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Bio-Engineered Skin and Soft Tissue Substitutes

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Surgery

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I. 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.

Breast Reconstruction

For individuals who are undergoing breast reconstruction who receive allogeneic ADM products, the evidence includes a randomized controlled trial (RCT) and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. A recent systematic review found no difference in overall complication rates with ADM allograft compared to standard procedures for breast reconstruction. Reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM. However, capsular contracture and malposition of implants may be reduced. Thus, in cases where there is limited tissue coverage, including but not limited to when the use of ADM allows a single-stage reconstruction, the available evidence may be considered sufficient to permit conclusions about health outcomes that may inform patient decision making about reconstruction options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Tendon Repair

For individuals who are undergoing tendon repair who receive Graftjacket, the evidence includes 1 RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. One RCT identified found improved outcomes with Graftjacket ADM allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of patients is needed to evaluate consistency of the effect. The evidence is insufficient to determine the effects of the technology on health outcomes.

Surgical Repair of Hernias or Parastomal Reinforcement

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

Diabetic Lower-Extremity Ulcers

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

For individuals who have diabetic lower-extremity ulcers who receive other ADM products other than AlloPatch, AmnioBand Membrane, Apligraf, Dermagraft, or Integra Dermal Regeneration Template, cryopreserved skin allograft, or xenogenic skin substitutes, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Additional study with a larger number of subjects is needed to compare the effect of other human ADM products, cryopreserved skin allograft (TheraSkin) and xenogenic skin substitutes (eg, Oasis Wound Matrix, PriMatrix) to the standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

Lower-Extremity Ulcers due to Venous Insufficiency

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

For individuals who have lower-extremity ulcers due to venous insufficiency who receive bioengineered skin substitutes other than Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. In a moderately large RCT, Dermagraft was not shown to be more effective than controls for the primary or secondary end points in the entire population and was only slightly more effective than controls (an 8%-15% increase in healing) in subgroups of patients with ulcer durations of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of the xenogenic PriMatrix skin substitute versus the current standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

Dystrophic Epidermolysis Bullosa

For individuals who have dystrophic epidermolysis bullosa who receive OrCel, the evidence includes case series. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. OrCel was approved under a humanitarian drug exemption for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. Outcomes have been reported in small series (eg, 5 patients). The evidence is insufficient to determine the effects of the technology on health outcomes.

Deep Dermal Burns

For individuals who have deep dermal burns who receive bioengineered skin substitutes (ie, Epicel, Integra Dermal Regeneration Template), the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, there are few skin substitutes approved, and the evidence is limited for each product. Epicel (living cell therapy) has received Food and Drug Administration approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. Comparative studies have demonstrated improved outcomes for biosynthetic skin substitute Integra Dermal Regeneration Template for the treatment of burns. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Clinical Input

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

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

II. Criteria/Guidelines

- A. Allogeneic acellular dermal matrix products (i.e., AlloDerm[®], AlloMax[™], AlloMend[®], DermACELL[™], DermaMatrix[™], FlexHD[®], FlexHD[®] Pliable[™], Graftjacket[®]) or Strattice are covered (subject to Limitations and Administrative Guidelines) in breast reconstructive surgery when one of the following criteria is met:
1. There is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required;
 2. There are viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis; or
 3. The infra-mammary fold and lateral mammary folds have been undermined during

mastectomy and re-establishment of these landmarks is needed.

