N/A

**Policy Implementation/Update Information**

6/1/08 New policy; considered investigational.
1/8/09 Interim update. Policy statement revised to indicate procedure may be considered medically necessary with criteria. Coding updated. The change is effective 1/8/2009.
8/1/09 Coding update only.
1/1/10 No policy statement changes.
1/1/11 No policy statement changes. Coding updated.
8/11/11 Policy updated and scope expanded to include indications previously
addressed in policy 7.01.510 Skin Substitutes for Wound Healing; policy statements added for other indications; title changed to “Tissue-Engineered Skin Substitutes.”

1/1/12 Coding updated.

3/1/12 Title changed to “Bio-Engineered Skin and Soft Tissue Substitutes”. MatrixDerm® and StrataGraft added to list of investigational skin substitutes. Added use of AlloDerm® graft as an implant for reconstruction following removal of a malignant neoplasm is considered medically necessary

9/1/12 No policy statement changes.

3/1/13 Policy statement revised on Dermagraft. No longer considered medically necessary for dystrophic epidermolysis bullosa due to withdrawal of HDE [humanitarian device exemption] status. Other policy statements unchanged.

3/1/14 First policy statement expanded to include other acellular dermal matrix products. Updated investigational list. HCPCS codes updated.

3/1/15 Added EpiFix considered medically necessary for treatment of diabetic foot ulcers. Added complete name “Integra Dermal Regeneration Template” to medically necessary for 2nd and 3rd degree burns. Added several new skin substitute products in investigational policy.

8/1/15 HCPCS code C9356 added to code table.

2/1/16 No policy statement changes.

4/1/16 No policy statement changes.

8/1/16 Integra Dermal Regeneration Template and several amniotic membrane grafts considered medically necessary for the treatment of diabetic foot ulcers. TransCyte removed from medically necessary statement; it is no longer commercially available. HCPCS codes updated.

2/1/17 No policy statement changes.

3/1/17 Review of amniotic membrane products moved to policy 7.01.149. Products with new HCPCS codes (Microderm, TruSkin) added to investigational statement; Unite Biomatrix no longer available; MatriStem renamed Cytal; FortaDerm renamed PuraPly. AlloMend added to medically necessary statement for breast reconstructive surgery. AlloPatch added to medically necessary statement for diabetic lower-extremity ulcers. Investigational list updated with new products and name changes; Amniotic Membrane Graft* (including each of the following: Biovance®, Epifix®, Grafix™ removed from medically necessary statements. ACell® UBM Lyophilized Wound Dressing, Affinity™, AlloPatch HD™, Allowrap™, Alphaplex™ with MariGen Omega3™, Amniox®, Avaulta Plus™, BioDfence/BioDfactor, Clarix® Flo, Collagen Sponge (Innocoll), CollaSorb™, CRXa™, Dermavest™, GUARDIAN, HA Absorbent Wound Dressing, Helicoll, Jaloskin®, MatriStem® Burn Matrix, MatriStem® Micromatrix, Matrix Collagen Wound Dressing, MediHoney®, Neox® Flo, NuShield™, Revitalon™, SIS Wound Dressing II, SS Matrix™, Stimulen™ Collagen removed from Investigational statement.

8/1/17 No policy statement changes.
State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.