

7.01.113	Bioengineered Skin and Soft Tissue Substitutes		
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Section:	7.0 Surgery	Page:	Page 1 of 55

Policy Statement

- I. Breast reconstructive surgery using allogeneic acellular dermal matrix products^a (including each of the following: AlloDerm[®], AlloMend[®], Cortiva[®] [AlloMax™], DermACELL™, DermaMatrix™, FlexHD[®], FlexHD[®] Pliable™, GraftJacket[®]; see Policy Guidelines) may be considered **medically necessary** for **any** of the following:
 - A. When there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required
 - B. When there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis
 - C. The inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed

- II. Treatment of chronic, noninfected, full-thickness diabetic lower-extremity ulcers may be considered **medically necessary** using **any** of the following tissue-engineered skin substitutes:
 - A. AlloPatch^{®a}
 - B. Apligraf^{®b}
 - C. Dermagraft^{®b}
 - D. Integra[®] Omnigraft™ Dermal Regeneration Matrix (also known as Omnigraft™) and Integra Flowable Wound Matrix

- III. Treatment of chronic, noninfected, partial- or full-thickness lower-extremity skin ulcers due to venous insufficiency, which have not adequately responded following a 1-month period of conventional ulcer therapy may be considered **medically necessary** using **either** of the following tissue engineered skin substitutes:
 - A. Apligraf^{®b}
 - B. Oasis™ Wound Matrix^c

- IV. Treatment of dystrophic epidermolysis bullosa may be considered **medically necessary** using the following tissue-engineered skin substitutes:
 - A. 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 U.S. Food and Drug Administration [FDA])^d

- V. Treatment of second- and third-degree burns may be considered **medically necessary** using **either** of the following tissue-engineered skin substitutes:
 - A. Epicel[®] (for the treatment of deep dermal or full-thickness burns comprising a total body surface area greater than or equal to 30% when provided in accordance with the HDE specifications of the FDA)^d
 - B. Integra[®] Dermal Regeneration Template^b.
 - ^a Banked human tissue.
 - ^b FDA premarket approval.
 - ^c FDA 510(k) clearance.
 - ^d FDA-approved under an HDE.

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

- VII. All other **skin and breast** soft tissue substitutes not listed above are considered **investigational**, including, but not limited to:
1. ACell® UBM Hydrated/Lyophilized Wound Dressing
 2. AlloSkin™
 3. AlloSkin™ RT
 4. Aongen™ Collagen Matrix
 5. Architec^t® ECM, PX, FX
 6. ArthroFlex™ (Flex Graft)
 7. AxoGuard® Nerve Protector (AxoGen)
 8. Biobrane®/Biobrane-L
 9. Bio-ConneKt® Wound Matrix
 10. CollaCare®
 11. CollaCare® Dental
 12. Collagen Wound Dressing (Oasis Research)
 13. CollaGUARD®
 14. CollaMend™
 15. CollaWound™
 16. Coll-e-derm
 17. Collexa®
 18. Collieva®
 19. Conexa™
 20. Coreleader Colla-Pad
 21. CorMatrix®
 22. Cymetra™ (Micronized AlloDerm)™
 23. Cytal™ (previously MatriStem®)
 24. Dermadapt™ Wound Dressing
 25. Derma-gide
 26. DermaPure™
 27. DermaSpan™
 28. DressSkin
 29. Endoform Dermal Template™
 30. ENDURAGen™
 31. Excellagen®
 32. ExpressGraft™
 33. E-Z Derm™
 34. Flexigraft®
 35. FlowerDerm™
 36. GammaGraft
 37. Geistlich Derma-Gide™
 38. GraftJacket® Xpress, injectable
 39. Helicoll™
 40. hMatrix®
 41. Hyalomatrix®
 42. Hyalomatrix® PA
 43. Integra™ Bilayer Wound Matrix
 44. Integra® Matrix Wound Dressing (previously Avagen)
 45. InteguPly®
 46. Keramatrix®
 47. Keroxx™
 48. Marigen™/Kerecis™ Omega3
 49. MatriDerm®
 50. MatriStem
 51. Matrix HD™
 52. MicroMatrix®

53. Miroderm[®]
54. Mediskin[®]
55. MemoDerm[™]
56. Microderm[®] biologic wound matrix
57. MyOwn skin
58. Oasis[®] Burn Matrix
59. Oasis[®] Ultra
60. Ologen[™] Collagen Matrix
61. Omega3 Wound (originally Merigen wound dressing)
62. Permacol[™]
63. PriMatrix[™]
64. PriMatrix[™] Dermal Repair Scaffold
65. Progenamatrix
66. Puracol[®] and Puracol[®] Plus Collagen Wound Dressings
67. PuraPly[™] Wound Matrix (previously FortaDerm[™])
68. PuraPly[™] AM (Antimicrobial Wound Matrix)
69. Puros[®] Dermis
70. RegenePro[™]
71. Repliform[®]
72. Recell[®]
73. Repriza[™]
74. SkinTE[™]
75. StrataGraft[®]
76. Strattice[™]
77. Suprathel[®]
78. SurgiMend[®]
79. Talymed[®]
80. TenoGlide[™]
81. TenSIX[™] Acellular Dermal Matrix
82. TissueMend
83. TheraForm[™] Standard/Sheet
84. TheraSkin[®]
85. TransCyte[™]
86. TruSkin[™]
87. Veritas[®] Collagen Matrix
88. XCM Biologic[®] Tissue Matrix
89. XenMatrix[™] AB

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Note that amniotic and placental products are reviewed in Blue Shield of California Medical Policy: Amniotic Membrane and Amniotic Fluid.

This policy is not intended for use other than for skin and breast soft tissue products. Products related to neurosurgical/spinal surgery use (i.e., onlay graft products such as DuraGen, or synthetic hydrogel sealant products such as DuraSeal, etc.) are not intended to be applied to this policy.

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

See the Agency for Healthcare Research and Quality Technology Review by Snyder et al (2020) for detailed description of skin substitute products for treatment of chronic wounds.

Coding

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

The following CPT code is a specific add-on for the use of these materials as an implant:

- **15777:** Implantation of biologic implant (e.g., acellular dermal matrix) for soft tissue reinforcement (i.e., breast, trunk) (List separately in addition to code for primary procedure)

The HCPCS codes for these products used in outpatient and office settings are listed in the Coding section of the policy. There are also HCPCS 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

Description

Bioengineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman tissue (xenographic), synthetic materials, or a composite of these materials. Bioengineered skin and soft tissue substitutes are being evaluated for 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.

Note that amniotic and placental products are reviewed in Blue Shield of California Medical Policy: Amniotic Membrane and Amniotic Fluid.

Related Policies

- Amniotic Membrane and Amniotic Fluid
- Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

A large number of artificial skin and soft-tissue products are commercially available or in development. The following section summarizes commercially available skin and soft-tissue substitutes that have substantial relevant evidence on efficacy. Information on additional products is

available in a 2020 Technical Brief on skin substitutes for treating chronic wounds that was commissioned by the Agency for Healthcare Research and Quality.¹

Acellular Dermal Matrix Products

Allograft ADM products derived from donated cadaveric human skin tissue are supplied by tissue banks compliant with standards of the American Association of Tissue Banks and U.S. Food and Drug Administration (FDA) guidelines. The processing removes the cellular components (i.e., epidermis, all viable dermal cells) that can lead to rejection and infection. ADM products from human skin tissue are regarded as minimally processed and not significantly changed in structure from the natural material; FDA classifies ADM products as banked human tissue and, therefore, not requiring FDA approval for homologous use.

In 2017, FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps)²

HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

1. "The HCT/P is minimally manipulated;
 2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
 3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
 4. Either:
 - i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
 - ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and: a) Is for autologous use; b) Is for allogeneic use in a first-degree or second-degree blood relative; or c) Is for reproductive use."
- AlloDerm[®] (LifeCell Corp.) is an ADM (allograft) tissue-replacement product created from native human skin and processed so that the basement membrane and cellular matrix remain intact. Originally, AlloDerm[®] required refrigeration and rehydration before use. It is currently available in a ready-to-use product stored at room temperature. An injectable micronized form of AlloDerm[®] (Cymetra) is available.
 - Cortiva[®] (previously marketed as AlloMax[™] Surgical Graft and before that NeoForm[™]) is an acellular non-crosslinked human dermis allograft.
 - AlloPatch[®] (Musculoskeletal Transplant Foundation) is an acellular human dermis allograft derived from the reticular layer of the dermis and marketed for wound care. This product is also marketed as FlexHD[®] for postmastectomy breast reconstruction.
 - FlexHD[®] and the newer formulation FlexHD[®] Pliable[™] (Musculoskeletal Transplant Foundation) are acellular hydrated reticular dermis allograft derived from donated human skin.
 - DermACELL[™] (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL[®] and PRESERVON[®].
 - DermaMatrix[™] (Synthes) is a freeze-dried ADM derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation.

- DermaPure™ (Tissue Regenix Wound Care) is a single-layer decellularized human dermal allograft for the treatment of acute and chronic wounds.
- GraftJacket® Regenerative Tissue Matrix (also called GraftJacket Skin Substitute; KCI) is an acellular regenerative tissue matrix that has been processed from human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells while preserving dermal structure. GraftJacket Xpress® is an injectable product.

Although frequently used by surgeons for breast reconstruction, FDA does not consider this homologous use and has not cleared or approved any surgical mesh device (synthetic, animal collagen-derived, or human collagen-derived) for use in breast surgery. The indication of surgical mesh for general use in “Plastic and reconstructive surgery” was cleared by the FDA before surgical mesh was described for breast reconstruction in 2005. FDA states that the specific use of surgical mesh in breast procedures represents a new intended use and that a substantial equivalence evaluation via 510(k) review is not appropriate and a pre-market approval evaluation is required.³

In March 2019, the FDA held an Advisory Committee meeting on breast implants, at which time the panel noted that while there is data about ADM for breast reconstruction, the FDA has not yet determined the safety and effectiveness of ADM use for breast reconstruction. The panel recommended that patients are informed and also recommended studies to assess the benefit and risk of ADM use in breast reconstruction.³

In March 2021, FDA issued a Safety Communication to inform patients, caregivers, and health care providers that certain ADM products used in implant-based breast reconstruction may have a higher chance for complications or problems. An FDA analysis of patient-level data from real-world use of ADMs for implant-based breast reconstruction suggested that 2 ADMs—FlexHD and Allomax—may have a higher risk profile than others.⁴

In October 2021, an FDA advisory panel on general and plastic surgery voted against recommending FDA approval of the SurgiMend mesh for the specific indication of breast reconstruction. The advisory panel concluded that the benefits of using the device did not outweigh the risks.⁴ FDA product codes: FTM, OXF.

Xenogeneic Products

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

Helicoll (Encol) is an acellular collagen matrix derived from bovine dermis. In 2004, it was cleared for marketing by the 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 (e.g., abrasions, lacerations, second-degree burns, skin tears), and surgical wounds including donor sites/grafts.

Keramatrix® (Keraplast Research) is an open-cell foam comprised of freeze-dried keratin that is derived from acellular animal protein. In 2009, it was cleared for marketing by the FDA through the 510(k) 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.

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

Permacol™ (Covidien) is xenogeneic and composed of cross-linked porcine dermal collagen. Cross-linking improves tensile strength and long-term durability but decreases pliability.

PriMatrix™ (TEI Biosciences; a subsidiary of Integra Life Sciences) is a xenogeneic ADM processed from fetal bovine dermis. It was cleared for marketing by the 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, a subsidiary of Integra Life Sciences) is a xenogeneic ADM processed from fetal and neonatal bovine dermis.

Strattice™ Reconstructive Tissue Matrix (LifeCell Corp.) is a xenogeneic 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 collagen scaffold (extracellular matrix) derived from porcine small intestinal submucosa. In 2000, it was cleared for marketing by the 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 bilayered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. Apligraf® is supplied as needed, in 1 size, with a shelf-life of 10 days. In 1998, it was approved by the FDA for use in conjunction with compression therapy for the treatment of noninfected, partial- and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower extremity ulcers nonresponsive to standard wound therapy. FDA product code: FTM.

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

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

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

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

Biosynthetic Products

Biobrane®/Biobrane-L (Smith & Nephew) is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially embedded into the film. The fabric creates a complex 3-dimensional structure of trifilament thread, which chemically binds collagen. Blood/sera clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs. FDA product code: FRO.

Integra® Dermal Regeneration Template (also marketed as Omnigraft Dermal Regeneration Matrix; Integra LifeSciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It was approved by the FDA for use in the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable because of the physiologic condition of the patient, and for certain diabetic foot ulcers. Integra® Matrix Wound Dressing and Integra® Meshed Bilayer Wound Matrix are substantially equivalent skin substitutes and were cleared for marketing by the FDA through the 510(k) process for other indications. Integra® Bilayer Matrix Wound Dressing (Integra LifeSciences) is designed to be used in conjunction with negative pressure wound therapy. The meshed bilayer provides a flexible wound covering and allows drainage of wound exudate. FDA product code: MDD.