- B. The use of allograft products is covered (subject to Limitations and Administrative Guidelines) for shoulder tendon repair.
- C. Treatment of chronic, non-infected, full-thickness diabetic lower extremity ulcers using AlloPatch®, Amnioband Membrane, Apligraf®, Dermagraft®, Apligraf, Dermagraft, Integra® Dermal Regeneration Template, Amniotic Membrane Graft (e.g., Biovance, Epifix, Grafix) is covered (subject to Limitations and Administrative Guidelines) when all of the following criteria are met:
 1. The ulcers have not adequately responded after six weeks of standard wound therapy*;
 2. The patient is on a comprehensive diabetic management program; and
 3. Reduction in pressure on a foot ulcer has been accomplished with appropriate modalities.
- D. Treatment of chronic, non-infected, partial or full-thickness lower extremity skin ulcers due to venous insufficiency with Apligraf® or Oasis™ Wound Matrix is covered (subject to Limitations and Administrative Guidelines) when all of the following criteria are met:
 1. The ulcers have not adequately responded after six weeks of standard wound therapy*;
 2. Compression bandages and/or graduated compression garments have been consistently applied; and
 3. Leg elevation and exercise have been encouraged.
- E. Treatment of dystrophic epidermolysis bullosa with OrCel™ is covered (subject to Limitations and Administrative Guidelines).
- F. Treatment of second- and third-degree burns using the following tissue-engineered skin substitutes is covered (subject to Limitations and Administrative Guidelines).
 1. Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30% when provided in accordance with the HDE specifications of the FDA).
 2. Integra Dermal Regeneration Template™

* Standard wound therapy includes:

- Evaluation of wound with documentation of measurements (length, width and depth) at baseline and at least weekly by a licensed medical professional;
- Application of moist topical dressings;
- Debridement of necrotic tissue, if present;
- Treatment of infection, if present;
- Evaluation and provision of adequate nutrition;
- Management of diabetes mellitus, if applicable; and
- Evaluation and management of peripheral artery disease, if applicable.

III. Limitations

- A. Bio-engineered skin and soft tissue substitutes have not been shown to improve health outcomes for all other conditions not listed under Criteria/Guidelines.
- B. All other bio-engineered skin and soft tissue substitutes have not been shown to improve health outcomes, including, but not limited to:
 1. ACell® UBM Hydrated Wound Dressing
 2. ACell® UBM Lyophilized Wound Dressing

3. Affinity™
4. AlloSkin™
5. AlloSkin™ RT
6. AlloWrap™
7. Alphaplex™ with MariGen Omega3™
8. AmnioFix®
9. Aongen™ Collagen Matrix
10. ArthroFlex™ (Flex Graft)
11. Atlas Wound Matrix
12. Atracent
13. Avagen Wound Dressing
14. Avaulta Plus™
15. Biobrane®
16. BioDfence/BioDfactor
17. CellerateRX®
18. Clarix® Flo
19. Collagen Sponge (Innocoll)
20. Collagen Wound Dressing (Oasis Research)
21. CollaGUARD®
22. CollaSorb™
23. CollaWound™
24. Collexa®
25. Collieva®
26. Conexa™
27. Coreleader Colla-Pad
28. CorMatrix®
29. CRXa™
30. Cymetra®
31. Cystal
32. Dermadapt™ Wound Dressing
33. DermaPure™
34. DressSkin
35. Dermavest™
36. Durepair Regeneration Matrix®
37. Endoform Dermal Template™
38. ENDURAGen™
39. Excellagen
40. E-Z Derm™
41. GammaGraft
42. Graftjacket® Xpress, injectable
43. GUARDIAN
44. HA Absorbent Wound Dressing
45. Helicoll
46. Hyalomatrix® (Laserskin®)

47. Hyalomatrix® PA
48. hMatrix®
49. Integra™ Flowable Wound Matrix
50. Integra™ Bilayer Wound Matrix
51. Jaloskin®
52. MariGen
53. MatriDerm®
54. MatriStem® Burn Matrix
55. MatriStem® Micromatrix
56. Matrix Collagen Wound Dressing
57. Matrix HD™
58. MediHoney®
59. Mediskin®
60. MemoDerm™
61. Microderm
62. Neox® Flo
63. NuShield™
64. Oasis® Burn Matrix
65. Oasis® Ultra Tri-Layer Matrix
66. Permacol™
67. PriMatrix™
68. PriMatrix™ Dermal Repair Scaffold
69. PuraPly
70. Puros® Dermis
71. Repliform®
72. Repriza™
73. Revitalon™
74. SIS Wound Dressing II
75. SS Matrix™
76. Stimulen™ Collagen
77. StrataGraft®
78. Suprathel®
79. SurgiMend®
80. Talymed®
81. TenoGlide™
82. TheraForm™ Standard/Sheet
83. TheraSkin®
84. TruSkin
85. Veritas® Collagen Matrix

