PHP_7.01.113	Bioengineered Skin and Soft Tissue Substitutes		
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Section:	7.0 Surgery	**Page:**	Page 1 of 57

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. Department of Health Care Services (DHCS) Provider Manual Guideline:
- Surgery: Integumentary System (surg integ)

Below is an excerpt of the guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Bio-Engineered Skin Substitutes
Usage
- Apligraf (HCPCS code Q4101) is indicated for applications at least three weeks apart, not to exceed a total of four applications.
- Integra (HCPCS code Q4104) is indicated for one application. Repeat application to the same wound as appropriate only if there has been measurable response to the first application. Treating the same wound again in less than one year is not medically appropriate.
- Dermagraft (HCPCS code Q4106) is reimbursable for treatment of full-thickness, diabetic foot ulcers with greater than six-weeks duration, which extend through the dermis, but without tendon, muscle, joint capsule or bone exposure. Dermagraft should be used in conjunction with standard wound care regimens and on patients who have adequate blood supply to the involved foot. Dermagraft is indicated for a once weekly application, not to exceed a total of eight applications.

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:
- N/A

Policy Statement

Any criteria that are not specifically addressed in the above Provider Manual, please refer to the criteria below.

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] ***(Per Medi-Cal guidelines and for Medi-Cal members only: Dermagraft (HCPCS code Q4106) is reimbursable for treatment of full-thickness, diabetic foot ulcers with greater than six-weeks duration, which extend through the dermis, but without tendon, muscle, joint capsule or bone exposure. Dermagraft should be used in conjunction with standard wound care regimens and on patients who have adequate blood supply to the involved foot.)***
D. Integra® Omnigraft™ Dermal Regeneration Matrix (also known as Omnigraft™) and Integra Flowable Wound Matrix
E. mVASC®
F. TheraSkin®

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 reviewed herein 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** for indications reviewed herein, including, but not limited to:
1. ACell® UBM Hydrated/Lyophilized Wound Dressing,
2. AlloSkin™,
3. AlloSkin™ RT,

4. Apis®,
5. Aongen™ Collagen Matrix,
6. Architect® ECM, PX, FX,
7. Artacent® Wound,
8. ArthroFlex™ (Flex Graft),
9. AxoGuard® Nerve Protector (AxoGen),
10. Biobrane®/Biobrane-L,
11. Bio-ConneKt® Wound Matrix,
12. CollaCare®,
13. CollaCare® Dental,
14. Collagen Wound Dressing (Oasis Research),
15. CollaGUARD®,
16. CollaMend™,
17. CollaWound™,
18. Coll-e-derm,
19. Collexa®,
20. Collieva®,
21. Conexa™,
22. Coreleader Colla-Pad,
23. CorMatrix®,
24. Cymetra™ (Micronized AlloDerm)™,
25. Cytal™ (previously MatriStem®),
26. DeNovoSkin™,
27. Dermadapt™ Wound Dressing,
28. Derma-gide,
29. DermaPure™,
30. DermaSpan™,
31. DressSkin,
32. Durepair Regeneration Matrix®,
33. Endoform Dermal Template™,
34. *ENDURA*Gen™,
35. Excellagen®,
36. ExpressGraft™,
37. E-Z Derm™,
38. Flexibile Collagen Nerve Cuff (Collagen Matrix, Inc),
39. FlowerDerm™,
40. Foundation Dermal Regeneration Scaffold (DRS) Solo,
41. GammaGraft,
42. Geistlich Derma-Gide™,
43. GraftJacket® Xpress, injectable,
44. Helicoll™,
45. hMatrix®,
46. Hyalomatrix®,
47. Hyalomatrix® PA,
48. Integra™ Bilayer Wound Matrix,
49. Integra® Matrix Wound Dressing (previously Avagen),
50. InteguPly®,
51. Keramatrix®,
52. Kerecis™ Omega3,
53. Keroxx™,
54. InnovaMatrix®,
55. MatriDerm®,
56. MatriStem,
57. Matrix HD™,

58. MicroMatrix®,
59. Miro3D Fibers Wound Matrix,
60. MiroTract Wound Matrix,
61. Miroderm®,
62. Mediskin®,
63. MemoDerm™,
64. Microderm® biologic wound matrix,
65. Microlyte matrix®,
66. Mochida Nerve Cuff (Mochida Pharmaceutical Co.),
67. MyOwn skin,
68. Myriad matrix,
69. Myriad morcells,
70. NervAlign Nerve Cuff (Renerve, Ltd),
71. Nerve tape (BioCircuit Technologies, Inc),
72. Neurawrap (Integra LifeSciences, Corp),
73. NeuroMend (Stryker Orthopedics),
74. NeuroShield (Monarch bioimplants, GmBH),
75. Novosorb™ Biodegradable Temporizing Matrix (BMT),
76. Oasis® Burn Matrix,
77. Oasis® Ultra,
78. Ologen™ Collagen Matrix,
79. Omega3 Wound (originally Merigen wound dressing),
80. Omeza® Collagen Matrix,
81. Permacol™,
82. PermeaDerm® B,
83. PermeaDerm® C,
84. PermeaDerm® Glove,
85. Phoenix™ Wound Matrix,
86. PriMatrix™,
87. PriMatrix™ Dermal Repair Scaffold,
88. Progenamatrix™,
89. Puracol® and Puracol® Plus Collagen Wound Dressings,
90. PuraPly™ Wound Matrix (previously FortaDerm™),
91. PuraPly™ AM (Antimicrobial Wound Matrix),
92. Puros® Dermis,
93. RegenePro™,
94. Reinforce flexible Collagen Nerve Cuff (Collagen Matrix, Inc),
95. Repliform®,
96. ReCell®,
97. Repriza™,
98. Restrata®,
99. Restrata MiniMatrix,
100. SkinTE™,
101. StrataGraft®,
102. Strattice™,
103. SUPRA SDRM®,
104. Suprathel®,
105. SurgiMend®,
106. Symphony™,
107. Talymed®,
108. TenoGlide™,
109. TenSIX™ Acellular Dermal Matrix,
110. TissueMend,
111. TheraForm™ Standard/Sheet,

112. TheraGenesis®,
113. TransCyte™,
114. TruSkin™,
115. Tutomesh™ Fenestrated Bovine Pericardium,
116. Veritas® Collagen Matrix,
117. Versawrap nerve protector (Alafair Biosciences, Inc),
118. Xcellistem®,
119. XCM Biologic® Tissue Matrix,
120. XenMatrix™ AB.