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

Synthetic Products

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

Rationale

Background

Skin and Soft Tissue Substitutes

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

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

Applications

There are a large number of potential applications for artificial skin and soft tissue products. One large category is nonhealing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, nonhealing lower-extremity wounds represent an ongoing risk for infection,

sepsis, limb amputation, and death. Bioengineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

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

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function^{3/4}including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Breast Reconstruction

Clinical Context and Therapy Purpose

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 purpose of bioengineered soft tissue substitutes in patients who are undergoing breast reconstruction is to provide a treatment option that is an alternative to or an improvement on breast reconstruction without use of a biological or biosynthetic matrix.

The question addressed in this evidence review is: Do bioengineered soft tissue substitutes in patients who are undergoing breast reconstruction improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients who are undergoing breast reconstruction, typically following mastectomy.

Interventions

The therapy being considered is bioengineered soft tissue substitutes as a biological matrix that is used to facilitate one-stage tissue expander reconstruction. As noted in the regulatory status section, the U.S. Food and Drug Administration (FDA) has not cleared or approved any surgical mesh device (synthetic, animal collagen-derived, or human collagen-derived) for use in breast surgery. In October 2021, an FDA advisory panel on general and plastic surgery voted against recommending FDA approval of the SurgiMend mesh for the specific indication of breast reconstruction. The advisory panel concluded that the benefits of using the device did not outweigh the risks.⁴

Comparators

The following therapies are currently being used to make decisions about soft tissue substitutes or biological matrices: 2-stage tissue expander reconstruction without a biological matrix.

Outcomes

The general outcomes of interest are symptoms, morbid events, functional outcomes, QOL, and treatment-related morbidity. Specific outcomes are the time to permanent implant, pain during and after the procedure, and adverse events including seroma, infection, and necrosis rates, rates of capsular contracture, and malposition of implants. Short-term outcomes would be measured within 3 months with longer-term outcomes apparent by 2 years.

Study Selection Criteria

- To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for RCTs*.
- In the absence of such trials, we sought comparative observational studies, with preference for prospective studies.
- To assess longer-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.
- Within each category of study design, we prefer larger sample size studies and longer duration studies.
- We excluded studies with duplicative or overlapping populations.

* Includes various RCT designs such as adaptive trials, pragmatic trials, and cluster trials.

Review of Evidence

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.⁵ Complication rates did not differ significantly between the ADM-assisted (5.5%) and the submuscular tissue expander groups (5.3%; p=.68). Rates of reconstruction-related complications, major complications, and 30-day reoperation did not differ significantly between cohorts.

Systematic Reviews

A meta-analysis by Lee and Mun (2016) included 23 studies (total N=6199 cases) on implant-based breast reconstruction that were published between February 2011 and December 2014.⁶ The analysis included an RCT and 3 prospective comparative cohort studies; the remainder was 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, 79.63; 95% confidence interval [CI], 41.99 to 117.26; $p < .001$) and percentage of intraoperative filling (mean difference, 13.30; 95% CI, 9.95 to 16.65; $p < .001$), and reduced the frequency of injections to complete expansion (mean difference, -1.56; 95% CI, -2.77 to -0.35; $p = .01$).

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

Outcome Measure	Relative Risk	95% Confidence Interval	p
Infection	1.42	1.02 to 1.99	.04
Seroma	1.41	1.12 to 1.78	.004
Mastectomy flap necrosis	1.44	1.11 to 1.87	.006
Unplanned return to the operating room	1.09	0.63 to 1.90	<i>NS</i>
Implant loss	1.00	0.68 to 1.48	<i>NS</i>
Total complications	1.08	0.87 to 1.34	<i>NS</i>
Capsular contracture	0.26	0.15 to 0.47	<.001
Implant malposition	0.21	0.07 to 0.59	.003

Adapted from Lee and Mun (2016).⁶

ADM: acellular dermal matrix; *NS*: not significant.

AlloDerm

Randomized Controlled Trials

McCarthy et al (2012) reported on a multicenter, blinded RCT of AlloDerm in 2-stage expander/implant reconstruction.⁷ Seventy 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 to detect the secondary endpoint 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, although the total number of adverse events was small.

Comparisons Between Products

AlloDerm Versus AlloMax

Hinchcliff et al (2017) conducted an RCT that compared AlloDerm with AlloMax (n=15 each) for implant-based breast reconstruction.⁸ Complications were assessed 7, 14, and 30 days postoperatively and biopsies of the ADMs were taken during implant exchange. Vessel density in the AlloMax biopsies was higher than in the AlloDerm biopsies. Complications were reported in 26.1% of AlloMax cases and 8.0% of AlloDerm cases; these complication rates did not differ statistically with the 30 patients in this trial.

AlloDerm Versus DermaMatrix

Mendenhall et al (2017) conducted an RCT that compared AlloDerm with DermaMatrix in 111 patients (173 breasts).⁹ There were no significant differences in overall rates of complications (AlloDerm, 15.4%; DermaMatrix, 18.3%; $p = .8$) or implant loss (AlloDerm, 2.2%; DermaMatrix, 3.7%; $p = .5$) between the 2 ADMs.

AlloDerm Versus FlexHD

A retrospective review by Liu et al (2014) compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts).¹⁰ 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 the 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.

AlloDerm Versus FlexHD Pliable and DermACELL

Chang and Liu (2017) reported on a prospective comparison of FlexHD Pliable (32 breasts), AlloDerm (22 breasts), and DermACELL (20 breasts) in breast reconstruction.¹¹ The choice of ADM was based on different years when each ADM was available for use at the investigators' institution; patient demographics were comparable between groups. The pieces of ADM used were all the same size (8 × 16 cm) to eliminate an effect of size on outcomes. The time to drain removal was longer with AlloDerm (26 days) than with FlexHD (20 days) or DermACELL (15 days; $p=.001$). Complications were low (4 in the Flex Pliable group, 2 in the AlloDerm group, 1 in the DermACELL group), with no significant differences between groups. At the time of exchange for a permanent implant or free flap reconstruction, all grafts had completely incorporated into the mastectomy skin flaps. No patients developed complications requiring removal of the ADM.

Pittman et al (2017) reported a retrospective pilot study of the use of AlloDerm (50 breasts) and DermACELL (50 breasts).¹² The choice of ADM was based on products available during different years and patient demographics were similar between the 2 groups. Patients in the DermACELL group had a significantly lower incidence of "red breast syndrome" (0% vs. 26%, $p=.001$) and fewer days until drain removal (15.8 days vs. 20.6 days, $p=.017$). There were no significant differences in the rates of other complications.

Strattice

Dikmans et al (2017) reported on early safety outcomes from an open-label multicenter RCT that compared porcine ADM-assisted 1-stage expansion with 2-stage implant-based breast reconstruction (see Table 2).¹³ One-stage breast reconstruction with porcine ADM was associated with a higher risk of surgical complications, reoperation, and with removal of implant, ADM, or both (see Table 3). The trial was stopped early due to safety concerns, but it cannot be determined from this study design whether the increase in complications was due to the use of the xenogeneic ADM or to the comparison between 1-stage and 2-stage reconstruction.

Table 2. Summary of Key RCT Characteristics

Author	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Dikmans et al (2017) ¹³	EU	8	2013-2015	Women intending to undergo skin-sparing mastectomy and immediate IBBR	59 patients (91 breasts) undergoing 1-stage IBBR with ADM	62 women (92 breasts) undergoing 2-stage IBBR

ADM: acellular dermal matrix; IBBR: implant-based breast reconstruction; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Outcomes

Study	Surgical Complications	Severe Adverse Events	Reoperation	Removal of Implant, ADM, or Both
Dikmans et al (2017) ¹³				
1-stage with ADM, n (%)	27 (46)	26 (29)	22 (37)	24 (26)
2-stage with ADM, n (%)	11 (18)	5 (5)	9 (15)	4 (5)
OR (95% CI)	3.81 (2.67 to 5.43)		3.38 (2.10 to 5.45)	8.80 (8.24 to 9.40)
p	<.001		<.001	<.001

ADM: acellular dermal matrix; CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial.

Section Summary: Breast Reconstruction

Results of a systematic review found no difference in overall complication rates between ADM allograft and standard procedures for breast reconstruction. Although reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM, rates of capsular contracture and malposition of implants may be reduced. Thus, in cases where there is limited tissue coverage, the available studies may be considered sufficient to permit informed decision-making about risks and benefits of using allogeneic ADM for breast reconstruction.

Tendon Repair**Clinical Context and Therapy Purpose**

The purpose of bioengineered soft tissue substitutes in patients who are undergoing tendon repair is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Do bio-engineered soft tissue substitutes in patients undergoing tendon repair improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients undergoing tendon repair.

Interventions

The therapy being considered is bioengineered soft-tissue substitutes.

Comparators

The following therapies are currently being used to make decisions about tendon repair: tendon repair without bioengineered soft-tissue substitutes.

Outcomes

The general outcomes of interest are symptoms, morbid events, functional outcomes, QOL, and treatment-related morbidity. Short-term outcomes would be measured within 3 months with longer-term outcomes apparent by 2 years..

Study Selection Criteria

- To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for RCTs*.
- In the absence of such trials, we sought comparative observational studies, with preference for prospective studies.
- To assess longer-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.
- Within each category of study design, prefer larger sample size studies and longer duration studies.
- We excluded studies with duplicative or overlapping populations.

* Includes various RCT designs such as adaptive trials, pragmatic trials, and cluster trials.

Review of Evidence**GraftJacket**

Barber et al (2012) 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.¹⁴ 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=.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 ($p=.008$). 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.

Rashid et al (2020) reported disruption of the native extracellular matrix with either GraftJacket or Permacol (porcine acellular dermis) as a patch overlay for rotator cuff repair in a small controlled study with 13 patients.¹⁵ The disruption was greater in the Permacol group and there was an immune response in 1 of 3 patients following use of the xenograft.

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 promising, additional study with a larger number of patients is needed to corroborate these findings and determine the effects of this technology with greater certainty.

Surgical Repair of Hernias or Parastomal Reinforcement

Clinical Context and Therapy Purpose

The purpose of bioengineered soft tissue substitutes in patients who are undergoing surgical repair of hernias or require parastomal reinforcement is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Do bioengineered soft tissue substitutes in patients undergoing surgical repair of hernias or requiring parastomal reinforcement improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients undergoing surgical repair of hernias or requiring parastomal reinforcement.

Interventions

The therapy being considered is bioengineered matrix support.

Comparators

The following therapies are currently being used for surgical repair of hernias or parastomal reinforcement: synthetic mesh.

Outcomes

The general outcomes of interest are symptoms, morbid events, functional outcomes, QOL, and treatment-related morbidity. Specific outcomes are surgical site occurrence of postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, or mechanical failure. Short-term outcomes would be measured within 3 months with longer-term outcomes apparent by 2 years.

Study Selection Criteria

- To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for RCTs*.
- In the absence of such trials, we sought comparative observational studies, with preference for prospective studies.
- To assess longer-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.

- Within each category of study design, prefer larger sample size studies and longer duration studies.
- We excluded studies with duplicative or overlapping populations.

* Includes various RCT designs such as adaptive trials, pragmatic trials, and cluster trials.

Review of Evidence

Systematic Reviews

A 2013 systematic review evaluated the clinical effectiveness of acellular collagen-based scaffolds for the repair of incisional hernias.¹⁶ 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 were 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 (e.g., postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, mechanical failure) was 82.6% for porcine small intestine mucosa, 50.7% for xenogeneic dermis, 48.3% for human dermis, and 6.3% for xenogeneic pericardium. No comparative data were identified that could establish superiority to permanent synthetic meshes.

AlloDerm as an Overlay

Espinosa-de-los-Monteros et al (2007) retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases.¹⁷ 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 Versus Surgisis Gold

Gupta et al (2006) compared the efficacy and complications associated with use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair.¹⁸ 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 Versus FlexHD

A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery.¹⁹ 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.

FlexHD Versus Strattice

Roth et al (2017) reported on a prospective study assessing clinical and QOL outcomes following complex hernia repair with a human (FlexHD) or porcine (Strattice) ADM.²⁰ The study was funded by the Musculoskeletal Transplant Foundation, which prepares and supplies FlexHD. Patients were enrolled if they had a hernia at least 6 cm in the transverse dimension, active or prior infection of the abdominal wall, and/or enterocutaneous fistula requiring mesh removal. Eighteen (51%) of the 35 patients had undergone a previous hernia repair. After abdominal wall repair with the ADM, 20 (57%) patients had a surgical site occurrence, and nearly one-third had hospital readmission. The type of biologic material did not impact hernia outcomes. There was no comparison with synthetic mesh in this study, limiting interpretation.

Strattice Versus Synthetic Mesh

Bellows et al (2014) reported early results of an industry-sponsored multicenter RCT that compared Strattice (non-cross-linked porcine ADM, n=84) with a standard synthetic mesh (n=88) for the repair of inguinal hernias.²¹ The trial was designed by the surgeons and was patient- and assessor-blinded to reduce risk of bias. Blinding 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, 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 Versus No Reinforcement

Also in 2014, the Parastomal Reinforcement With Strattice (PRISM) Study Group reported a multicenter, double-blinded, randomized trial of Strattice for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies.²² Patients were randomized 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).

Adverse Events

Permacol (porcine acellular dermal matrix) was reported in a case series of 13 patients to result in recurrent intestinal fistulation and intestinal failure when used for abdominal reconstructive surgery.²³

Section Summary: Surgical Repair of Hernias or Parastomal Reinforcement

Current evidence does not support a benefit of ADMs in hernia repair or prevention of parastomal hernia. Additional RCTs are needed to compare biologic mesh with synthetic mesh and to determine if there is a patient population that would benefit from these products.