IV. Administrative Guidelines

- A. Precertification is required for the application of Apligraf, Dermagraft, Epicel, OrCel, Integra Dermal Regeneration Template, Amniotic Membrane graft (e.g., Biovance, Epifix, Grafix), TransCyte, and Oasis Wound Matrix. To precertify, complete HMSA's [Precertification Request](#) and mail or fax the form, or use iExchange as indicated. Include the following information if applicable:
1. Clinical notes documenting patient's compliance with a diabetic management program.
 2. The exact location of the ulcer and initial ulcer size.
 3. Duration and description of the standard treatments that were tried and failed.
 4. Documentation of the presence of dystrophic epidermolysis bullosa if this is the indication.
- B. Precertification is not required for acellular dermal matrix products or Strattice when used in breast reconstruction surgery. HMSA reserves the right to perform retrospective reviews using the above criteria to validate if services rendered met payment determination criteria.
- C. Precertification is not required for allograft products used in shoulder tendon repair. HMSA reserves the right to perform retrospective reviews using the above criteria to validate if services rendered met payment determination criteria.
- D. Applicable HCPCS codes:

HCPCS Code	Description
Q4100	Skin substitute, not otherwise specified
Q4101	Apligraf, per square centimeter
Q4102	Oasis Wound Matrix, per square centimeter
Q4105	Integra Dermal Regeneration Template (DRT), per square centimeter
Q4106	Dermagraft, per square centimeter
Q4107	Graftjacket, per square centimeter
Q4116	AlloDerm, per square centimeter
Q4122	Dermacell, per square centimeter
Q4124	Oasis Ultra Tri-Layer Wound Matrix, per square centimeter
Q4128	Flex HD, Allopatch HD or Matrix HD, per square centimeter [when used for Flex HD]
Q4130	Strattice TM, per square centimeter
Q4132	Grafix core, per square centimeter
Q4133	Grafix prime, per square centimeter
Q4145	Epifix, injectable, 1 mg
Q4151	Amnioband or Guardian, per square centimeter
Q4154	Biovance, per square centimeter
Q4186	Epifix, per square centimeter

- E. HCPCS codes that do not meet payment determination criteria:

HCPCS Code	Description
C9349	Puraply, and Puraply Antimicrobial, any type, per square centimeter
C9354	Acellular pericardial tissue matrix of nonhuman origin (Veritas), per square centimeter