Policy Guidelines

There is no standard definition of "skin substitute". Products in this review cover products that do not require U.S. Food and Drug Administration (FDA) approval or clearance as well as a number of products cleared through the 510(k) pathway with a variety of FDA product codes. The FDA product codes that include these products are not limited to skin substitute products and may include other indications not related to wounds. The list of products named in this review is not a complete list of all commercially available products.

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

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.

The Women's Health and Cancer Rights Act (WHCRA) helps protect many women with breast cancer who choose to have their breasts rebuilt (reconstructed) after a mastectomy. Mastectomy is surgery to remove all or part of the breast. This federal law requires most group insurance plans that cover mastectomies to also cover breast reconstruction. It was signed into law on October 21, 1998. The United States Departments of Labor and Health and Human Services oversee this law.

Coding

See the Codes table for details.

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.

Summary of Evidence

Breast Reconstruction

For individuals who are undergoing breast reconstruction who receive allogeneic acellular dermal matrix (ADM) products, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life (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 studies 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, Integra, mVASC, or TheraSkin, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. Randomized controlled trials reporting complete wound healing outcomes with at least 12 weeks of follow-up have demonstrated the efficacy of AlloPatch (reticular ADM), Apligraf and Dermagraft (living cell therapy), Integra (biosynthetic), mVASC, and TheraSkin over the standard of care (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, Integra, mVASC, or TheraSkin, 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, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies. An RCT of Omega3 Wound (Kerecis) has been published and 2 larger RCTs are registered and reported as completed but have not been published. 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. Randomized controlled trials 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% to 15% increase in healing) in subgroups of patients with ulcer durations of 12 months or less or size of 10 cm or less. Additional studies 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.

Deep Dermal Burns
For individuals who have deep dermal burns who receive bioengineered skin substitutes (i.e., 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 U.S. Food and Drug Administration approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. Comparative studies have demonstrated improved outcomes for biosynthetic skin substitute Integra Dermal Regeneration Template for the treatment of burns. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have deep dermal burns who are treated with the ReCell autologous cell harvesting device, the evidence includes 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. 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 a 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 a small series (e.g., 5 patients). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
Not applicable.

Related Policies

- Amniotic Membrane and Amniotic Fluid

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

Regulatory Status

State
The Women's Health and Cancer Rights Act (WHCRA) helps protect many women with breast cancer who choose to have their breasts rebuilt (reconstructed) after a mastectomy. Mastectomy is surgery to remove all or part of the breast. This federal law requires most group insurance plans that cover mastectomies to also cover breast reconstruction. It was signed into law on October 21, 1998. The United States Departments of Labor and Health and Human Services oversee this law.

The U.S. Food and Drug Administration (FDA) does not refer to any single product or class of products as "skin substitutes". Products in this review cover products that do not require FDA approval or clearance as well as a number of products cleared through the 510(k) pathway with a variety of FDA product codes. A large number of artificial skin and soft-tissue products are commercially available or in development. Commercial availability is not a reflection of a product's regulatory status. The following section summarizes a subset of commercially available skin and soft-tissue substitutes. This is not a complete list of all commercially available products. 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 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.

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.

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

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

mVASC® (MicroVascular Tissues, Inc.) is a microvascular tissue structural allograft made of small blood vessels and extracellular matrix, inherent non-viable cells, and associated biological signaling factors harvested from subcutaneous tissue of cadaveric human donors.

TheraSkin® (LifeNet Health) 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.

Although frequently used by surgeons for breast reconstruction, the 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. The 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, the 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

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

Helicoll (Encol) is an acellular collagen matrix derived from bovine dermis. In 2004, it was cleared 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 bums, 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 to IV) and venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, donor sites, and grafts.

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

Oasis™ Wound Matrix (Cook Biotech) is a collagen scaffold (extracellular matrix) derived from porcine small intestinal 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.

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.

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.

FDA Product codes: KGN, FTL, FTM.

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.

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.

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.

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 codes: FTM, PFC, OCE, ODS.

Autologous Cell Harvesting Device
Recell® (Avita Medical) was initially approved by the FDA in September 2018 under the premarket approval (PMA) process (PMA BP170122). It is an autologous cell harvesting device indicated for the treatment of acute partial-thickness thermal burn wound when used by an appropriately-licensed healthcare professional at the patient's point of care to prepare autologous RES Regenerative Epidermal Suspension. The initial indication was for use in patients 18 years of age and older in combination with meshed autografting. Subsequently, indications were expanded to include direct application to acute partial-thickness thermal burn wounds in patients 18 years of age and older or application in combination with meshed autografting for acute full-thickness thermal burn wounds in pediatric as well as adult patients and for and full-thickness skin defects after traumatic avulsion (e.g., degloving) or surgical excision (e.g., necrotizing tissue infection) or resection (e.g., skin cancer) in patients 15 years of age and older.

FDA product code: QCZ.

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.

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.

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.

FDA product codes: FRO, MDD, MGR.

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.

Nerve Wraps
Nerve wraps can be used for peripheral nerve repair. They are often made from biocompatible materials like collagen, designed to encase injured peripheral nerves. It provides a barrier between the nerve and surrounding tissue, minimizing scarring and promoting a conducive environment for nerve healing. Their application is ideal for cases where the nerve is intact, but needs protection from scarring or compression.