Diabetic Lower-Extremity Ulcers

Clinical Context and Therapy Purpose

The purpose of bioengineered soft tissue substitutes in patients who have diabetic lower extremity ulcers is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Do bioengineered soft tissue substitutes in patients with diabetic lower extremity ulcers improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with diabetic lower extremity ulcers.

Interventions

The therapy being considered is bioengineered skin substitutes.

Comparators

The following therapies are currently being used: standard wound care which involves regular debridement and moist wound covering.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, and QOL. The primary endpoints of interest for trials of wound closure are as follows, consistent with guidance from the FDA for industry in developing products for treatment of chronic cutaneous ulcer and burn wounds:

- Incidence of complete wound closure.
- Time to complete wound closure (reflecting accelerated wound closure).
- Incidence of complete wound closure following surgical wound closure.
- Pain control.

Time to wound closure can be measured at 6 months with longer-term outcomes apparent by 1 year. More complex wounds may require more than 6 months to heal.

Study Selection Criteria

- To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for RCTs.
- In the absence of such trials, we sought comparative observational studies, with preference for prospective studies.
- To assess longer-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.
- Within each category of study design, prefer larger sample size studies and longer duration studies.
- We excluded studies with duplicative or overlapping populations.

* Includes various RCT designs such as adaptive trials, pragmatic trials, and cluster trials.

Review of Evidence

Systematic Reviews

A 2016 Cochrane review evaluated skin substitutes for the treatment of diabetic foot ulcers.²⁴ Seventeen trials (N=1655) 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 (relative risk, 1.55; 95% CI, 1.30 to 1.85). Use of skin substitutes also led to a statistically significant reduction in amputations (relative risk, 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.

Martinson and Martinson (2016) conducted an industry-sponsored analysis of Medicare claims data (13193 treatment episodes) to compare efficacy and cost of skin substitutes for the management of diabetic foot ulcers.²⁵ 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.

Guo et al (2017) reported a systematic review of ADM for the treatment of diabetic foot ulcers.²⁶ Most data were from an RCT of Integra Dermal Regeneration Template, which is a bilayer product with the outer layer composed of a thin silicone film and not a pure ADM.

Apligraf, Dermagraft, AlloPatch, Integra Dermal Regeneration Template, or Integra Flowable Wound Matrix

Apligraf

Veves et al (2001) reported on a randomized prospective trial on the effectiveness of Apligraf (previously called Graftskin), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers.²⁷ The trial involved 24 centers in the United States; 208 patients were randomized 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 ($p=.004$). The Kaplan-Meier method median time to complete closure was 65 days for Apligraf, which was significantly lower than the 90 days observed in the control group ($p=.003$). The rates of adverse reactions were similar between groups, except osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf group. Trialists concluded that application of Apligraf for a maximum of 4 weeks resulted in higher healing rates than state-of-the-art treatment and was not associated with any significant adverse events. This trial 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.²⁸

Steinberg et al (2010) 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.²⁹ The study design and patient population were similar to the 208-subject U.S. study (previously described), which led to 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 plus standard therapy (sharp debridement, standard wound care, off-loading) with 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 adverse events by 12 weeks were comparable across treatment groups in the 2 studies. Efficacy measures demonstrated superiority of Apligraf treatment over control-treated groups in both studies. Combining the data from both studies, 55.2% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared with 34.3% (46/134) of control subjects ($p<.001$), and Apligraf subjects had a significantly shorter time to complete wound closure ($p<.001$). 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 ulcers.

Kirsner et al (2010) analyzed 2517 patients with diabetic neuropathic foot ulcers treated between 2001 and 2004.³⁰ This retrospective analysis used a wound care database; the patients received advanced biologic therapy, specifically, Apligraf (446 patients), Regranex, or Procuren. The analysis found that advanced biologic 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 biologic therapy were 31% more likely to heal than wounds first treated with topical recombinant growth factor ($p<.001$) and 40% more likely to heal than those first treated with platelet releasate ($p=.01$). Wound size, wound grade, duration of wound, and time to initiation of advanced biologic 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.³¹ 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 adverse events 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%). A 2015 retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft (5.5% vs. 12.6%, $p=.031$).³² Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

AlloPatch

AlloPatch Pliable human reticular acellular dermis was compared with SOC in an industry-sponsored multicenter trial by Zelen et al (2017, 2018).^{33,34} The initial trial with 20 patients per group was extended to determine the percent healing at 6 weeks with 40 patients per group. Healing was evaluated by the site investigator and confirmed by an independent panel. At 6 weeks, 68% (27/40) of wounds treated using AlloPatch had healed compared with 15% (6/40) in the SOC-alone group ($p<.001$). At 12 weeks, 80% (32/40) of patients in the AlloPatch group had healed compared to 30% (12/40) in the control group. Mean time to heal within 12 weeks was 38 days (95% CI: 29-47 days) for the HR-ADM group and 72 days (95% CI: 66-78 days) for the SOC group ($p<.001$).

Integra Omnigraft Dermal Regeneration Template or Integra Flowable Wound Matrix

Integra Dermal Regeneration Template is a biosynthetic skin substitute that is FDA approved for life-threatening thermal injury. The FOUNDER (Foot Ulcer New Dermal Replacement) multicenter study (32 sites) assessed Integra Dermal Regeneration Template (marketed as Omnigraft) for chronic nonhealing diabetic foot ulcers under an FDA regulated investigational device exemption.³⁵ 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 (sodium chloride gel 0.9%). 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%, $p=.001$) and a shorter median time to closure (43 days vs. 78 days, $p=.001$). 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. Trial strengths 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 intention-to-treat (ITT) analysis.

Integra Flowable Wound Matrix is composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. It is supplied as a granular product that is mixed with saline. Campitiello et al (2017) published an RCT that compared the flowable matrix with wet dressing in 46 patients who had Wagner grade 3 diabetic foot ulcers.³⁶ The ulcers had developed over 39 weeks. Complete healing at 6 weeks was achieved in significantly more patients in the Integra Flowable Wound Matrix group than in the control group, while the risk of rehospitalization and major amputation was reduced with Integra Flowable Wound Matrix (see Table 4).

Table 4. Probability of Wound Healing With IFWM Versus SOC

Study	Complete Wound Healing	Rehospitalization	Major Amputation
Campitiello et al (2017) ³⁶			
IFWM, n (%)	20 (86.95)	2 (6.69)	1 (4.34)
SOC, n (%)	12 (52.17)	10 (43.47)	7 (30.43)
RR (95% CI)	1.67 (1.09 to 2.54)	0.10 (0.01 to 0.72)	0.16 (0.02 to 1.17)

Study	Complete Wound Healing	Rehospitalization	Major Amputation
p	.010	.001	.028

CI: confidence interval; IFWM: Integra Flowable Wound Matrix; RR: relative risk; SOC: standard of care.

Section Summary: Apligraf, Dermagraft, AlloPatch, or Integra for Diabetic Lower-Extremity Ulcers

RCTs have demonstrated the efficacy of Apligraf, Dermagraft, AlloPatch, Integra Dermal Regeneration Template, and Integra Flowable Wound Matrix over SOC for the treatment of diabetic lower-extremity ulcers.

Bioengineered Skin Substitutes Other Than Apligraf, Dermagraft, AlloPatch, or Integra GraftJacket Regenerative Tissue Matrix

Brigido et al (2004) reported a small (N=40) randomized pilot study comparing GraftJacket with conventional treatment for chronic nonhealing diabetic foot ulcers.³⁷ Control patients received conventional therapy with debridement, 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%), respectively. 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.

Reyzelman et al (2009) reported an industry-sponsored multicenter randomized study that compared a single application of GraftJacket with SOC in 86 patients with diabetic foot ulcers.³⁸ 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%) than for 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 about whether the difference in mean time to healing is statistically or clinically significant.

Reyzelman and Bazarov (2015)³⁹ 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)⁴⁰ with 28 patients (N=154). The time to heal was estimated for the Brigido (2004) study, 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 et al (2009). The odds ratio in the smaller study by Brigido (2006) was considerably larger, with a lack of precision in the estimate (odds ratio, 15.0; 95% CI, 2.26 to 99.64), and the combined odds (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 (2015), 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.

DermACELL Versus GraftJacket Regenerative Tissue Matrix or Standard of Care

DermACELL and GraftJacket are both composed of human ADM. Walters et al (2016) reported on a multicenter randomized comparison of DermACELL, GraftJacket, or SOC (2:1:2 ratio) in 168 patients with diabetic foot ulcers.⁴¹ 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 ($p=.039$). 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).

A second report from this study was published in 2017.⁴² This analysis compared DermACELL with SOC and did not include the GraftJacket arm. The authors reported that either 1 or 2 applications of DermACELL led to a greater proportion of wounds healed compared with SOC in per-protocol analysis (see Table 5), but there was no significant difference between DermACELL (1 or 2 applications) and SOC when analyzed by ITT. For the group of patients who received only a single application, the percentage of patients who achieved complete wound healing was significantly higher than SOC at 16 and 24 weeks, but not at 12 weeks. Although reported as an ITT analysis, results were analyzed only for the group who received a single application of DermACELL. This would not typically be considered ITT unless the number of DermACELL applications was prespecified.

Table 5. Probability of Wound Healing in Per Protocol Analysis of DermACELL Versus SOC

	% With Wound Healing at 12 Wk	% With Wound Healing at 16 Wk	% With Wound Healing at 24 Wk	% With Wound Healing at 12 Wk	% With Wound Healing at 16 Wk	% With Wound Healing at 24 Wk
Cazzell et al (2017)⁴²						
DermACELL, %	65.0%	82.5%	89.7%	NR	67.9%	83.7%
SOC, %	41.1%	48.1%	67.3%	NR	48.1%	67.3%
HR (95% CI)	1.97 (1.1 to 3.5)	2.40 (1.4 to 4.1)	2.11 (1.3 to 3.5)		1.72 (1.04 to 2.83)	1.55 (0.98 to 2.44)
p	.012	<.001	<.001	<i>NS</i>	.028	.049

CI: confidence interval; HR: hazard ratio; NR; not reported; *NS*: not significant; SOC: standard of care.

TheraSkin Versus Standard of Care

An industry-funded retrospective study by Gurtner et al (2020) was a matched comparison of TheraSkin to standard of care alone in 3994 lower extremity wounds of multiple etiologies.⁴³ Data were collected from electronic medical records from 644 wound care centers that were managed by a single large wound management company. Patients were matched for 8 characteristics including wound size, severity, duration, comorbidities and body mass index. Diabetic wounds comprised 42% of the total cases and venous ulcers 29%. The next most frequent etiologies were pressure ulcers (~8%), surgical wounds (~9%), and trauma (~8%). Patients were excluded from analysis if they had greater than 50% wound closure during a 4 week run-in period. The overall healing rate was 68.3% in the allograft group and 60.3% for standard of care ($p<.001$). Diabetic wounds were treated with an average of 2.8 allografts prior to closure with a difference in closure rates of approximately 12% (67.5% vs 55.1%). A limitation of this retrospective analysis is that although the groups were well-matched on a number of variables, the application of the TheraSkin allograft was at the investigators' discretion and not standardized.

TheraSkin Versus Dermagraft

Sanders et al (2014) reported on 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.⁴⁴ 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 ($p=.51$). 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 ($p < .049$). At 20 weeks, complete wound healing was observed in 90.9% of the TheraSkin-treated ulcers compared with 66.7% of the Dermagraft group ($p = .428$).

TheraSkin Versus Apligraf

DiDomenico et al (2011) compared TheraSkin with Apligraf for the treatment of diabetic foot ulcers in a small ($N = 29$) RCT.⁴⁵ 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 (1.53 for Apligraf, 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.

Cyral (MatriStem) Versus Dermagraft

Frykberg et al (2017) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cyral (a porcine urinary bladder-derived extracellular matrix) versus Dermagraft in 56 patients with diabetic foot ulcers.⁴⁶ 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. ITT analysis found complete wound closure in 5 (18.5%) wounds treated with Cyral compared with 2 (6.9%) wounds treated with Dermagraft ($p = \text{not significant [NS]}$). QOL, measured by the Diabetic Foot Ulcer Scale, improved from 181.56 to 151.11 in the Cyral group and from 184.46 to 195.73 in the Dermagraft group ($p = .074$). 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.

PriMatrix

Randomized Controlled Trial

Lantis et al (2021) reported on a multicenter RCT comparing PriMatrix plus standard of care to PriMatrix alone in 226 patients with diabetic foot ulcers (Tables 6 and 7).⁴⁷

Study subjects underwent a 2-week run-in period of SOC treatment and were excluded if they had a wound reduction of 30% or more. Patients randomized to the SOC group received weekly treatment at the study site identical to the SOC treatment applied during the screening period. In addition, control group patients performed daily dressing changes, which consisted of wound cleaning, application of saline gel and secondary dressings. The primary endpoint was the percentage of subjects with complete wound closure, defined as 100% re-epithelialization without drainage during the 12-week treatment phase.

Significantly more patients in the PriMatrix group experienced complete wound closure at 12 weeks (45.6% vs 27.9%; $p = .008$). It is unclear if this difference (17.7%) is clinically significant; the study was powered to detect a 20% difference between groups. The time to complete healing did not differ between groups for the wounds that healed. Major study limitations include lack of blinding, limited generalizability, and insufficient duration of follow-up to assess wound recurrence (Tables 8 and 9).