C9356	Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per square centimeter
C9358	Dermal substitute, native, non-denatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters
C9360	Dermal substitute, native, non-denatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters
C9363	Skin substitute, Integra Meshed Bilayer Wound Matrix, per square centimeter
C9364	Porcine implant, Permacol, per square centimeter
Q4103	Oasis Burn Matrix, per square centimeter
Q4104	Integra Bilayer Matrix Wound Dressing (BMWWD), per square centimeter
Q4108	Integra Matrix, per square centimeter
Q4110	PriMatrix, per square centimeter
Q4111	GammaGraft, per square centimeter
Q4112	Cymetra, injectable, 1 cc
Q4113	Graftjacket Xpress, injectable, 1 cc
Q4114	Integra Flowable Wound Matrix, injectable, 1 cc
Q4115	AlloSkin, per square centimeter
Q4116	AlloDerm, per square centimeter
Q4117	Hyalomatrix, per square centimeter
Q4118	Matristem micromatrix, per square centimeter
Q4119	Matristem wound matrix, per square centimeter
Q4120	MatriStem burn matrix, per square centimeter
Q4121	Theraskin, per square centimeter
Q4123	Alloskin RT, per square centimeter
Q4125	Arthroflex, per square centimeter
Q4126	Memoderm, Dermaspan, Transgraft or Integuply, per square centimeter
Q4127	Talymed, per square centimeter
Q4129	Unite Biomatrix, per square centimeter
Q4134	hMatrix, per square centimeter
Q4135	Mediskin, per square centimeter
Q4136	EZ-derm, per square centimeter
Q4137	Amnioexcel or BioDExCel, per square centimeter
Q4138	Biodfence Dryflex, per square centimeter
Q4139	Amniomatrix or BioDMatrix, injectable, 1 cc
Q4140	Biodfence, per square centimeter
Q4141	Alloskin AC, per square centimeter
Q4142	Xcm biologic tissue matrix, per square centimeter
Q4143	Repriza, per square centimeter
Q4146	TenSIX, per square centimeter
Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per square
Q4148	Neox 1k, per square centimeter
Q4149	Excellagen, 0.1 cc

Q4150	Allowrap DS or dry, per square centimeter
Q4152	Dermapure, per square centimeter
Q4153	Dermavest and Plurivest, per square centimeter
Q4155	Neox Flo or Clarix Flo, 1 mg
Q4156	Neox 100, per square centimeter
Q4157	Revitalon, per square centimeter
Q4158	MariGen, per square centimeter
Q4159	Affinity, per square centimeter
Q4160	NuShield, per square centimeter
Q4161	Bio-connekt wound matrix, per square centimeter
Q4162	Amniopro flow, bioskin flow, biorenew flow, woundex flow, amniogen-a, amniogen-c, 0.5 cc
Q4163	Amniopro, bioskin, biorenew, woundex, amniogen-45, amniogen-200, per square centimeter
Q4164	Helicoll, per square centimeter
Q4165	Keramatrix, per square centimeter
Q4169	Artacent wound, per square centimeter

V. Background

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

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.

The preferred outcomes for the healing of lower-extremity ulcers and burn wounds are the

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

Other situations in which bioengineered skin products might substitute for living skin grafts include certain postsurgical states (eg, 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 (eg, bullous diseases) may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. Acellular dermal matrix products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and other conditions.

Regulatory Status

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

Acellular Dermal Matrix Products

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

AlloDerm® (LifeCell Corp.) is an ADM (allograft) tissue-replacement product created from native human skin and processed so that the basement membrane and cellular matrix remain intact. Originally, AlloDerm® required refrigeration and rehydration before use. It is currently available in a ready-to-use product stored at room temperature. An injectable micronized form of AlloDerm® (Cymetra) is available.

- AlloMax™ Surgical Graft (Bard Davol) is an acellular non-cross-linked human dermis allograft. (AlloMax was previously marketed as NeoForm™.)
- AlloPatch® (Musculoskeletal Transplant Foundation) is an acellular human dermis allograft derived from the reticular layer of the dermis and marketed for wound care. This product is also marketed as FlexHD® for postmastectomy breast reconstruction.
- FlexHD® (Musculoskeletal Transplant Foundation) is an acellular hydrated reticular dermis allograft derived from donated human skin.

- DermACELL™ (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL® and PRESERVON®.
- DermaMatrix™ (Synthes) is a freeze-dried ADM derived from donated human skin tissue.
- DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation.
- DermaPure™ (Tissue Regenix Wound Care) is a single-layer decellularized human dermal allograft for the treatment of acute and chronic wounds.
- Graftjacket® Regenerative Tissue Matrix (also called Graftjacket Skin Substitute; KCI) is an acellular regenerative tissue matrix that has been processed from human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells, while preserving dermal structure. Graftjacket Xpress® is an injectable product.

FDA product codes: FTM, OXF.