AxoGuard® nerve connector (Axogen, Inc) is an implant derived from small intestine submucosa designed to protect injured and compressed nerves. Other FDA 510K approved nerve wraps include: Flexibile Collagen Nerve Cuff (Collagen Matrix, Inc), Mochida Nerve Cuff (Mochida Pharmaceutical Co.), NervAlign Nerve Cuff (Renerve, Ltd), Nerve tape (BioCircuit Technologies, Inc), Neurawrap (Integra LifeSciences, Corp), NeuroMend (Stryker Orthopedics), NeuroShield (Monarch bioimplants, GmBH), Reinforce flexible Collagen Nerve Cuff (Collagen Matrix, Inc), and Versawrap nerve protector (Alafair Biosciences, Inc).

FDA product code: JXI.

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

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 - 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.

There is no standard definition of "skin substitute". Products reviewed in the following sections include products that do not require U.S. Food and Drug Administration (FDA) approval or clearance as well as a number of products cleared through the 510(k) pathway with a variety of FDA product codes. The FDA product codes that include these products are not limited to skin substitute products and may include other indications not related to wound healing or wound care.

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

Populations

The relevant population of interest is individuals 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 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

Ng et al (2024) conducted a systematic review and meta-analysis comparing postoperative complications and patient-reported outcomes between patients who received ADM and those who did not.[6] Prospective cohort studies and RCTs were included (9 studies; N=3161). There were no significant differences in postoperative outcomes between the ADM and non-ADM groups for key complications such as seroma (p=.51), hematomas (p=.20), infections (p=.21), wound dehiscence (p=.09), reoperations (p=.70), implant loss (p=.27), or skin necrosis (p=.21).

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.[7] 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	*NS*
Implant loss	1.00	0.68 to 1.48	*NS*
Total complications	1.08	0.87 to 1.34	*NS*
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).[7]
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.[8] 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.[9] 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).[10] 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 at 3 months postoperative.[10] There were no statistically significant differences in the overall complication rates (6% vs. 13%; p=.3), severity of complications, or patient satisfaction between the AlloDerm and DermaMatrix groups at 2 years after definitive reconstruction.[11]

AlloDerm Versus DermACELL

Davison et al (2024) conducted a prospective randomized trial comparing AlloDerm with DermACELL in 55 patients undergoing bilateral nipple and/or skin-sparing mastectomies.[12] Patients served as their own controls and were blinded to the random assignment of the two products to the left or right breast. The findings revealed no significant differences in drain removal time or average drain output between the two groups. However, a notable difference was observed in seroma rates, with 30.91% of AlloDerm breasts experiencing seromas compared to 14.55% in DermACELL breasts (p<.05).

Additionally, incorporation rates were significantly higher for DermACELL at 99.8% compared to AlloDerm's 93.4% (p<.05). Both AlloDerm and DermACELL demonstrated a high success rate of 94.55% for reconstruction outcomes. Nonetheless, AlloDerm was associated with a higher incidence of seromas and a trend towards lower incorporation rates.

AlloDerm Versus Cortiva

Keane et al (2024) conducted an RCT comparing Cortiva with AlloDerm in patients who underwent either direct-to-implant (DTI) or tissue expander (TE) reconstruction (N=302).[13] The primary outcome measured was reconstructive failure, defined as premature explantation of TEs or DTI reconstructions before three months postoperatively. A total of 151 patients received AlloDerm (280 breasts) and 151 received Cortiva (277 breasts). The results showed no significant difference in reconstructive failure rates between the two ADMs, with AlloDerm at 9.3% and Cortiva at 8.3% (p=.68). Additionally, there were no notable differences in other complications or patient-reported outcomes between the groups. Seroma formation was more prevalent in the AlloDerm group (12%) compared to Cortiva (7.6%) and was statistically significant (odds ratio: 1.93; 95% CI: 1.01 to 3.67; p=.047).

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).[14] 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

					Interventions	
Author	Countries	Sites	Dates	Participants	Active	Comparator
Dikmans et al (2017)[14]	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; EU: European Union; 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)[14]				
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 individuals who are undergoing tendon repair is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals 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.[15] Twenty-two patients were randomized to GraftJacket augmentation and 20 patients to no augmentation. At a mean follow-up of 24 months (range, 12 to 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.[16] 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 individuals 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 following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals 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.[17] 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 (eg, 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.[18] 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.[19] 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.[20] From 2005 to 2007, AlloDerm was used to repair large (>200 cm^2) 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.[21] 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.[22] 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 (i.e., 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.[23] 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.[24]

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 individuals who have diabetic lower extremity ulcers is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

The relevant population of interest is individuals 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 12 weeks and 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.[25] 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.

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

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.[26] 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 Technology Evaluation Center (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.[27]

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.[28] 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).[29] 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).[30,31] 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 to 47 days) for the human reticular ADM group and 72 days (95% CI: 66 to 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.[32] 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.[33] 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)[33]			
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)
p	.010	.001	.028

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

mVASC

Tables 5 and 6 summarize the trial characteristics and results for RCTs of mVASC. Tables 7 and 8 evaluate study limitations.