Table 6. Randomized Controlled Trial of PriMatrix for Diabetic Food Ulcers- Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Lantis et al (2021) ⁴⁷ , NCT03010319	US	21	2019-2020	Diabetic foot ulcer for a minimum of 2 weeks, adequate vascular perfusion to the affected extremity	PriMatrix plus standard of care n = 103	Standard of care n = 104

Table 7. Randomized Controlled Trial of PriMatrix for Diabetic Food Ulcers- Results

Study	Wound Healed at 12 weeks	Median Time to Heal, days (range)	AEs
Lantis et al (2021) ⁴⁷ , NCT03010319			
Number analyzed	207	76	226
Primatrix	47/103 (45.6%)	43 (22 to 93)	Any AE: 44.8%
Standard Care	29/104 (27.9%)	57 (16 to 88)	Any AE: 46.4%
Treatment Effect	HR 2.02 (95% CI 1.3 to 3.2)		
p	.008	.362	

AE: adverse events; CI: confidence interval; HR: hazard ratio

Table 8. Randomized Controlled Trial of PriMatrix for Diabetic Food Ulcers- Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Lantis et al (2021) ⁴⁷ , NCT03010319	4. Race and ethnicity of the study population was not reported and is not included in the demographics table.		3. Standard of care patients received additional dressing changes at home, which could have potentially exposed the wound to unknown factors.		4-week follow-up not sufficient to determine ulcer recurrence.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 9. Randomized Controlled Trial of PriMatrix for Diabetic Foot Ulcers- Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e Statistical ^f
Lantis et al (2021)⁴⁷ NCT03010319	3. Allocation concealment not described.	1. Patients and investigator not blinded		1. 24 subjects from the treatment group and 22 from the control group discontinued from each arm prior to meeting the protocol-defined primary endpoint and were counted as treatment failures. 207 of 226 randomized were included in primary analysis (91.6%)	3. Confidence intervals not reported

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other

Nonrandomized Studies

Kavros et al (2014) 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.⁴⁸ The average duration of ulcers before treatment was 286 days, and the 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.

Karr (2011) published a retrospective comparison of PriMatrix and Apligraf in 40 diabetic foot ulcers.⁴⁹ 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 of 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 with current SOC or advanced wound therapies.

Oasis Wound Matrix Versus Regranex Gel

Niezgoda et al (2005) compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix (a porcine acellular wound care product) to Regranex Gel.⁵⁰ 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 secondary dressing. Wounds were cleaned and debrided, 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=.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 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.

Autologous Grafting on HYAFF Scaffolds

Uccioli et al (2011) reported a multicenter RCT of cultured expanded fibroblasts and keratinocytes grown on an HYAFF scaffold (benzyl ester of hyaluronic acid) compared with paraffin gauze for difficult diabetic foot ulcers.⁵¹ A total of 180 patients were randomized. At 12 weeks, complete ulcer healing was similar for the 2 groups (24% treated vs. 21% controls). At 20 weeks, complete ulcer healing was achieved in a similar proportion of the treatment group (50%) and the control group (43%, log-rank test = 0.344). Subgroup analysis, adjusted for baseline factors and possibly post-hoc, found a statistically significant benefit of treatment on dorsal ulcers but not plantar ulcers.

Omega3 Wound

Lullove et al (2021, 2022)^{52,53} reported interim results of a RCT of Omega3 Wound plus standard wound care compared to standard care alone in individuals with diabetic lower extremity skin ulcers (Table 10). The 2021 publication⁵² was an initial report of 49 patients and the 2022 publication⁵³ was an unscheduled interim analysis of these same 49 participants plus an additional 45 participants. One-year follow-up is planned but results have not yet been published.⁵² The primary outcome of the trial was healing at 12 weeks. Complete ulcer healing was based on the site investigator's assessment, as evidenced by complete (100%) re-epithelialization without drainage and need of dressing. An independent panel of wound care experts who were blinded to the patient allocation process and the principal investigator's assessment reviewed all study-related decisions made by the site investigators and confirmed healing status. Secondary outcomes were time to heal and wound area reduction by percentage at 12 weeks. Patients underwent a 2-week run-in period prior to randomization. If the ulcer reduced in area by 20% or more after 14 days of standard care, the patient was excluded as a screening failure. If the wound area was reduced by less than 20%, the patient was randomized and enrolled in the study.

Study results are summarized in Table 11. At 12 weeks, the complete healing rate was significantly higher in the intervention arm (63.0% vs 31.3%), but time to healing did not differ between groups for wounds that healed completely. Among the subset of wounds that did not heal completely by 12 weeks (n = 40), there was a larger percent wound reduction in the intervention group (69.3% vs 44.2%; p = .015). Adverse events were not reported in either publication.

Study limitations are detailed in Tables 12 and 13. It will not be possible to adequately assess this trial until the final results are published, as key details (e.g., exclusions from analyses, precision estimates) are lacking in the interim analyses published to date.

Table 10. Randomized Controlled Trial of Omega3 Wound for Diabetic Food Ulcers- Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Lullove et al (2021) ^{52,53} , NCT04133493	US	5	2019-2020	Diabetic foot ulcer for a minimum of 4 weeks, adequate renal function and perfusion to the affected extremity	Omega3 Wound plus standard of care	Standard of care

Table 11. Randomized Controlled Trial of Omega3 Wound for Diabetic Food Ulcers- Results

Study	Wound Healed at 12 weeks	Time to Heal	Percent Wound Reduction at 12 Weeks for Wounds that did not heal)	Adverse events
Lullove et al (2021) ^{52,53} , NCT04133493				
N analyzed	94		40	
Omega3 Wound	63.0% (29/46)	Mean 7 weeks in both groups	69.3% (SD not reported)	Not reported
Standard Care	31.3% (15/48)		44.2% (SD not reported)	
p	.0036		.015	

SD: standard deviation

Table 12. Randomized Controlled Trial of Omega3 Wound for Diabetic Food Ulcers- Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Lullove et al (2021) ^{52,53} , NCT04133493	4. Race and ethnicity of the study population was not reported and is not included in the demographics table.		3. Standard of care patients received additional dressing changes at home, which could have potentially exposed the wound to unknown factors.	3. No data on adverse events reported	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 13. Randomized Controlled Trial of Omega3 Wound for Diabetic Food Ulcers- Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e	3. Confidence intervals not reported

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Lullove et al (2021) ^{52,53} NCT04133493						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other

Section Summary: Bioengineered Skin Substitutes Other Than Apligraf, Dermagraft, AlloPatch, or Integra for Diabetic Lower-Extremity Ulcers

Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients who only required a single application of the ADM. Studies are needed to further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of GraftJacket, TheraSkin, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies.

Lower-Extremity Ulcers due to Venous Insufficiency Clinical Context and Therapy Purpose

The purpose of bio-engineered soft tissue substitutes in patients who have lower extremity ulcers due to venous insufficiency is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Do bio-engineered soft tissue substitutes in patients with venous ulcers improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients who have lower extremity ulcers due to venous insufficiency.

Interventions

The therapy being considered is bioengineered skin substitutes.

Comparators

The following therapies are currently being used: SOC which includes debridement of necrotic tissue and compression.

A Cochrane review by O' Meara et al (2012) that evaluated compression for venous leg ulcers included 48 RCTs with 59 different comparisons.⁵⁴ Most RCTs were small. Measures of healing were the time to complete healing, the proportion of ulcers healed within the trial period (typically 12 weeks), the change in ulcer size, and the rate of change in ulcer size. Evidence from 8 trials indicated that venous ulcers healed more rapidly with compression than without. Findings suggested that multicomponent

systems (bandages or stockings) were more effective than single-component compression. Also, multicomponent systems containing an elastic bandage appeared more effective than those composed mainly of inelastic constituents. Although these meta-analyses did not include time to healing, studies included in the review reported the mean time to ulcer healing was approximately 2 months, while the median time to healing in other reports was 3 to 5 months.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, and QOL. The primary endpoints of interest for trials of wound closure are as follows, consistent with guidance from the FDA for industry in developing products for treatment of chronic cutaneous ulcer and burn wounds:

- Incidence of complete wound closure.
- Time to complete wound closure (reflecting accelerated wound closure).
- Incidence of complete wound closure following surgical wound closure.
- Pain control.

Time to wound closure can be measured at 6 months with longer-term outcomes apparent by 1 year. Complex wounds may require more than 6 months to heal.

Study Selection Criteria

- To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for RCTs*.
- In the absence of such trials, we sought comparative observational studies, with preference for prospective studies.
- To assess longer-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.
- Within each category of study design, we prefer larger sample size studies and longer duration studies.
- We excluded studies with duplicative or overlapping populations.

* Includes various RCT designs such as adaptive trials, pragmatic trials, and cluster trials.

Review of Evidence

Apligraf

Falanga et al (1998) reported on a multicenter randomized trial of Apligraf living cell therapy.⁵⁵ 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 endpoints 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 adverse events 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.²⁸

Oasis Wound Matrix

Mostow et al (2005) reported on an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment using Oasis Wound Matrix (xenogeneic collagen scaffold from porcine small intestinal mucosa) with SOC in 120 patients who had chronic ulcers due to venous insufficiency that had not adequately responded to conventional therapy.⁵⁶ 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 quasi-randomized study, Romanelli et al(2007) compared the efficacy of 2 extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid).⁵⁷ 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).

Romanelli et al(2010) compared Oasis with a moist wound dressing (SOC) in 23 patients with mixed arteriovenous ulcers and 27 patients with venous ulcers.⁵⁸ 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%).

Subsection Summary: Apligraf or Oasis Wound Matrix for Lower-Extremity Ulcers due to Venous Insufficiency

RCTs have demonstrated the efficacy of Apligraf or Oasis Wound Matrix over SOC for lower-extremity ulcers due to venous insufficiency.

Bioengineered Skin Substitutes Other Than Apligraf or Oasis Wound Matrix for Lower-Extremity Ulcers due to Venous Insufficiency

Dermagraft

Dermagraft living cell therapy has been approved by the FDA for repair of diabetic foot ulcers. Use of Dermagraft for venous ulcers is an off-label indication. Harding et al (2013) reported an open-label multicenter RCT that compared Dermagraft plus compression therapy (n=186) with compression therapy alone (n=180).⁵⁹ The trial had numerous inclusion and exclusion criteria that restricted the population to patients who had nonhealing ulcers with compression therapy but had the 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.

PriMatrix

Karr (2011) published a retrospective comparison of PriMatrix (xenogeneic ADM) and Apligraf in 28 venous stasis ulcers.⁴⁹ 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.

DermACELL

Cazzell (2019) published an RCT on DermACELL ADM for venous leg ulcers in 18 patients (see Table 14).⁶⁰ This was part of a larger study of the acellular dermal matrix for chronic wounds of the lower extremity in 202 patients; the component on diabetic lower extremity ulcers was previously reported by Cazzell et al (2017) and is described above.⁴² When including patients who required more than 1 application of the ADM, the percent of wounds closed at 24 weeks was 29.4% with DermACELL and 33.3% with SOC, suggesting no benefit DermACELL for the treatment of venous ulcers in this small substudy.

Table 14. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Cazzell (2019) NCT01970163	US	7	2013- 2016	Venous leg ulcer present for at least 60 days (n=18)	1 or 2 applications of DermACELL plus SOC (n=18)	SOC (debridement and compression, n=10)

RCT: randomized controlled trial; SOC: standard of care

TheraSkin Versus Standard of Care

In the propensity matched study by Gurtner et al (2020) described above, Theraskin did not improve the healing rate of venous ulcers (66.1%) compared to SOC (70.1%).⁴³

Section Summary: Bioengineered Skin Substitutes Other Than Apligraf or Oasis Wound Matrix 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 endpoints 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. An initial study with 18 patients found that and DermACELL (ADM) was not more effective than SOC. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment compared with current SOC.

Deep Dermal Burns

Clinical Context and Therapy Purpose

The purpose of bio-engineered soft tissue substitutes in patients who have deep dermal burns is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Do bio-engineered soft tissue substitutes in patients with deep dermal burns improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with deep dermal burns.

Interventions

The therapy being considered is bioengineered skin substitutes.

Comparators

The following therapies are currently being used: standard therapy for burns.

Outcomes

The general outcomes of interest are disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related morbidity.

The primary endpoints of interest for trials of wound closure are as follows, consistent with guidance from the FDA for industry in developing products for treatment of chronic cutaneous ulcer and burn wounds:

- Incidence of complete wound closure.
- Time to complete wound closure (reflecting accelerated wound closure).
- Incidence of complete wound closure following surgical wound closure.
- Pain control.

Time to wound closure can be measured at 6 months with longer-term outcomes apparent by 1 year.

Study Selection Criteria

- To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for RCTs*.
- In the absence of such trials, we sought comparative observational studies, with preference for prospective studies.
- To assess longer-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.
- Within each category of study design, we prefer larger sample size studies and longer duration studies.
- We excluded studies with duplicative or overlapping populations.

* Includes various RCT designs such as adaptive trials, pragmatic trials, and cluster trials.

Review of Evidence

Epicel

One case series from 2000 has described the treatment of 30 severely burned patients with Epicel.⁶¹ The cultured epithelial autografts were applied to a mean of 37% of total body surface area (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 with split-thickness skin graft and with viscose cellulose sponge (Cellonex), using 3, 10¹5 cm test sites on each of 10 burn patients.⁶² 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.