Xenogenic Products

Keramatrix® (Keraplast Research) is an open-cell foam comprised of freeze-dried keratin that is derived from acellular animal protein. In 2009, it was cleared for marketing by FDA through the 510(k) process under the name of Keratec. The wound dressings are indicated in the management of the following types of dry, light, and moderately exuding partial and full-thickness wounds: pressure (stage I-IV) and venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, donor sites, and grafts.

Helicoll (Encol) is an acellular collagen matrix derived from bovine dermis. In 2004, it was cleared for marketing by FDA through the 510(k) process for topical wound management that includes partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (eg, abrasions, lacerations, second-degree burns, skin tears), and surgical wounds including donor sites/grafts.

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

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

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

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

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

Oasis™ Wound Matrix (Cook Biotech) is a xenogeneic collagen scaffold derived from porcine small intestinal mucosa. In 2000, it was cleared for marketing by FDA through the 510(k) process for the management of partial- and full-thickness wounds, including pressure ulcers, venous ulcers,

diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds. FDA Product code: KGN.

Living Cell Therapy

Apligraf® (Organogenesis) is a bilayered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. Apligraf® is supplied as needed, in 1 size, with a shelf-life of 10 days. In 1998, it was approved by FDA for use in conjunction with compression therapy for the treatment of noninfected, partial- and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower-extremity ulcers nonresponsive to standard wound therapy. FDA product code: FTM.

Dermagraft® (Organogenesis) is composed of cryopreserved human-derived fibroblasts and collagen derived from newborn human foreskin and cultured on a bioabsorbable polyglactin mesh scaffold.

Dermagraft has been approved by FDA for repair of diabetic foot ulcers. FDA product code: PFC.

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

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

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

Biosynthetic Products

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

Integra® Dermal Regeneration Template (marketed as Omnigraft Dermal Regeneration Matrix; Integra LifeSciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It was approved by FDA for use in postexcisional

treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable because of the physiologic condition of the patient.

Integra™ Matrix Wound Dressing and Integra™ meshed Bilayer Wound Matrix are substantially equivalent skin substitutes that were cleared for marketing by FDA through the 510(k) process for other indications. Integra® Bilayer Wound Matrix (Integra LifeSciences) is designed to be used in conjunction with negative pressure wound therapy. The meshed bilayer provides a flexible wound covering and allows drainage of wound exudate. FDA product code: MDD.

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

Synthetic Products

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

VI. Rationale

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

Breast Reconstruction

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

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

Systematic Reviews

A 2016 meta-analysis by Lee and Mun included 23 studies (total N=6199 cases) on implant-based breast reconstruction that were published between February 2011 and December 2014. The analysis included 1 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 [MD], 79.63; 95% confidence interval [CI], 41.99 to 117.26; $p < 0.001$) and percentage of intraoperative filling (MD=13.30; 95% CI, 9.95 to 16.65; $p < 0.001$), and reduced the frequency of injection to complete expansion (MD = -1.56; 95% CI, -2.77 to -0.35; $p = 0.01$).

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

Outcome Measure	Relative Risk	95% Confidence Interval	p
Infection	1.42	1.02 to 1.99	0.04
Seroma	1.41	1.12 to 1.78	0.004
Mastectomy flap necrosis	1.44	1.11 to 1.87	0.006
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	<0.001
Implant malposition	0.21	0.07 to 0.59	0.003

ADM: acellular dermal matrix.

AlloDerm

Randomized Controlled Trials

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

Comparisons Between Products

AlloDerm vs DermaMatrix or FlexHD

A 2014 retrospective review by Liu et al compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts). Eighty-one percent of the sample was immediate reconstruction: 165 used AlloDerm and 97 used FlexHD. Mean follow-up was 6.4 months.