Gould et al (2023) reported results of the HIFLO (Healing in Diabetic Foot Ulcers with Microvascular Tissue) Trial, a multicenter (6 US sites) RCT comparing weekly application of the processed microvascular tissue (PMVT) allograft, mVASC in addition to a standardized diabetic foot ulcer protocol versus standard wound care with a collagen alginate dressing control in 100 adults with Wagner Grade 1 and 2 diabetic foot ulcers of ≥4 weeks and <52 weeks duration.[34] Wound and local peripheral neuropathy assessment were performed weekly. The primary outcome of the study was complete wound closure at 12 weeks. The investigator and a blinded physician made the initial determination of wound closure, followed by adjudication and confirmation by an independent, blinded panel of plastic surgeons. All participants who attended at least 1 treatment visit were included in the analysis. There was missing data for 15 participants at week 12 (3 in mVASC vs. 12 in control) and 14 of these were missing due to adverse events related to the wound. These were included in the primary analysis and counted as wound healing failures. The mean age of participants was 60 years, 90% of participants were White and 10% were Black, and 66% of participants were men. At randomization, the mean size of the wound area was 3.3 cm and the mean duration of the wound was 15 weeks. The proportion of participants with complete wound closure at week 12 was 74% (37/50) for mVASC versus 38% (19/50) for control (p<.001). Of the wounds that healed, the mean time to healing was also statistically significantly faster for the mVASC group (54 days; 95% CI, 46 to 61 vs 64 days; 95% CI, 57 to 72; p=.009). The 10-point Semmes-Weinstein monofilament (SWM) test of peripheral neuropathy also favored mVASC (118% vs. 11%; p=.028). No adverse events or serious adverse events related to the study treatment or the procedure were reported. There were 11 adverse events (3, mVASC vs. 8, control) reported that were related to the wound.

Table 5. Randomized Controlled Trial of mVASC for Diabetic Foot Ulcers- Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Gould 2023; HIFLO[34]	US	6	2017-2020	Adults with chronic Wagner Grade 1 or 2 DFU Mean age, 60 y 90% White 10% Black 66% Male Mean wound size 3.3 cm	mVASC + SOC (n=50)	SOC (n=50)

DFU: Diabetic Foot Ulcers; HIFLO: Healing in Diabetic Foot Ulcers with Microvascular Tissue; SOC: Standard of Care

Table 6. Randomized Controlled Trial of mVASC for Diabetic Foot Ulcers- Results

Study	Wounds Healed	Time to Heal	% Area Reduction	Adverse events
Gould 2023; HIFLO[34]	at 12 weeks	by 12 weeks	at 12 weeks	
N analyzed	100	56	100	100
mVASC	74% (37/50)	Mean, 54 d	76%	3
SOC	38% (19/50)	Mean, 64 d	24%	8
p-value	<.001	.009	.009	

HIFLO: Healing in Diabetic Foot Ulcers with Microvascular Tissue; SOC: Standard of Care

Table 7. Randomized Controlled Trial of mVASC for Diabetic Foot Ulcers- Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Gould 2023; HIFLO[34]	4. Lack of racial and ethnic diversity				1. follow-up not sufficient to determine ulcer recurrence.

HIFLO: Healing in Diabetic Foot Ulcers with Microvascular Tissue

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 8. Randomized Controlled Trial of mVASC for Diabetic Foot Ulcers- Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Gould 2023; HIFLO[34]			1. Registered retrospectively in European registry			3. Confidence intervals not reported

HIFLO: Healing in Diabetic Foot Ulcers with Microvascular Tissue
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

TheraSkin Versus Standard of Care

Tables 9 and 10 summarize the trial characteristics and results for RCTs of TheraSkin compared to SOC. Tables 11 and 12 evaluate study limitations.

Armstrong et al (2022) reported results of an RCT including 100 adults with non-healing Wagner 1 diabetic foot ulcers comparing Theraskin (n=50) to SOC (n=50).[35] The index ulcer had to have been present for greater than 4 weeks and less than 1 year with a minimum size of 1.0 cm^2 and a maximum size of 25 cm^2. Standard of care included glucose monitoring, weekly debridement as appropriate, and an offloading device. The dressing in the SOC group was calcium alginate (Fibracol Plus). The primary outcome was the proportion of full-thickness wounds healed at 12 weeks. Wound healing was assessed initially by the investigator and confirmed by blinded adjudication panel. Wounds were closed when there was 100% re-epithelization and no drainage. The mean age of participants was 60 years; 53% of participants were male, 70% were White, and 15% were Black. The mean wound area at baseline was 4.1 cm^2. Participants who did not have healing of at least 50% by 6 weeks were allowed to seek alternative rescue wound care (TheraSkin, n=1; SOC, n=11). In addition, 3 participants in the TheraSkin group and 8 in the SOC group had worsening of the wound or an adverse event before week 12. All enrolled participants were included in analysis and missing data were imputed using last observation carried forward. The percent of participants with complete wound healing at week 12 was 76% (38/50) in the intervention group compared with 36% (18/50) in the SOC group ($p<.01$). The mean percent area reduction at 12 weeks was 77.8% in the TheraSkin group compared with 49.6% in the SOC group ($p<.01$). There were no statistically significant differences between groups in QOL or pain score measures.

Table 9. Randomized Controlled Trial of TheraSkin vs. SOC for Diabetic Foot Ulcers- Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Armstrong (2022); NCT04040426[35]	US	5	2019-2021	Adults with non-healing Wagner 1 DFUs Mean wound area, 4.1 cm^2 Mean age, 60 yrs 53% male 70% White 15% Black	TheraSkin (n=50)	SOC with calcium alginate dressing (n=50)

DFU: Diabetic Foot Ulcers;; SOC: standard of care

Table 10. Randomized Controlled Trial of TheraSkin vs. SOC for Diabetic Foot Ulcers- Results

Study	Wounds Healed	Time to Heal	% Area Reduction	Adverse events
Armstrong (2022); NCT04040426[35]	at 12 weeks	by 12 weeks	at 12 weeks	
N analyzed	100	100	100	100
TheraSkin	76% (38/50)	Mean, 47 days (95% CI, 39 to 55)	78% (SD=63)	2
SOC	36% (18/50)	Mean, 65 days (95% CI, 58 to 73)	50% (SD=98)	4
p-value	<.01	<.01	<.01	NR

CI: confidence interval; NR: not reported; SD: standard deviation; SOC: standard of care

Table 11. Randomized Controlled Trial of TheraSkin vs. SOC for Diabetic Foot Ulcers- Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Armstrong (2022); NCT04040426[35]	4. Lack of racial and ethnic diversity				1. follow-up not sufficient to determine ulcer recurrence.