Branski et al (2007) reported on 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).⁶³ 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.

Heimbach et al (2003) reported on 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.⁶⁴ 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%. Hicks et al (2019) conducted a systematic review of Integra dermal regeneration template for the treatment of acute full thickness burns and burn reconstruction.⁶⁵ A total of 72 studies with 1084 patients (4 RCTs, 4 comparative studies, 5 cohort studies, 2 case control studies, 24 case series, and 33 case reports) were included in the review. The majority of patients (74%) were treated with Integra for acute burns, and the remainder (26%) for burn reconstruction. The take of the skin substitute was 86% (range 0–100%) for acute burn injuries and 95% (range 0–100%) for reconstruction. The take of the split-thickness skin graft over the template was 90% for acute burn injuries and 93% for reconstruction. There was high variability in reporting of outcomes, but studies generally supported satisfactory cosmetic results in patients who have insufficient autograft and improvement in range of motion in patients who were treated with Integra for burn reconstruction. There was an overall complication rate of 13%; primarily due to infection, graft loss, hematoma formation, and contracture.

An infection rate of 18% was noted in a systematic review of complication rates in 10 studies that used Integra dermal regeneration template for burns.⁶⁶

Omega3 Wound

Luze et al (2022) conducted a systematic review of the use of acellular fish skin grafts in burn wound management.⁶⁷ The reviewers identified 5 studies of Omega3 Wound but no RCTs. The identified studies were preclinical (animal), case series, retrospective observational, and 1 small (N = 21) cohort study. The review authors concluded that while the approach is promising, large-cohort studies are needed.

ReCell Autologous Cell Harvesting Device

Two RCTs have evaluated Recell for deep dermal burns (Table 15).^{68,69} In both studies, 2 similar areas with a burn injury in the same individual were randomized to the control or treatment intervention (i.e., all participants received both treatments). The studies differed in their populations, interventions, and outcome measures. In the earlier study, participants all had deep partial thickness burns, while in the 2019 study the population included individuals with mixed-depth, full thickness burns. Holmes 2018 was a head-to-head comparison of ReCell alone versus skin grafting alone, and Holmes et al (2019) compared ReCell in combination with skin grafting. In the earlier study, the primary effectiveness endpoints were the incidence of wound closure at 4 weeks and the incidence of complete donor site healing at 1 week. In the 2019 trial, the co-primary effectiveness endpoints were non-inferiority of the incidence of RECELL-treated site closure by week 8 when compared to the control, and the superiority of the 37% relative reduction in donor skin for the ReCell treatment when compared with the control.

Study results are detailed in Table 16 and limitations in Tables 17 and 18. Although the ReCell device was comparable to standard care on outcomes such as complete wound closure; confidence in the strength of the overall body of evidence is limited by individual study limitations and heterogeneity of populations, interventions, and outcome measures across studies. Additional RCT evidence in the intended use population is needed.

Table 15. Randomized Controlled Trials of ReCell for Thermal Burns- Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
Holmes et al (2018) ⁶⁹ , NCT01138917	US	9	2010-2015	Individuals ages 18 to 65 years, with acute, deep partial-thickness thermal burns from 1% to 20% TBSA that required autografting for definitive closure.	Active ReCell device N = 101	Comparator Meshed STSG Treatment N = 101
Holmes et al (2019) ⁶⁸ , NCT02380612	US	6	2015-2017	Individuals ages 5 years or older, with acute thermal burn involving 5% to 50% of TBSA that underwent autografting for definitive closure	ReCell device treatment applied over STSG N = 30	Meshed STSG Treatment Alone N = 30

STSG:: Split-thickness skin grafts; TBSA: total body surface area.

Table 16. Randomized Controlled Trials of ReCell for Thermal Burns- Results

Study	Wound Closure (95% re-epithelialization) at 4 weeks	Wound Closure (95% re-epithelialization) at 8 weeks	Complete donor site healing at 1 week (100% re-epithelialization)	Relative Reduction in Donor Skin	Pain (VAS)	Participant Satisfaction and Scar Assessment	Adverse Events (Incidence)
Holmes et al (2018)⁶⁹, NCT01138917							
ReCell	81/83 (97.6%)		21.8%		NSD at 16 weeks (data in figure)	NSD in subject satisfaction with appearance or in scarring at 16, 24, and 52 weeks (data in figures)	Treatment site: 35.6% Donor site: 4.0%
STSG	83/83 (100%)		10.0%				Treatment site: 21.8% Donor site: 6.9%
Between-group difference	-2.4% (95% CI: -8.4% to 2.3%)		p = .04				Treatment site: p = .0013 Donor site: 6.9% p = .25
Holmes et al (2019)⁶⁸, NCT02380612							
ReCell plus STSG	50%	24/26 (92%)		368 (SD 150) cm ²	NSD between groups in treatment area	NSD in subject satisfaction with appearance or in scar assessment at any time point	NSD between groups in pre-specified safety events 17 individuals (57%) experienced AEs at control and ReCell sites; 27% had mild AEs, 37% moderate
STSG alone	48%	22/26 (85%)		264 (SD 119) cm ²	32%; p <.001		
Between-group difference		-7.7% Upper limit of the 97.5% CI 6.4% (i.e. within the pre-defined non-inferiority margin (10%))					

Study	Wound Closure (95% re-epithelialization) at 4 weeks	Wound Closure (95% re-epithelialization) at 8 weeks	Complete donor site healing at 1 week (100% re-epithelialization)	Relative Reduction in Donor Skin	Pain (VAS)	Participant Satisfaction and Scar Assessment	Adverse Events (Incidence)
							AEs. 1 death, attributed to underlying condition

AE: adverse events; CI: confidence interval; ND: no significant difference.

Table 17. Randomized Controlled Trials of ReCell for Thermal Burns- Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Duration of Follow-up ^e
Holmes et al (2018) ⁶⁹ , NCT01138917					
Holmes et al (2019) ⁶⁸ , NCT02380612	2. Participants had mixed depth full-thickness burns			5. Unclear if 32% reduction in donor site skin is clinically meaningful	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 18. Randomized Controlled Trials of ReCell for Thermal Burns- Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Data Completeness ^d	Power ^e	Statistical ^f
Holmes et al (2018) ⁶⁹ , NCT01138917				83/101 participants evaluated in modified per protocol analysis	noninferiority margin based on 90 subjects	
Holmes et al (2019) ⁶⁸ , NCT02380612				26/30 participants evaluated in per protocol analysis		3. confidence intervals not reported

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

^b Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Deep Dermal Burns

Epicel is FDA-approved under a humanitarian device exemption (HDE) for the treatment of deep dermal or full-thickness burns comprising a TBSA of 30% or more, with patient survival of 90%.

Integra Dermal Regeneration Template has been compared with autograft in a within-subject study and with autograft-allograft in a small RCT with 10 patients per group. Outcomes are at least as good as with autograft or allograft, with a reduction in scarring and without risks associated with cadaver skin. This product has also been studied in a large series with over 222 burn patients, showing a take rate of 76% and with a take rate of epidermal autograft placed over Integra of 87.7%.

The ReCell device has been evaluated in 2 RCTs. One RCT evaluated ReCell as an adjunct to meshed autologous skin grafting and the other compared ReCell head-to-head with skin grafting. Although the ReCell device was comparable to standard care on outcomes such as complete wound closure, confidence in the strength of the overall body of evidence is limited by individual study limitations and heterogeneity of populations, interventions, and outcome measures across studies. Additional RCT evidence in the intended use population is needed.

Other Indications

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. HDE status has been withdrawn for Dermagraft for this indication.

Fivenson et al (2003) reported the off-label use of Apligraf in 5 patients with recessive dystrophic epidermolysis bullosa who underwent syndactyly release.⁷⁰

Section Summary: Dystrophic Epidermolysis Bullosa

Dystrophic epidermolysis bullosa is a rare disorder. Because this is a rare disorder, it is unlikely that RCTs will be conducted to evaluate whether OrCel improves health outcomes for this condition. Therefore, the HDE for OrCel is considered sufficient.

Punch Biopsy Wounds

Baldursson et al (2015) reported a double-blinded RCT with 81 patients (162 punch biopsy wounds) that compared Kerecis Omega3 Wound (derived from fish skin) with Oasis SIS ECM (porcine small intestinal submucosa extracellular matrix).⁷¹ The primary outcome (the percentage of wounds healed at 28 days) was similar for the fish skin ADM (95%) and the porcine SIS ECM (96.3%). The rate of healing was faster with Kerecis Omega3 ($p=.041$). At 21 days, 72.5% of the fish skin ADM group had healed compared with 56% of the porcine SIS ECM group. Interpretation of this study is limited because it did not include an accepted control condition for this indication.

Split-Thickness Donor Sites

There is limited evidence to support the efficacy of OrCel compared with SOC for the treatment of split-thickness donor sites in burn patients. Still et al (2003) examined the safety and efficacy of bilayered OrCel to facilitate wound closure of split-thickness donor sites in 82 severely burned patients.⁷² Each patient had 2 designated donor sites that were randomized to 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.

Pressure Ulcers

Brown-Etris et al (2019) reported an RCT of 130 patients with stage 3 or stage 4 pressure ulcers who were treated with Oasis Wound Matrix (extracellular collagen matrix derived from porcine small intestinal submucosa) plus SOC or SOC alone.⁷³ At 12 weeks, the proportion of wounds healed in the collagen matrix group was 40% compared to 29% in the SOC group. This was not statistically significant ($p=.111$). There was a statistical difference in the proportion of patients who achieved 90% wound healing (55% vs. 38% $p=.037$), but complete wound healing is the preferred and most reliable measure. It is possible that longer follow-up may have identified a significant improvement in the percent of wounds healed. The study did include 6-month follow-up, but there was high loss to follow-up and an insufficient number of patients at this time point for statistical comparison. In the propensity matched study by Gurtner et al (2020) described above, Theraskin improved the healing rate of pressure ulcers by 20% (66.7% vs 46.8%).⁴³

Miscellaneous

In addition to indications previously reviewed, off-label uses of bioengineered skin substitutes have included inflammatory ulcers (eg, pyoderma gangrenosum, vasculitis), scleroderma digital ulcers, postkeloid removal wounds, genetic conditions, and variety of other conditions.⁷⁴ Products that have been FDA-approved or -cleared for one indication (e.g., lower-extremity ulcers) have also been used off-label in place of other FDA-approved or -cleared products (e.g., for burns).⁷⁵ No controlled trials were identified for these indications.

Summary of Evidence

Breast Reconstruction

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

Tendon Repair

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

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, QOL, 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 insufficient to determine that the technology results in an improvement in the net health outcome.

Diabetic Lower-Extremity Ulcers

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

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

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 symptoms, change in disease status, morbid events, and QOL. RCTs have demonstrated the efficacy of Apligraf living cell therapy and xenogeneic Oasis Wound Matrix over the SOC. The evidence is sufficient to determine that the technology results in an 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 QOL. In a moderately large RCT, Dermagraft was not shown to be more effective than controls for the primary or secondary endpoints 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 xenogeneic PriMatrix skin substitute versus the current SOC. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Dystrophic Epidermolysis Bullosa

For individuals who have dystrophic epidermolysis bullosa who receive OrCel, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. 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 (e.g., 5 patients). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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, QOL, and treatment-related morbidity. Overall, few skin substitutes have been approved, and the evidence is limited for each product. Epicel (living cell therapy) has received FDA approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a TBSA 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 an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence (NICE) updated its guidance on the prevention and management of diabetic foot problems.⁷⁶ The Institute 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."

In 2019, NICE published guidance on the ReCell system for treating skin loss, scarring, and depigmentation after burn injury.⁷⁷ The guidance recommended that additional research was needed to address the uncertainties regarding the potential benefits of ReCell.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (CMS) issued the following national coverage determination: porcine (pig) skin dressings are covered, if reasonable and necessary for the individual patient as an occlusive dressing for burns, donor sites of a homograft, and decubiti and other ulcers.⁷⁸

In 2019, CMS reported that it is finalizing the proposal to continue the policy established in CY 2018 to assign skin substitutes to the low cost or high-cost group.⁷⁹ In addition, CMS presented several payment ideas to change how skin substitute products are paid and solicited comments on these ideas to be used for future rulemaking. In 2022, CMS proposed changing the terminology of skin substitutes to "wound care management products", and to treat and pay for these products as incident to supplies under the Physician Fee Schedule beginning on January 1, 2024. However, in November 2022, CMS posted this update on the process: "After reviewing comments on the proposals, we understand that it would be beneficial to provide interested parties more opportunity to comment on the specific details of changes in coding and payment mechanisms prior to finalizing a specific date when the transition to more appropriate and consistent payment and coding for these products will be completed. We plan to conduct a Town Hall in early CY 2023 with interested parties to address commenters' concerns as well as discuss potential approaches to the methodology for payment of skin substitute products under the PFS. We will take into account the comments we received in response to CY 2023 rulemaking and feedback received in association with the Town Hall in order to strengthen proposed policies for skin substitutes in future rulemaking."⁸⁰

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 19.