Compared with breast reconstruction without use of AlloDerm or FlexHD, ADM had a higher rate of

delayed healing (20.2% vs 10.3%), although this finding might have been related to differences in fill volumes. In univariate analysis, there were no significant differences in complications (return to operating room, surgical site infection, seroma, hematoma, delayed healing, implant loss) between AlloDerm and FlexHD. In multivariate analysis, there were no significant differences between AlloDerm and FlexHD for the return to the operating room, surgical site infection, seroma, or delayed healing. Independent risk factors for implant loss included the use of FlexHD, single-stage reconstruction, and smoking.

Brooke et al (2012) retrospectively reviewed complication rates when AlloDerm (n=49), DermaMatrix (n=110), or FlexHD (n=62) were used for tissue expander breast reconstruction.⁸ Clinically significant complications were defined as cellulitis, abscess, seroma, expander leak or puncture, skin necrosis,

wound dehiscence, or hematoma. Total clinically significant complication rates were 22% with AlloDerm, 15% with DermaMatrix, and 16% with FlexHD (p=NS). Infectious complication rates for the 3 products were the same (10%). When compared to breast reconstruction without an ADM (n=64), there were no significant differences in the total complication rates (17% vs 11%), but there was a trend toward a higher incidence of infectious complications (10% vs 2%, p=0.09)

Section Summary: Breast Reconstruction

Results of a systematic review found no difference in overall complication rates with ADM allograft compared to standard procedures for breast reconstruction. Reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM. However, rates of capsular contracture and malposition of implants may be reduced. Thus, in cases where there is limited tissue coverage, including but not limited to when the use of ADM allows a single-stage reconstruction, the available studies may be considered sufficient to permit conclusions about health outcomes.

Tendon Repair

Graftjacket

In 2012, Barber et al reported an industry-sponsored multicenter RCT of augmentation with Graftjacket acellular human dermal matrix for arthroscopic repair of large (>3 cm) rotator cuff tears involving 2 tendons. Twenty-two patients were randomized to Graftjacket augmentation, and 20 patients were randomized to no augmentation. At a mean follow-up of 24 months (range, 12-38) the American Shoulder and Elbow Surgeons score improved from 48.5 to 98.9 in the Graftjacket group and from 46.0 to 94.8 in the control group (p=0.035). The Constant score improved from 41 to 91.9 in the Graftjacket group and from 45.8 to 85.3 in the control group (p=0.008). The University of California, Los Angeles score was not significantly different between the 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 patients (14%) in the Graftjacket group and 9 patients (45%) in the control group. Although these results are promising, additional study with a larger number of patients is needed.

Section Summary: Tendon Repair

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

Surgical Repair of Hernias or Parastomal Reinforcement

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

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

AlloDerm as an Overlay

In 2007, Espinosa-de-los-Monteros et al retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases. 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. remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7 to 10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in 8 (24%) hernia recurrences. Fifteen (45%) of the AlloDerm patients developed a diastasis or bulging at the repair site. Seroma formation was only a problem in 2 patients.

AlloDerm vs FlexHD

A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery. From 2005 to 2007, AlloDerm was used to repair large (>200 cm²) symptomatic complicated ventral hernias that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD was used to repair

large complicated ventral hernias in patients meeting the same criteria (n=40). The 2 groups were comparable at baseline. At 1-year follow-up, all AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, true recurrence) requiring a second repair. Eleven (31%) patients in the FlexHD group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

Strattice vs Synthetic Mesh

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

Strattice vs No Reinforcement

Also in 2014, the PRISM Study Group reported a multicenter, double-blinded, randomized trial of Strattice for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies. 16 Patients were randomly assigned to standard stoma construction with no reinforcement (n=58) or stoma construction with Strattice as parastomal reinforcement (n=55). At 24-month follow-up (n=75), the incidence of parastomal hernias was similar for the 2 groups (13.2% of controls, 12.2% of study group).