SOC: standard of care.

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 12. Randomized Controlled Trial of TheraSkin vs. SOC for Diabetic Foot Ulcers- Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Armstrong (2022); NCT04040426[35]		1. Investigators not blinded		2. Missing data imputed by last observation carried forward; no sensitivity analyses provided		

SOC: standard of care.
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

TheraSkin Versus Dermagraft

Sanders et al (2014) reported on an (N=23) industry-funded randomized comparison of TheraSkin (cryopreserved human skin allograft with living fibroblasts and keratinocytes) and Dermagraft for diabetic foot ulcers.[36] Wound size at baseline ranged from 0.5 to 18.02 cm^2; the average wound size was about 5 cm^2 and was similar for the 2 groups (p=.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 (N=29) RCT.[37] 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.

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

RCTs reporting complete wound healing outcomes with at least 12 weeks of follow-up have demonstrated the efficacy of Apligraf, Dermagraft, AlloPatch, Integra Dermal Regeneration Template, Integra Flowable Wound Matrix, mVASC, and TheraSkin over SOC for the treatment of diabetic lower-extremity ulcers.

Bioengineered Skin Substitutes Other Than Apligraf, Dermagraft, AlloPatch, Integra, mVASC, or TheraSkin

GraftJacket Regenerative Tissue Matrix

Brigido et al (2004) reported a (N=40) randomized pilot study comparing GraftJacket with conventional treatment for chronic nonhealing diabetic foot ulcers.[38] 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.[39] 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 to 12 weeks) and 7.0 weeks for control (range, 2 to 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.

Reyzelman and Bazarov (2015)[40] 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)[41] 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 Rey Zelman 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.[42] 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.[43] 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 13), 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.

Table 13. 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)[43]						
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	*NS*	.028	.049

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

Cytal (MatriStem) Versus Dermagraft

Frykberg et al (2017) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cytal (a porcine urinary bladder-derived extracellular matrix) versus Dermagraft in 56 patients with diabetic foot ulcers.[44] The mean duration of ulcers before treatment was 263 days (range, 30 to 1095 days). The primary outcome was the percent wound closure with up to 8 weeks of treatment using blinded evaluation of photographs. The ITT analysis found complete wound closure in 5 (18.5%) wounds treated with Cytal compared with 2 (6.9%) wounds treated with Dermagraft (p=not significant [*NS*]). Quality of life, measured by the Diabetic Foot Ulcer Scale, improved from 181.56 to 151.11 in the Cytal group and from 184.46 to 195.73 in the Dermagraft group (p=.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

Lantis et al (2021) reported on a multicenter RCT comparing PriMatrix plus SOC to PriMatrix alone in 226 patients with diabetic foot ulcers (Tables 14 and 15).[45]

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 16 and 17).

Table 14. Randomized Controlled Trial of PriMatrix for Diabetic Foot Ulcers- Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Lantis et al (2021)[45] NCT03010319	US	21	2019-2020	Diabetic foot ulcer for a minimum of 2 weeks, adequate vascular	PriMatrix plus standard of	Standard of care n = 104

Study	Countries	Sites	Dates	Participants	Interventions
				perfusion to the affected extremity	care n = 103

Table 15. Randomized Controlled Trial of PriMatrix for Diabetic Foot Ulcers- Results

Study	Wound Healed at 12 weeks	Median Time to Heal, days (range)	AEs
Lantis et al (2021)[45] 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-value	.008	.362	

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

Table 16. Randomized Controlled Trial of PriMatrix for Diabetic Foot Ulcers- Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Lantis et al (2021)[45] 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.		1. 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 17. 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)[45] 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

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.[46] 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.[47] 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.

Kerecis Omega3 Wound

Lullove et al (2021, 2022) reported interim results and Lantis et al (2023) reported the final results of a RCT of Omega3 Wound (Kerecis) plus standard wound care compared to standard care alone in individuals with diabetic lower extremity skin ulcers (Table 18).[48,49,50] 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 19. At 12 weeks, the complete healing rate was significantly higher in the intervention arm (57% vs 31%), 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 = 65), there was a larger percent wound reduction in the intervention group (86% vs 64%; p =.03). Of the 45 participants whose wound healed during the 12 weeks of the trial, 42 were available for follow-up 6 to 12 months following healing. 3 (11%) ulcer recurrences were reported in the intervention arm compared to 1 (7%) in the control arm.

Study limitations are detailed in Tables 20 and 21. Notably, 2 larger RCTs are registered and reported as completed but have not been published.

Table 18. Randomized Controlled Trial of Omega3 Wound for Diabetic Foot Ulcers-Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Lantis et al (2023)[50] Lullove et al (2021)[48,49] NCT04133493	US	16	2019-2022	Diabetic foot ulcer for a minimum of 4 weeks, adequate renal function and perfusion to the affected extremity Mean age, 60 y 69% Men 80% White 7% Black Mean wound size, 4.4 cm	Omega3 Wound plus standard of care (n=51)	Standard of care (n=51)

Table 19. Randomized Controlled Trial of Omega3 Wound for Diabetic Foot 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
Lantis et al (2023)[50] Lullove et al (2021)[48,49] NCT04133493				
N analyzed	102		65	
Omega3 Wound	57 % (29/ 51)	Mean 7 weeks in both groups	86%	3
Standard Care	31 % (16/ 51)		64%	5
p-value	.02		. 03	

Table 20. Randomized Controlled Trial of Omega3 Wound for Diabetic Foot Ulcers- Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Lantis et al (2023)[50] Lullove et al (2021)[48,49] NCT04133493	4. Lack of racial and ethnic diversity		3.Standard of care patients received additional dressing changes at home, which could have potentially exposed the wound to unknown factors.		