Table 19. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT04537520 ^a	Interventional Multi-Center Post Market Randomized Controlled Open-Label Clinical Trial Comparing Kerecis Omega3 Wound Versus SOC in Hard to Heal Diabetic Foot Wounds	180	Dec 2022
NCT04257370 ^a	An Open Label, Randomized Controlled Study to Compare Healing of Severe Diabetic Foot Ulcers and Forefoot Amputations in Diabetics With and Without Moderate Peripheral Arterial Disease Treated With Kerecis Omega3 Wound and SOC vs. SOC Alone	330	Oct 2022
NCT02587403 ^a	A Randomized, Prospective Study Comparing Fortiva™ Porcine Dermis vs. Strattice™ Reconstructive Tissue Matrix in Patients Undergoing Complex Open Primary Ventral Hernia Repair	120	Feb 2024
NCT04133493 ^a	A Multi-center, Randomized Controlled Clinical Trial Evaluating the Effect of Omega3 Wound Fish Skin Graft in the Treatment of Diabetic Foot Ulcers	100	Jan 2023

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

References

1. Snyder DL, Sullivan N, Margolis DJ, Schoelles K. Skin substitutes for treating chronic wounds. Technology Assessment Program Project ID No. WNDT0818. (Prepared by the ECRI Institute-Penn Medicine Evidence-based Practice Center under Contract No. HHS 290-2015-00005-1) Rockville, MD: Agency for Healthcare Research and Quality. February 2020. Available at: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/skin-substitute_0.pdf. Accessed January 5, 2023.
2. U.S. Food and Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. December 2017. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal>. Accessed December 22, 2022.
3. U.S. Food and Drug Administration. Executive Summary Breast Implant Special Topics. March 2019. <https://www.fda.gov/media/122956/download>. Accessed December 23, 2022.
4. U.S. Food & Drug Administration. Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication. March 2021. <https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication>. Accessed December 27, 2022.
5. Davila AA, Seth AK, Wang E, et al. Human Acellular Dermis versus Submuscular Tissue Expander Breast Reconstruction: A Multivariate Analysis of Short-Term Complications. *Arch Plast Surg*. Jan 2013; 40(1): 19-27. PMID 23362476
6. Lee KT, Mun GH. Updated Evidence of Acellular Dermal Matrix Use for Implant-Based Breast Reconstruction: A Meta-analysis. *Ann Surg Oncol*. Feb 2016; 23(2): 600-10. PMID 26438439
7. McCarthy CM, Lee CN, Halvorson EG, et al. The use of acellular dermal matrices in two-stage expander/implant reconstruction: a multicenter, blinded, randomized controlled trial. *Plast Reconstr Surg*. Nov 2012; 130(5 Suppl 2): 575-66S. PMID 23096987
8. Hinchcliff KM, Orbay H, Busse BK, et al. Comparison of two cadaveric acellular dermal matrices for immediate breast reconstruction: A prospective randomized trial. *J Plast Reconstr Aesthet Surg*. May 2017; 70(5): 568-576. PMID 28341592

9. Mendenhall SD, Anderson LA, Ying J, et al. The BREASTrial Stage II: ADM Breast Reconstruction Outcomes from Definitive Reconstruction to 3 Months Postoperative. *Plast Reconstr Surg Glob Open*. Jan 2017; 5(1): e1209. PMID 28203509
10. Liu DZ, Mathes DW, Neligan PC, et al. Comparison of outcomes using AlloDerm versus FlexHD for implant-based breast reconstruction. *Ann Plast Surg*. May 2014; 72(5): 503-7. PMID 23636114
11. Chang EI, Liu J. Prospective unbiased experience with three acellular dermal matrices in breast reconstruction. *J Surg Oncol*. Sep 2017; 116(3): 365-370. PMID 28444764
12. Pittman TA, Fan KL, Knapp A, et al. Comparison of Different Acellular Dermal Matrices in Breast Reconstruction: The 50/50 Study. *Plast Reconstr Surg*. Mar 2017; 139(3): 521-528. PMID 28234811
13. Dikmans RE, Negenborn VL, Bouman MB, et al. Two-stage implant-based breast reconstruction compared with immediate one-stage implant-based breast reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial. *Lancet Oncol*. Feb 2017; 18(2): 251-258. PMID 28012977
14. Barber FA, Burns JP, Deutsch A, et al. A prospective, randomized evaluation of acellular human dermal matrix augmentation for arthroscopic rotator cuff repair. *Arthroscopy*. Jan 2012; 28(1): 8-15. PMID 21978432
15. Rashid MS, Smith RDJ, Nagra N, et al. Rotator cuff repair with biological graft augmentation causes adverse tissue outcomes. *Acta Orthop*. Dec 2020; 91(6): 782-788. PMID 32691656
16. Bellows CF, Smith A, Malsbury J, et al. Repair of incisional hernias with biological prosthesis: a systematic review of current evidence. *Am J Surg*. Jan 2013; 205(1): 85-101. PMID 22867726
17. Espinosa-de-los-Monteros A, de la Torre JI, Marrero I, et al. Utilization of human cadaveric acellular dermis for abdominal hernia reconstruction. *Ann Plast Surg*. Mar 2007; 58(3): 264-7. PMID 17471129
18. Gupta A, Zahriya K, Mullens PL, et al. Ventral herniorrhaphy: experience with two different biosynthetic mesh materials, Surgisis and Alloderm. *Hernia*. Oct 2006; 10(5): 419-25. PMID 16924395
19. Bochicchio GV, De Castro GP, Bochicchio KM, et al. Comparison study of acellular dermal matrices in complicated hernia surgery. *J Am Coll Surg*. Oct 2013; 217(4): 606-13. PMID 23973102
20. Roth JS, Zachem A, Plymale MA, et al. Complex Ventral Hernia Repair with Acellular Dermal Matrices: Clinical and Quality of Life Outcomes. *Am Surg*. Feb 01 2017; 83(2): 141-147. PMID 28228200
21. Bellows CF, Shaddock P, Helton WS, et al. Early report of a randomized comparative clinical trial of Strattice™ reconstructive tissue matrix to lightweight synthetic mesh in the repair of inguinal hernias. *Hernia*. Apr 2014; 18(2): 221-30. PMID 23543334
22. Fleshman JW, Beck DE, Hyman N, et al. A prospective, multicenter, randomized, controlled study of non-cross-linked porcine acellular dermal matrix fascial sublay for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies. *Dis Colon Rectum*. May 2014; 57(5): 623-31. PMID 24819103
23. Kalaiselvan R, Carlson GL, Hayes S, et al. Recurrent intestinal fistulation after porcine acellular dermal matrix reinforcement in enteric fistula takedown and simultaneous abdominal wall reconstruction. *Hernia*. Jun 2020; 24(3): 537-543. PMID 31811593
24. Santema TB, Poyck PP, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev*. Feb 11 2016; 2(2): CD011255. PMID 26866804
25. Martinson M, Martinson N. A comparative analysis of skin substitutes used in the management of diabetic foot ulcers. *J Wound Care*. Oct 01 2016; 25(Sup10): S8-S17. PMID 27681811
26. Guo X, Mu D, Gao F. Efficacy and safety of acellular dermal matrix in diabetic foot ulcer treatment: A systematic review and meta-analysis. *Int J Surg*. Apr 2017; 40: 1-7. PMID 28232031

27. Veves A, Falanga V, Armstrong DG, et al. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care*. Feb 2001; 24(2): 290-5. PMID 11213881
28. Blue Cross and Blue Shield Technology Evaluation Center (TEC). Graftskin for the treatment of skin ulcers. *TEC Assessments*. 2001;Volume 16:Tab 12.
29. Steinberg JS, Edmonds M, Hurley DP, et al. Confirmatory data from EU study supports Apligraf for the treatment of neuropathic diabetic foot ulcers. *J Am Podiatr Med Assoc*. 2010; 100(1): 73-7. PMID 20093548
30. Kirsner RS, Warriner R, Michela M, et al. Advanced biological therapies for diabetic foot ulcers. *Arch Dermatol*. Aug 2010; 146(8): 857-62. PMID 20713816
31. Marston WA, Hanft J, Norwood P, et al. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care*. Jun 2003; 26(6): 1701-5. PMID 12766097
32. Frykberg RG, Marston WA, Cardinal M. The incidence of lower-extremity amputation and bone resection in diabetic foot ulcer patients treated with a human fibroblast-derived dermal substitute. *Adv Skin Wound Care*. Jan 2015; 28(1): 17-20. PMID 25407083
33. Zelen CM, Orgill DP, Serena T, et al. A prospective, randomised, controlled, multicentre clinical trial examining healing rates, safety and cost to closure of an acellular reticular allogenic human dermis versus standard of care in the treatment of chronic diabetic foot ulcers. *Int Wound J*. Apr 2017; 14(2): 307-315. PMID 27073000
34. Zelen CM, Orgill DP, Serena TE, et al. An aseptically processed, acellular, reticular, allogenic human dermis improves healing in diabetic foot ulcers: A prospective, randomised, controlled, multicentre follow-up trial. *Int Wound J*. Oct 2018; 15(5): 731-739. PMID 29682897
35. Driver VR, Lavery LA, Reyzelman AM, et al. A clinical trial of Integra Template for diabetic foot ulcer treatment. *Wound Repair Regen*. 2015; 23(6): 891-900. PMID 26297933
36. Campitiello F, Mancone M, Della Corte A, et al. To evaluate the efficacy of an acellular Flowable matrix in comparison with a wet dressing for the treatment of patients with diabetic foot ulcers: a randomized clinical trial. *Updates Surg*. Dec 2017; 69(4): 523-529. PMID 28497218
37. Brigido SA, Boc SF, Lopez RC. Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. *Orthopedics*. Jan 2004; 27(1 Suppl): s145-9. PMID 14763548
38. Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *Int Wound J*. Jun 2009; 6(3): 196-208. PMID 19368581
39. Reyzelman AM, Bazarov I. Human acellular dermal wound matrix for treatment of DFU: literature review and analysis. *J Wound Care*. Mar 2015; 24(3): 128; 129-34. PMID 25764957
40. Brigido SA. The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. *Int Wound J*. Sep 2006; 3(3): 181-7. PMID 16984575
41. Walters J, Cazzell S, Pham H, et al. Healing Rates in a Multicenter Assessment of a Sterile, Room Temperature, Acellular Dermal Matrix Versus Conventional Care Wound Management and an Active Comparator in the Treatment of Full-Thickness Diabetic Foot Ulcers. *Eplasty*. 2016; 16: e10. PMID 26933467
42. Cazzell S, Vayser D, Pham H, et al. A randomized clinical trial of a human acellular dermal matrix demonstrated superior healing rates for chronic diabetic foot ulcers over conventional care and an active acellular dermal matrix comparator. *Wound Repair Regen*. May 2017; 25(3): 483-497. PMID 28544150
43. Gurtner GC, Garcia AD, Bakewell K, et al. A retrospective matched-cohort study of 3994 lower extremity wounds of multiple etiologies across 644 institutions comparing a bioactive human skin allograft, TheraSkin, plus standard of care, to standard of care alone. *Int Wound J*. Feb 2020; 17(1): 55-64. PMID 31729833

44. Sanders L, Landsman AS, Landsman A, et al. A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. *Ostomy Wound Manage.* Sep 2014; 60(9): 26-38. PMID 25211605
45. DiDomenico L, Landsman AR, Emch KJ, et al. A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. *Wounds.* Jul 2011; 23(7): 184-9. PMID 25879172
46. Frykberg RG, Cazzell SM, Arroyo-Rivera J, et al. Evaluation of tissue engineering products for the management of neuropathic diabetic foot ulcers: an interim analysis. *J Wound Care.* Jul 2016; 25 Suppl 7: S18-25. PMID 27410467
47. Lantis JC, Snyder R, Reyzelman AM, et al. Fetal bovine acellular dermal matrix for the closure of diabetic foot ulcers: a prospective randomised controlled trial. *J Wound Care.* Jul 01 2021; 30(Sup7): S18-S27. PMID 34256588
48. Kavros SJ, Dutra T, Gonzalez-Cruz R, et al. The use of PriMatrix, a fetal bovine acellular dermal matrix, in healing chronic diabetic foot ulcers: a prospective multicenter study. *Adv Skin Wound Care.* Aug 2014; 27(8): 356-62. PMID 25033310
49. Karr JC. Retrospective comparison of diabetic foot ulcer and venous stasis ulcer healing outcome between a dermal repair scaffold (PriMatrix) and a bilayered living cell therapy (Apligraf). *Adv Skin Wound Care.* Mar 2011; 24(3): 119-25. PMID 21326023
50. Niezgoda JA, Van Gils CC, Frykberg RG, et al. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care.* Jun 2005; 18(5 Pt 1): 258-66. PMID 15942317
51. Uccioli L, Giurato L, Ruotolo V, et al. Two-step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. *Int J Low Extrem Wounds.* Jun 2011; 10(2): 80-5. PMID 21693443
52. Lullove EJ, Liden B, Winters C, et al. A Multicenter, Blinded, Randomized Controlled Clinical Trial Evaluating the Effect of Omega-3-Rich Fish Skin in the Treatment of Chronic, Nonresponsive Diabetic Foot Ulcers. *Wounds.* Jul 2021; 33(7): 169-177. PMID 33872197
53. Lullove EJ, Liden B, McEneaney P, et al. Evaluating the effect of omega-3-rich fish skin in the treatment of chronic, nonresponsive diabetic foot ulcers: penultimate analysis of a multicenter, prospective, randomized controlled trial. *Wounds.* Apr 2022; 34(4): E34-E36. PMID 35797557
54. O'Meara S, Cullum N, Nelson EA, et al. Compression for venous leg ulcers. *Cochrane Database Syst Rev.* Nov 14 2012; 11(11): CD000265. PMID 23152202
55. Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. *Arch Dermatol.* Mar 1998; 134(3): 293-300. PMID 9521027
56. Mostow EN, Haraway GD, Dalsing M, et al. Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. *J Vasc Surg.* May 2005; 41(5): 837-43. PMID 15886669
57. Romanelli M, Dini V, Bertone M, et al. OASIS wound matrix versus Hyaloskin in the treatment of difficult-to-heal wounds of mixed arterial/venous aetiology. *Int Wound J.* Mar 2007; 4(1): 3-7. PMID 17425543
58. Romanelli M, Dini V, Bertone MS. Randomized comparison of OASIS wound matrix versus moist wound dressing in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. *Adv Skin Wound Care.* Jan 2010; 23(1): 34-8. PMID 20101114
59. Harding K, Sumner M, Cardinal M. A prospective, multicentre, randomised controlled study of human fibroblast-derived dermal substitute (Dermagraft) in patients with venous leg ulcers. *Int Wound J.* Apr 2013; 10(2): 132-7. PMID 23506344
60. Cazzell S. A Randomized Controlled Trial Comparing a Human Acellular Dermal Matrix Versus Conventional Care for the Treatment of Venous Leg Ulcers. *Wounds.* Mar 2019; 31(3): 68-74. PMID 30720443
61. Carsin H, Ainaud P, Le Bever H, et al. Cultured epithelial autografts in extensive burn coverage of severely traumatized patients: a five year single-center experience with 30 patients. *Burns.* Jun 2000; 26(4): 379-87. PMID 10751706