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 21. Randomized Controlled Trial of Omega3 Wound 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 (2023)[50] Lullove et al (2021)[48,49] NCT04133493			3. Two larger RCTs are reported as completed on clinicaltrials.gov but have not been published (NCT04257370 and NCT04537520)	1, 2. 25% of participants did not complete week 12. Although they were included in the primary ITT analysis, the method of imputation was unclear.		3. Confidence intervals not reported

ITT: intention-to-treat; RCT: randomized controlled trial.
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, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies. Keresis has RCTs that are reported as completed on clinicaltrials.gov but which have not been published (NCT04257370 and NCT04537520).

Lower-Extremity Ulcers Due to Venous Insufficiency

Clinical Context and Therapy Purpose

The purpose of bio-engineered soft tissue substitutes in individuals 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 following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals 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.[51] 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.[52] 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 mm^2) 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.[27]

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.[53] 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).[54] 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.[55] 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%).

Section 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).[56] 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. The 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.

DermACELL
Cazzell (2019) published an RCT on DermACELL ADM for venous leg ulcers in 18 patients (see Table 22).[57] 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.[43] 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 22. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Cazzell (2019) NCT01970163[57]	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

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% to 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 DermACELL (ADM) was not more effective than SOC.

Deep Dermal Burns
Clinical Context and Therapy Purpose
The purpose of bio-engineered soft tissue substitutes in individuals who have deep dermal burns is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations
The relevant population of interest is individuals 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.[58] 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, 10´5 cm test sites on each of 10 burn patients.[59] 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).[60] Once vascularized (about 14 to 21 days), the Silastic epidermis was stripped and replaced with thin (0.05 to 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 to 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% to 95%) who were treated with Integra Dermal Regeneration Template.[61] 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.[62] 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 to 100%) for acute burn injuries and 95% (range 0 to 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.[63]

Omega3 Wound

Luze et al (2022) conducted a systematic review of the use of acellular fish skin grafts in burn wound management.[64] 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 23).[65,66]

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 24 and limitations in Tables 25 and 26. 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 23. Randomized Controlled Trials of ReCell for Thermal Burns- Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Holmes et al (2018)[66] 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 autografing for definitive closure.	ReCell device N = 101	Meshed STSG Treatment N = 101
Holmes et al (2019)[65] 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 24. 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)[66] 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)[65] NCT02380612							
ReCell plus STSG	50%	24/26 (92%)		368 (SD 150) cm^2	NSD between groups in treatment	NSD in subject satisfaction with	NSD between groups in pre-
STSG alone	48%	22/26 (85%)		264 (SD 119) cm^2			

Between-group difference	-7.7% Upper limit of the 97.5% CI 6.4% (i.e., within the pre-defined non-inferiority margin 10%)		32%; p <.001	area pain from week 1 to week 12 or week 52	appearance or in scar assessment at any time point	specified safety events 17 individuals (57%) experienced AEs at control and ReCell sites; 27% had mild AEs, 37% moderate AEs. 1 death, attributed to underlying condition

AE: adverse events; CI: confidence interval; NSD: no significant difference; SD: standard deviation; STSG: Split-thickness skin grafts; VAS: visual analog scale.

Table 25. 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)[66] NCT01138917					
Holmes et al (2019)[65] 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 26. 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)[66] NCT01138917				83/101 participants evaluated in modified per protocol analysis	noninferiority margin based on 90 subjects	
Holmes et al (2019)[65] NCT02380612				26/30 participants evaluated in		3. confidence intervals not reported

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
				per protocol analysis		

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.[67]

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.

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 porcine small intestinal submucosa (SIS) extracellular matrix (ECM).[68] 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.[69] 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.[70] 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%).[71]

Peripheral Nerve Injuries

The Cochrane Collaboration published a meta-analysis of bioengineered nerve conduits and wraps for repairs of peripheral nerves of the upper extremity.[72] The authors included only RCTs or quasi-RCT experimental studies and found 5 which included the desired interventions and had follow-up periods of at least 12 months. A total of 213 participants were included in the studies, which compared nerve reconstruction with artificial wraps or conduits to standard repair either with direct end-to-end epineural repair or with autologous nerve grafting. Sensory recovery assessed with the British Medical Research Council (BMRC) grading scale was higher in the wrap or conduit group than in standard repair with very low certainty of evidence on Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) at 12 months (mean difference [MD], 0.03; range, -0.43 to 0.49) and 24 months follow-up (MD, 0.01; 95% CI, -0.06 to 0.08). Rosen model instrument (RMI) comparisons between conduit or wrap versus standard repair revealed no between-group differences through 24 months (MD, -0.17; 95% CI, -0.38 to 0.05; p=.13) and was determined to have low certainty of evidence; findings at 5 years follow-up in a single study found a greater improvement in the conduit or wrap group, but the estimate also had low certainty of evidence (MD, 0.23; 95% CI, 0.07 to 0.38). The rate of adverse event occurrence may be greater in patients treated with nerve wraps or conduits than with standard techniques, but the evidence had a GRADE rating reflected a very low certainty of evidence (risk ratio [RR], 7.15; 95% CI, 1.74 to 29.42). The authors also sought BMRC muscle strength scores, which were not reported in the included studies. The authors concluded that based on the currently available high-quality evidence, the use of currently available nerve repair devices is not supported over the standard of care due to heterogeneity in included participants, the pattern of injury, timing of repair, timing of outcome assessment, and choice of outcome measurement scales. A limitation of this systematic review is that they did not explicitly separate studies by the use of nerve conduits versus wraps for further analysis.

Miscellaneous

In addition to indications previously reviewed, off-label uses of bioengineered skin substitutes have included inflammatory ulcers (e.g., pyoderma gangrenosum, vasculitis), scleroderma digital ulcers, postkeloid removal wounds, genetic conditions, and variety of other conditions.[73] 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).[74] No controlled trials were identified for these indications.

Summary of Evidence

Breast Reconstruction

For individuals who are undergoing breast reconstruction who receive allogeneic acellular dermal matrix (ADM) products, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life (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 studies 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, Integra, mVASC, or TheraSkin, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. Randomized controlled trials reporting complete wound healing outcomes with at least 12 weeks of follow-up have demonstrated the efficacy of AlloPatch (reticular ADM), Apligraf and Dermagraft (living cell therapy), Integra (biosynthetic), mVASC, and TheraSkin over the standard of care (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, Integra, mVASC, or TheraSkin, 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, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies. An RCT of Omega3 Wound

(Kerecis) has been published and 2 larger RCTs are registered and reported as completed but have not been published. 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. Randomized controlled trials 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% to 15% increase in healing) in subgroups of patients with ulcer durations of 12 months or less or size of 10 cm or less. Additional studies 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.

Deep Dermal Burns

For individuals who have deep dermal burns who receive bioengineered skin substitutes (i.e., 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 U.S. Food and Drug Administration approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. Comparative studies have demonstrated improved outcomes for biosynthetic skin substitute Integra Dermal Regeneration Template for the treatment of burns. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have deep dermal burns who are treated with the ReCell autologous cell harvesting device, the evidence includes 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. 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 a 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 a small series (e.g., 5 patients). The evidence is insufficient 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 U.S. professional society, an international society with U.S. 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 2023, NICE updated its guidance on the prevention and management of diabetic foot problems.[75] 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.[76] 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.[77]

In 2019, CMS reported that it is finalizing the proposal to continue the policy established in calendar year (CY) 2018 to assign skin substitutes to the low cost or high-cost group.[78] 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 (PFS) 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."[79]

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 27.

Table 27. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06616844[a]	Evaluating the Efficacy of Porcine Placental Extracellular Matrix Augmented Wound Care Against Standard Wound Care for the Management of Diabetic Foot Ulcers: a Multi-center, Prospective, Observer-blinded, Randomized Controlled Clinical Trial.	194	Jul 2026
NCT06449638[a]	A Multicenter, Prospective, Randomized Controlled Modified Platform Trial Assessing the Efficacy of Multiple Human Placental-Based Skin Substitutes and Standard of Care Versus SOC Alone in the Treatment of Hard-to-Heal Diabetic Foot Ulcers	272	Aug 2026
NCT06831760	A Randomized, Controlled Clinical Trial Evaluating the Efficacy of Type-I Collagen-based Skin Substitute vs. Dehydrated Human Amnion/Chorion Membrane in the Treatment of Venous Leg Ulcers	50	Jun 2026
NCT06745557[a]	A Multicentre, Intra-patient Randomised Controlled Phase III Study to Confirm the Efficacy and Safety of DenovoSkin™, a Bilayer Engineered Collagen-based Skin Graft Composed of Autologous Fibroblasts and Keratinocytes, for the Treatment of Patients with Deep Partial and Full-thickness Burns	70	Jun 2028
NCT06557122[a]	A Randomized Controlled Clinical Trial Evaluating the Efficacy of a Unique Advanced Bioengineered Skin Substitute With Standard of Care Versus an Active Comparator With Standard of Care in the Treatment of Non-Healing Diabetic Foot Ulcers	24	Oct 2024
NCT05291169	A Randomized, Multicenter, Open Label Study Comparing Omeza Combination Therapy with Standard of Care to Standard of Care alone for Chronic Venous Leg Ulcers over the course of 4 weeks	54 (actual)	Mar 2024
NCT05084183	An Adaptive, Randomized, Controlled Trial Evaluating the Effectiveness of PermeaDerm® (PD) as Compared to Mepilex Ag® Used as Standard of Care in the Treatment of Adult and Pediatric Partial Thickness Burns	68	Nov 2023
NCT05439746	Clinical Trial to Assess the Efficacy of Microlyte Matrix on the Healing of Surgically Created Partial Thickness Donor Site Wounds on Patients Requiring Split-thickness Skin Grafting	53	Jan 2024
NCT05506215	A Prospective, Multicenter, Open Label, Randomized, Controlled Clinical Study Evaluating the Effect of NovoSorb ® SynPath™ Dermal Matrix Compared to Standard of Care (SOC) In the Treatment of Nonresponsive, Chronic Diabetic Foot Ulcers.	25 (terminated)	Feb 2024
NCT05372809	Closure Obtained With Vascularized Epithelial Regeneration for DFUs With SkinTE®	42 (terminated)	Feb 2024
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	Sept 2023
NCT04927702	Assessment of Wound Closure Comparing Synthetic Hybrid-Scale Fiber Matrix (Restrata®) With Standard of Care in Treating Diabetic Foot Ulcers (DFU) and With Living Cellular Skin Substitute (Apligraf®) in Treating Venous Leg Ulcers (VLU)	47 (terminated)	Aug 2024
NCT06035536	A Multi-Center, Randomized Controlled Clinical Investigation Evaluating Wound Closure With Symphony™ Versus Standard of Care in the Treatment of Non-Healing Diabetic Foot Ulcers	120	Dec 2024
NCT05517902	A Phase 3 Multicenter, Single-Arm, Open-Label Study Evaluating the Safety, Tolerability and Efficacy of StrataGraft® Construct in Pediatric Subjects With Deep Partial Thickness (DPT) Thermal Burns	1 (actual)	May 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04090424	A Pivotal Study to Assess the Safety and Effectiveness of NovoSorb® Biodegradable Temporizing Matrix (BTM) in the Treatment of Severe Burn Skin Injuries	150	Dec 2025
NCT03394612	A Phase II, Prospective, Intra-patient Randomised Controlled, Multicentre Study to Evaluate the Safety and Efficacy of an Autologous Bio-engineered Dermo-epidermal Skin Substitute (EHSG-KF; denovoSkin) for the Treatment of Full-Thickness Defects in Adults and Children in Comparison to Autologous Split-thickness Skin Grafts (STSG)	20	Dec 2026
Unpublished			
NCT06470087	A Randomized Controlled Clinical Trial Comparing High Purity Type-I Collagen-based Skin Substitute to Dehydrated Human Amnion/Chorion Membrane in the Treatment of Diabetic Foot Ulcers	28	Sept 2024
NCT02322554	The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers	50,000	Jan 2020
NCT03935386[a]	A Prospective Randomized Clinical Trial Comparing Multi-layer Bandage Compression Therapy With and Without a Biologically Active Human Skin Allograft (Theraskin) for the Treatment of Chronic Venous Leg Ulcers	100	Dec 2020
NCT03589586[a]	An Open-Label Trial to Assess the Clinical Effectiveness of DermACELL AWM in Subjects With Chronic Venous Leg Ulcers	100	Mar 2021
NCT03881254	A Multi-center, Randomized Controlled Clinical Trial Evaluating the Effects of SkinTE™ in the Treatment of Wagner One Diabetic Foot Ulcers	100	Jul 2021
NCT04198441	A Randomized, Multicenter, Open Label Study Comparing the Omeza® Products Bundle to Standard of Care for Chronic Venous Leg Ulcers and Chronic Diabetic Foot Ulcers	78	Dec 2021
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	260 (actual)	Nov 2022
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
NCT04918784	Assessment of Wound Closure Comparing Synthetic Hybrid-Scale Fiber Matrix (Restrata®, Acera Surgical, Inc.) With Standard of Care in Treating Diabetic Foot Ulcer	46	Dec 2022
NCT05883098	Effectiveness of Supra SDRM® vs. Fibracol Plus Collagen in the Treatment of Diabetic Foot Ulcers: a Pilot Randomized Controlled Trial	30	Jun 2023