62. Lagus H, Sarlomo-Rikala M, Böhling T, et al. Prospective study on burns treated with Integra®, a cellulose sponge and split thickness skin graft: comparative clinical and histological study--randomized controlled trial. *Burns*. Dec 2013; 39(8): 1577-87. PMID 23880091
63. Branski LK, Herndon DN, Pereira C, et al. Longitudinal assessment of Integra in primary burn management: a randomized pediatric clinical trial. *Crit Care Med*. Nov 2007; 35(11): 2615-23. PMID 17828040
64. Heimbach DM, Warden GD, Luterman A, et al. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. *J Burn Care Rehabil*. 2003; 24(1): 42-8. PMID 12543990
65. Hicks KE, Huynh MN, Jeschke M, et al. Dermal regenerative matrix use in burn patients: A systematic review. *J Plast Reconstr Aesthet Surg*. Nov 2019; 72(11): 1741-1751. PMID 31492583
66. Gonzalez SR, Wolter KG, Yuen JC. Infectious Complications Associated with the Use of Integra: A Systematic Review of the Literature. *Plast Reconstr Surg Glob Open*. Jul 2020; 8(7): e2869. PMID 32802634
67. Luze H, Nischwitz SP, Smolle C, et al. The Use of Acellular Fish Skin Grafts in Burn Wound Management-A Systematic Review. *Medicina (Kaunas)*. Jul 09 2022; 58(7). PMID 35888631
68. Holmes JH, Molnar JA, Shupp JW, et al. Demonstration of the safety and effectiveness of the RECELL® System combined with split-thickness meshed autografts for the reduction of donor skin to treat mixed-depth burn injuries. *Burns*. Jun 2019; 45(4): 772-782. PMID 30578048
69. Holmes JH, Molnar JA, Carter JE, et al. A Comparative Study of the ReCell® Device and Autologous Split-Thickness Meshed Skin Graft in the Treatment of Acute Burn Injuries. *J Burn Care Res*. Aug 17 2018; 39(5): 694-702. PMID 29800234
70. Fivenson DP, Scherschun L, Cohen LV. Apligraf in the treatment of severe mitten deformity associated with recessive dystrophic epidermolysis bullosa. *Plast Reconstr Surg*. Aug 2003; 112(2): 584-8. PMID 12900618
71. Baldursson BT, Kjartansson H, Konrádssdóttir F, et al. Healing rate and autoimmune safety of full-thickness wounds treated with fish skin acellular dermal matrix versus porcine small-intestine submucosa: a noninferiority study. *Int J Low Extrem Wounds*. Mar 2015; 14(1): 37-43. PMID 25759413
72. Still J, Glat P, Silverstein P, et al. The use of a collagen sponge/living cell composite material to treat donor sites in burn patients. *Burns*. Dec 2003; 29(8): 837-41. PMID 14636761
73. Brown-Etris M, Milne CT, Hodde JP. An extracellular matrix graft (Oasis® wound matrix) for treating full-thickness pressure ulcers: A randomized clinical trial. *J Tissue Viability*. Feb 2019; 28(1): 21-26. PMID 30509850
74. Lazic T, Falanga V. Bioengineered skin constructs and their use in wound healing. *Plast Reconstr Surg*. Jan 2011; 127 Suppl 1: 75S-90S. PMID 21200276
75. Saffle JR. Closure of the excised burn wound: temporary skin substitutes. *Clin Plast Surg*. Oct 2009; 36(4): 627-41. PMID 19793557
76. National Institute for Health and Care Excellence (NICE). Diabetic Foot Problems: Prevention and Management [NG19]. 2019; <https://www.nice.org.uk/guidance/ng19/evidence>. Accessed December 27, 2022.
77. Peirce SC, Carolan-Rees G. ReCell® Spray-On Skin System for Treating Skin Loss, Scarring and Depigmentation after Burn Injury: A NICE Medical Technology Guidance. *Appl Health Econ Health Policy*. Apr 2019; 17(2): 131-141. PMID 30635844
78. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Porcine Skin and Gradient Pressure Dressings (270.5). n.d.; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=139&ncdver=1&bc=AgAAQAAAAAAAA&>. Accessed January 5, 2023.
79. Centers for Medicare & Medicaid Services (CMS). Fact Sheet: CMS finalizes Medicare Hospital Outpatient Prospective Payment System and Ambulatory Surgical Center Payment System changes for 2019 <https://www.cms.gov/newsroom/fact-sheets/cms-finalizes-medicare-hospital-outpatient-prospective-payment-system-and-ambulatory-surgical-center>. Accessed January 4, 2023.

80. Centers for Medicare & Medicaid Services. 2022. Fact Sheet. Calendar Year (CY) 2023 Medicare Physician Fee Schedule Final Rule. <https://www.cms.gov/newsroom/fact-sheets/calendar-year-cy-2023-medicare-physician-fee-schedule-final-rule>. Accessed January 3, 2023.

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
 - Specific diagnosis requiring skin or breast soft tissue substitute
 - Reason for use, including wound or defect description
 - Previous treatment plan and response
 - Progress notes for the past six months if applicable
- Exact brand name of skin or soft tissue substitute to be used including amount or number of units needed

Post Service (in addition to the above, please include the following):

- Procedure report(s)
- Skin or soft tissue substitute invoice (if applicable)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0627T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with fluoroscopic guidance, lumbar; first level
	0628T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with fluoroscopic guidance, lumbar; each additional level (List separately in addition to code for primary procedure)
	0629T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with CT guidance, lumbar; first level
	0630T	Percutaneous injection of allogeneic cellular and/or tissue-based product, intervertebral disc, unilateral or bilateral injection, with CT guidance, lumbar; each additional level (List separately in addition to code for primary procedure)
	15040	Harvest of skin for tissue cultured skin autograft, 100 sq cm or less
	15050	Pinch graft, single or multiple, to cover small ulcer, tip of digit, or other minimal open area (except on face), up to defect size 2 cm diameter
	15100	Split-thickness autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)

Type	Code	Description
	15101	Split-thickness autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15110	Epidermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
	15111	Epidermal autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15115	Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
	15116	Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15120	Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)
	15121	Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15130	Dermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
	15131	Dermal autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15135	Dermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
	15136	Dermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15150	Tissue cultured skin autograft, trunk, arms, legs; first 25 sq cm or less
	15151	Tissue cultured skin autograft, trunk, arms, legs; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
	15152	Tissue cultured skin autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15155	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 25 sq cm or less
	15156	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
	15157	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15200	Full thickness graft, free, including direct closure of donor site, trunk; 20 sq cm or less

Type	Code	Description
	15201	Full thickness graft, free, including direct closure of donor site, trunk; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
	15220	Full thickness graft, free, including direct closure of donor site, scalp, arms, and/or legs; 20 sq cm or less
	15221	Full thickness graft, free, including direct closure of donor site, scalp, arms, and/or legs; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
	15240	Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; 20 sq cm or less
	15241	Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
	15260	Full thickness graft, free, including direct closure of donor site, nose, ears, eyelids, and/or lips; 20 sq cm or less
	15261	Full thickness graft, free, including direct closure of donor site, nose, ears, eyelids, and/or lips; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
	15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
	15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
	15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
	15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
	15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
	15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
	15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
	15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

Type	Code	Description
	15777	Implantation of biologic implant (e.g., acellular dermal matrix) for soft tissue reinforcement (i.e., breast, trunk) (List separately in addition to code for primary procedure)
HCPCS	A2002	Mirragen Advanced Wound Matrix, per sq cm
	A2004	XCelliStem, 1 mg
	A2005	Microlyte Matrix, per sq cm
	A2006	NovoSorb SynPath dermal matrix, per sq cm
	A2007	Restrata, per sq cm
	A2008	TheraGenesis, per sq cm
	A2009	Symphony, per sq cm
	A2010	Apis, per sq cm
	A2011	Supra SDRM, per sq cm
	A2012	SUPRATHEL, per sq cm
	A2013	Innovamatrix FS, per sq cm
	A2014	Omeza Collagen Matrix, per 100 mg
	A2015	Phoenix Wound Matrix, per sq cm
	A2016	PermeaDerm B, per sq cm
	A2017	PermeaDerm Glove, each
	A2018	PermeaDerm C, per sq cm
	A2019	Kerecis Omega3 MariGen Shield, per sq cm <i>(Code effective 4/1/2023)</i>
	A2020	AC5 Advanced Wound System (AC5) <i>(Code effective 4/1/2023)</i>
	A2021	NeoMatriX, per sq cm <i>(Code effective 4/1/2023)</i>
	A2022	InnovaBurn or InnovaMatrix XL, per sq cm <i>(Code effective 10/1/2023)</i>
	A2023	InnovaMatrix PD, 1 mg <i>(Code effective 10/1/2023)</i>
	A2024	Resolve Matrix, per sq cm <i>(Code effective 10/1/2023)</i>
	A2025	Miro3D, per cu cm <i>(Code effective 10/1/2023)</i>
	A4100	Skin substitute, FDA-cleared as a device, not otherwise specified
	A6460	Synthetic resorbable wound dressing, sterile, pad size 16 sq. in. or less, without adhesive border, each dressing
	A6461	Synthetic resorbable wound dressing, sterile, pad size more than 16 sq. in. but less than or equal to 48 sq. in., without adhesive border, each dressing
	C1832	Autograft suspension, including cell processing and application, and all system components
	C1849	Skin substitute, synthetic, resorbable, per sq cm <i>(Deleted code effective 1/1/2023)</i>
	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, nondenatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm
	C9360	Dermal substitute, native, nondenatured 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	

Type	Code	Description
	Q4103	Oasis burn matrix, per sq cm
	Q4104	Integra bilayer matrix wound dressing (BMWD), per sq cm
	Q4105	Integra dermal regeneration template (DRT) or Integra Omnigraft dermal regeneration matrix, 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 sq cm
	Q4116	AlloDerm, per sq cm
	Q4117	HYALOMATRIX, per sq cm
	Q4118	MatriStem micromatrix, 1 mg
	Q4121	TheraSkin, per sq cm
	Q4122	DermACELL, DermACELL AWM or DermACELL AWM Porous, 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, DermaSpan, TranZgraft or InteguPly, per sq cm
	Q4127	Talymed, per sq cm
	Q4128	FlexHD, AllopatchHD, or Matrix HD, 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, Architect PX, or Architect FX, extracellular matrix, per sq cm
	Q4149	Excellagen, 0.1 cc
	Q4152	DermaPure, per sq cm
	Q4158	Kerecis omega3 per square cm
	Q4161	Bio-ConneKt wound matrix, per sq cm
	Q4164	Helicoll, per sq cm
	Q4165	Keramatrix or Kerasorb, per sq cm
	Q4166	Cytal, per sq cm
	Q4167	Truskin, per sq cm
	Q4175	Miroderm, per sq cm
	Q4179	FlowerDerm, per sq cm
	Q4182	Transcyte per square cm
	Q4193	Coll-e-derm, per square cm
	Q4195	Puraply, per square cm
	Q4196	Puraply am, per square cm
	Q4197	Puraply xt, per square cm

Type	Code	Description
	Q4200	Skin te, per square cm
	Q4202	Keroxx (2.5g/cc), 1cc
	Q4203	Derma-gide, per square cm
	Q4220	BellaCell HD or Surederm, per sq cm
	Q4222	ProgenaMatrix, per sq cm
	Q4226	MyOwn Skin, includes harvesting and preparation procedures, per sq cm
	Q4238	Derm-Maxx, per sq cm