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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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
  - Current treatment plan
  - 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
- Medical record documentation of need to combine specific products, when more than one product is requested at one time

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

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

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

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)
	15011	Harvest of skin for skin cell suspension autograft; first 25 sq cm or less ***(Code effective 1/1/2025)***
	15012	Preparation of skin cell suspension autograft, requiring enzymatic processing, manual mechanical disaggregation of skin cells, and filtration; first 25 sq cm or less of harvested skin ***(Code effective 1/1/2025)***
	15013	Preparation of skin cell suspension autograft, requiring enzymatic processing, manual mechanical disaggregation of skin cells, and filtration; first 25 sq cm or less of harvested skin ***(Code effective 1/1/2025)***
	15014	Preparation of skin cell suspension autograft, requiring enzymatic processing, manual mechanical disaggregation of skin cells, and filtration; each additional 25 sq cm of harvested skin or part thereof (List separately in addition to code for primary procedure) ***(Code effective 1/1/2025)***
	15015	Application of skin cell suspension autograft to wound and donor sites, including application of primary dressing, trunk, arms, legs; first 480 sq cm or less ***(Code effective 1/1/2025)***
	15016	Application of skin cell suspension autograft to wound and donor sites, including application of primary dressing, trunk, arms, legs; each additional 480 sq cm or part thereof (List separately in addition to code for primary procedure) ***(Code effective 1/1/2025)***
	15017	Application of skin cell suspension autograft to wound and donor sites, including application of primary dressing, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 480 sq cm or less ***(Code effective 1/1/2025)***
	15018	Application of skin cell suspension autograft to wound and donor sites, including application of primary dressing, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 480 sq cm or part thereof (List separately in addition to code for primary procedure) ***(Code effective 1/1/2025)***
HCPCS	A2002	Mirragen Advanced Wound Matrix, per sq cm

Type	Code	Description
	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
	A2020	AC5 Advanced Wound System (AC5)
	A2021	NeoMatriX, per sq cm
	A2022	InnovaBurn or InnovaMatrix XL, per sq cm
	A2023	InnovaMatrix PD, 1 mg
	A2024	Resolve or xenopatch sq cm
	A2025	Miro3D, per cu cm
	A2026	Restrata MiniMatrix, 5 mg
	A2027	Matriderm per sq cm
	A2028	Micromatrix flex, per mg
	A2029	Mirotract wound matrix sheet, per cu cm
	A2030	Miro3d Fibers, Per Milligram ***(Code effective 04/1/2025)***
	A2031	Mirodry Wound Matrix, Per Square Centimeter (***Code effective 04/1/2025)***
	A2032	Myriad Matrix, Per Square Centimeter (***Code effective 04/1/2025)***
	A2033	Myriad Morcells, 4 Milligrams (***Code effective 04/1/2025)***
	A2034	Foundation Drs Solo, Per Square Centimeter (***Code effective 04/1/2025)***
	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
	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

Type	Code	Description
	C9364	Porcine implant, Permacol, per sq cm
	Q4100	Skin substitute, not otherwise specified
	Q4101	Apligraf, per sq cm
	Q4102	Oasis wound matrix, per sq cm
	Q4103	Oasis burn matrix, per sq cm
	Q4104	Integra bilayer matrix wound dressing (BMWD), per sq cm
	Q4105	Integra dermal regeneration template (DRT) 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

Type	Code	Description
	Q4195	Puraply, per square cm
	Q4196	Puraply am, per square cm
	Q4197	Puraply xt, per square cm
	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
	Q4323	AlloPLY, 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
11/01/2025	New policy.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status
In making a determination that any procedure, treatment, therapy, drug, biological product, facility, equipment, device, or supply is "experimental or investigational" by the Plan, the Plan shall refer to evidence from the national medical community, which may include one or more of the following sources:

1. Evidence from national medical organizations, such as the National Centers of Health Service Research.
2. Peer-reviewed medical and scientific literature.
3. Publications from organizations, such as the American Medical Association (AMA).
4. Professionals, specialists, and experts.

5. Written protocols and consent forms used by the proposed treating facility or other facility administering substantially the same drug, device, or medical treatment.
6. An expert physician panel selected by one of two organizations, the Managed Care Ombudsman Program of the Medical Care Management Corporation or the Department of Managed Health Care.

Feedback

Blue Shield of California Promise Health Plan is 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 Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

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

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan 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 member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.