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/07/2011	Policy title change from Allograft Use in Breast Reconstructive Surgery with adoption of BCBSA Medical Policy
03/13/2012	Coding Update
07/06/2012	Policy title change from Tissue-Engineered Skin Substitutes with position change
10/05/2012	Policy revision with position change
02/22/2013	Coding Update
03/29/2013	Policy revision with position change
03/28/2014	Policy revision with position change
01/30/2015	Coding update
03/30/2015	Policy revision without position change
01/01/2016	Coding update
09/01/2016	Policy title change from Bio-Engineered Skin and Soft Tissue Substitutes Policy revision without position change
02/01/2017	Coding update
03/01/2017	Policy revision without position change
08/01/2017	Policy revision without position change
02/01/2018	Coding update
06/01/2018	Policy revision with position change
02/01/2019	Coding update
03/01/2019	Policy revision without position change
11/01/2019	Coding update
03/01/2020	Annual review. No change to policy statement. Literature review updated.
08/01/2020	Coding update
01/01/2021	Coding update
03/01/2021	Annual review. Policy statement, guidelines and literature review updated.
06/01/2021	Policy statement and guidelines updated.
03/01/2022	Annual review. Policy statement and literature review updated. Coding update.
06/01/2022	Coding update
08/01/2022	Coding update
12/01/2022	Coding update
03/01/2023	Annual review. Policy statement and literature review updated. Coding update.
06/01/2023	Coding update
12/01/2023	Coding update

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT

(No changes)

BEFORE	AFTER
<p data-bbox="107 334 800 362">Bioengineered Skin and Soft Tissue Substitutes 7.01.113</p> <p data-bbox="107 402 338 430">Policy Statement:</p> <ol style="list-style-type: none"> <li data-bbox="149 472 1024 899">I. Breast reconstructive surgery using allogeneic acellular dermal matrix products^a (including each of the following: AlloDerm[®], AlloMend[®], Cortiva[®] [AlloMax[™]], DermACELL[™], DermaMatrix[™], FlexHD[®], FlexHD[®] Pliable[™], GraftJacket[®]; see Policy Guidelines) may be considered medically necessary for any of the following: <ol style="list-style-type: none"> <li data-bbox="201 639 1024 732">A. When there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required <li data-bbox="201 740 1024 800">B. When there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis <li data-bbox="201 808 1024 899">C. The inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed <li data-bbox="149 943 1024 1206">II. Treatment of chronic, noninfected, full-thickness diabetic lower-extremity ulcers may be considered medically necessary using any of the following tissue-engineered skin substitutes: <ol style="list-style-type: none"> <li data-bbox="201 1040 394 1068">A. AlloPatch^{®a} <li data-bbox="201 1076 373 1104">B. Apligraf^{®b} <li data-bbox="201 1112 422 1140">C. Dermagraft^{®b} <li data-bbox="201 1148 1024 1206">D. Integra[®] Omnigraft[™] Dermal Regeneration Matrix (also known as Omnigraft[™]) and Integra Flowable Wound Matrix <li data-bbox="149 1247 1024 1471">III. Treatment of chronic, noninfected, partial- or full-thickness lower-extremity skin ulcers due to venous insufficiency, which have not adequately responded following a 1-month period of conventional ulcer therapy may be considered medically necessary using either of the following tissue engineered skin substitutes: <ol style="list-style-type: none"> <li data-bbox="201 1414 373 1442">A. Apligraf^{®b} <li data-bbox="201 1450 527 1477">B. Oasis[™] Wound Matrix^c 	<p data-bbox="1064 334 1757 362">Bioengineered Skin and Soft Tissue Substitutes 7.01.113</p> <p data-bbox="1064 402 1295 430">Policy Statement:</p> <ol style="list-style-type: none"> <li data-bbox="1106 472 1982 899">I. Breast reconstructive surgery using allogeneic acellular dermal matrix products^a (including each of the following: AlloDerm[®], AlloMend[®], Cortiva[®] [AlloMax[™]], DermACELL[™], DermaMatrix[™], FlexHD[®], FlexHD[®] Pliable[™], GraftJacket[®]; see Policy Guidelines) may be considered medically necessary for any of the following: <ol style="list-style-type: none"> <li data-bbox="1159 639 1982 732">A. When there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required <li data-bbox="1159 740 1982 800">B. When there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis <li data-bbox="1159 808 1982 899">C. The inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed <li data-bbox="1106 943 1982 1206">II. Treatment of chronic, noninfected, full-thickness diabetic lower-extremity ulcers may be considered medically necessary using any of the following tissue-engineered skin substitutes: <ol style="list-style-type: none"> <li data-bbox="1159 1040 1352 1068">A. AlloPatch^{®a} <li data-bbox="1159 1076 1327 1104">B. Apligraf^{®b} <li data-bbox="1159 1112 1379 1140">C. Dermagraft^{®b} <li data-bbox="1159 1148 1982 1206">D. Integra[®] Omnigraft[™] Dermal Regeneration Matrix (also known as Omnigraft[™]) and Integra Flowable Wound Matrix <li data-bbox="1106 1247 1982 1471">III. Treatment of chronic, noninfected, partial- or full-thickness lower-extremity skin ulcers due to venous insufficiency, which have not adequately responded following a 1-month period of conventional ulcer therapy may be considered medically necessary using either of the following tissue engineered skin substitutes: <ol style="list-style-type: none"> <li data-bbox="1159 1414 1331 1442">A. Apligraf^{®b} <li data-bbox="1159 1450 1484 1477">B. Oasis[™] Wound Matrix^c

POLICY STATEMENT

(No changes)

BEFORE	AFTER
<p>IV. Treatment of dystrophic epidermolysis bullosa may be considered medically necessary using the following tissue-engineered skin substitutes:</p> <p>A. 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 U.S. Food and Drug Administration [FDA])^d</p> <p>V. Treatment of second- and third-degree burns may be considered medically necessary using either of the following tissue-engineered skin substitutes:</p> <p>A. Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area greater than or equal to 30% when provided in accordance with the HDE specifications of the FDA)^d</p> <p>B. Integra® Dermal Regeneration Template^b.</p> <p>^a Banked human tissue. ^b FDA premarket approval. ^c FDA 510(k) clearance. ^d FDA-approved under an HDE.</p> <p>VI. All other uses of the bioengineered skin and breast soft tissue substitutes listed above are considered investigational.</p> <p>VII. All other skin and breast soft tissue substitutes not listed above are considered investigational, including, but not limited to:</p> <ol style="list-style-type: none"> 1. Cell® UBM Hydrated/Lyophilized Wound Dressing 2. AlloSkin™ 3. AlloSkin™ RT 4. Aongen™ Collagen Matrix 5. Architec^t® ECM, PX, FX 6. ArthroFlex™ (Flex Graft) 7. AxoGuard® Nerve Protector (AxoGen) 8. Biobrane®/Biobrane-L 9. Bio-ConneKt® Wound Matrix 10. CollaCare® 	<p>IV. Treatment of dystrophic epidermolysis bullosa may be considered medically necessary using the following tissue-engineered skin substitutes:</p> <p>A. 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 U.S. Food and Drug Administration [FDA])^d</p> <p>V. Treatment of second- and third-degree burns may be considered medically necessary using either of the following tissue-engineered skin substitutes:</p> <p>A. Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area greater than or equal to 30% when provided in accordance with the HDE specifications of the FDA)^d</p> <p>B. Integra® Dermal Regeneration Template^b.</p> <p>^a Banked human tissue. ^b FDA premarket approval. ^c FDA 510(k) clearance. ^d FDA-approved under an HDE.</p> <p>VI. All other uses of the bioengineered skin and breast soft tissue substitutes listed above are considered investigational.</p> <p>VII. All other skin and breast soft tissue substitutes not listed above are considered investigational, including, but not limited to:</p> <ol style="list-style-type: none"> 1. Cell® UBM Hydrated/Lyophilized Wound Dressing 2. AlloSkin™ 3. AlloSkin™ RT 4. Aongen™ Collagen Matrix 5. Architec^t® ECM, PX, FX 6. ArthroFlex™ (Flex Graft) 7. AxoGuard® Nerve Protector (AxoGen) 8. Biobrane®/Biobrane-L 9. Bio-ConneKt® Wound Matrix 10. CollaCare®

POLICY STATEMENT

(No changes)

BEFORE	AFTER
11. CollaCare® Dental 12. Collagen Wound Dressing (Oasis Research) 13. CollaGUARD® 14. CollaMend™ 15. CollaWound™ 16. Coll-e-derm 17. Collexa® 18. Collieva® 19. Conexa™ 20. Coreleader Colla-Pad 21. CorMatrix® 22. Cymetra™ (Micronized AlloDerm)™ 23. Cytal™ (previously MatriStem®) 24. Dermadapt™ Wound Dressing 25. Derma-gide 26. DermaPure™ 27. DermaSpan™ 28. DressSkin 29. Endoform Dermal Template™ 30. ENDURAGen™ 31. Excellagen® 32. ExpressGraft™ 33. E-Z Derm™ 34. Flexigraft® 35. FlowerDerm™ 36. GammaGraft 37. Geistlich Derma-Gide™ 38. GraftJacket® Xpress, injectable 39. Helicoll™ 40. hMatrix® 41. Hyalomatrix® 42. Hyalomatrix® PA 43. Integra™ Bilayer Wound Matrix 44. Integra® Matrix Wound Dressing (previously Avagen) 45. InteguPly® 46. Keramatrix® 47. Keroxx™	11. CollaCare® Dental 12. Collagen Wound Dressing (Oasis Research) 13. CollaGUARD® 14. CollaMend™ 15. CollaWound™ 16. Coll-e-derm 17. Collexa® 18. Collieva® 19. Conexa™ 20. Coreleader Colla-Pad 21. CorMatrix® 22. Cymetra™ (Micronized AlloDerm)™ 23. Cytal™ (previously MatriStem®) 24. Dermadapt™ Wound Dressing 25. Derma-gide 26. DermaPure™ 27. DermaSpan™ 28. DressSkin 29. Endoform Dermal Template™ 30. ENDURAGen™ 31. Excellagen® 32. ExpressGraft™ 33. E-Z Derm™ 34. Flexigraft® 35. FlowerDerm™ 36. GammaGraft 37. Geistlich Derma-Gide™ 38. GraftJacket® Xpress, injectable 39. Helicoll™ 40. hMatrix® 41. Hyalomatrix® 42. Hyalomatrix® PA 43. Integra™ Bilayer Wound Matrix 44. Integra® Matrix Wound Dressing (previously Avagen) 45. InteguPly® 46. Keramatrix® 47. Keroxx™

POLICY STATEMENT

(No changes)

BEFORE	AFTER
48. Marigen™ /Kerecis™ Omega3 49. MatriDerm® 50. MatriStem 51. Matrix HD™ 52. MicroMatrix® 53. Miroderm® 54. Mediskin® 55. MemoDerm™ 56. Microderm® biologic wound matrix 57. MyOwn skin 58. Oasis® Burn Matrix 59. Oasis® Ultra 60. Ologen™ Collagen Matrix 61. Omega3 Wound (originally Merigen wound dressing) 62. Permacol™ 63. PriMatrix™ 64. PriMatrix™ Dermal Repair Scaffold 65. Progenamatrix 66. Puracol® and Puracol® Plus Collagen Wound Dressings 67. PuraPly™ Wound Matrix (previously FortaDerm™) 68. PuraPly™ AM (Antimicrobial Wound Matrix) 69. Puros® Dermis 70. RegenePro™ 71. Repliform® 72. Recell® 73. Repriza™ 74. SkinTE™ 75. StrataGraft® 76. Strattice™ 77. Suprathel® 78. SurgiMend® 79. Talymed® 80. TenoGlide™ 81. TenSIX™ Acellular Dermal Matrix 82. TissueMend 83. TheraForm™ Standard/Sheet 84. TheraSkin®	48. Marigen™ /Kerecis™ Omega3 49. MatriDerm® 50. MatriStem 51. Matrix HD™ 52. MicroMatrix® 53. Miroderm® 54. Mediskin® 55. MemoDerm™ 56. Microderm® biologic wound matrix 57. MyOwn skin 58. Oasis® Burn Matrix 59. Oasis® Ultra 60. Ologen™ Collagen Matrix 61. Omega3 Wound (originally Merigen wound dressing) 62. Permacol™ 63. PriMatrix™ 64. PriMatrix™ Dermal Repair Scaffold 65. Progenamatrix 66. Puracol® and Puracol® Plus Collagen Wound Dressings 67. PuraPly™ Wound Matrix (previously FortaDerm™) 68. PuraPly™ AM (Antimicrobial Wound Matrix) 69. Puros® Dermis 70. RegenePro™ 71. Repliform® 72. Recell® 73. Repriza™ 74. SkinTE™ 75. StrataGraft® 76. Strattice™ 77. Suprathel® 78. SurgiMend® 79. Talymed® 80. TenoGlide™ 81. TenSIX™ Acellular Dermal Matrix 82. TissueMend 83. TheraForm™ Standard/Sheet 84. TheraSkin®

POLICY STATEMENT

(No changes)

BEFORE	AFTER
85. TransCyte™ 86. TruSkin™ 87. Veritas® Collagen Matrix 88. XCM Biologic® Tissue Matrix 89. XenMatrix™ AB	85. TransCyte™ 86. TruSkin™ 87. Veritas® Collagen Matrix 88. XCM Biologic® Tissue Matrix 89. XenMatrix™ AB