Section Summary: Surgical Repair of Hernias or Parastomal Reinforcement

Acknowledging that the 2014 Bellows trial has not reached its primary end point, the limited evidence available at this time does not support a benefit of ADMs in hernia repair or prevention of parastomal hernia.

Diabetic Lower Extremity

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

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

Apligraf

In 2001, Veves et al reported on a randomized prospective study on the effectiveness of Apligraf (previously called Graftskin), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers.¹⁹ The study involved 24 centers in the United States; 208 patients were randomly assigned to ulcer treatment with Apligraf (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical débridement and adequate foot off-loading, was provided in both groups. Apligraf was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of 5 applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Apligraf-treated patients achieved complete wound healing compared with 36 (38%) in the control group ($p=0.004$). The Kaplan-Meier method median time to complete closure was 65 days for Apligraf, significantly lower than the 90 days observed in the control group ($p=0.003$). The rates of adverse reactions were similar between groups, with the exception of osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf group. The study concluded that application of Apligraf for a maximum of 4 weeks resulted in a higher healing rates compared with state-of-the-art treatment and was not associated with any significant AEs. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf, in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.

In 2010, Steinberg et al reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of noninfected diabetic foot ulcers. Study design and patient population were similar to the 208-subject U.S. study (previously described), which led to Food and Drug Administration (FDA) approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with noninfected neuropathic diabetic foot ulcers present for at least 2 weeks were enrolled in prospective, multicenter, open-label RCTs that compared Apligraf use in conjunction with standard therapy (sharp débridement, standard wound care, off-loading) to standard therapy alone. Pooling of data was performed because of the similarity and consistency of the 2 studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration, which was significantly longer in the European study (21 months vs 10 months in the U.S. study). Reported AEs by 12 weeks were comparable across treatment groups in the 2 studies. Efficacy measures demonstrated superiority of Apligraf treatment over control-treated groups in both studies. Combining the data from both studies, 55.2% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared

with 34.3% (46/134) of control subjects ($p < 0.001$), and Apligraf subjects had a significantly shorter time to complete wound closure ($p < 0.001$). The authors concluded that both the EU and U.S. studies exhibited superior efficacy and comparable safety for subjects treated with Apligraf compared with control subjects, and that the studies provided evidence of the benefit of Apligraf in treating diabetic foot ulcer.

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

Dermagraft

A 2003 pivotal multicenter FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft (human-derived fibroblasts cultured on mesh) or control. Over the 12-week study, patients received up to 8 applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91% compared with 78% for the control group. Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious AEs were attributed to Dermagraft. Ulcer infections developed in 10.4% of the Dermagraft patients compared with 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group (19% vs 32.5%). Retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft (5.5% vs 12.6%, $p = 0.031$).²⁴ Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

Cytal (MatriStem) vs Dermagraft

Frykberg et al (2016) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cytal, a porcine urinary bladder derived extracellular matrix) versus Dermagraft in 56 patients with diabetic foot ulcers.²⁵ The mean duration of ulcers before treatment was 263 days (range, 30-1095 days). The primary outcome was the percent wound closure with up to 8 weeks of treatment using blinded evaluation of photographs. Intention-to-treat (ITT) analysis found complete wound closure in 5 (18.5%) wounds treated with Cytal compared to 2 (6.9%) wounds treated with Dermagraft ($p = NS$). Quality of life, measured by the Diabetic Foot Ulcer Scale, improved from 181.56 to 151.11 in the Cytal group and from 184.46 to 195.73 in the Dermagraft group ($p = 0.074$). It should be noted that this scale is a subjective measure and patients were not blinded to treatment. Power analysis indicated that 92 patients would be required; further recruitment is ongoing for completion of the study.

TheraSkin vs Dermagraft

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

TheraSkin vs Apligraf

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

AlloPatch

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

Graftjacket Regenerative Tissue Matrix

Brigido et al reported a small (N=40) randomized pilot study of Graftjacket compared with

conventional treatment for chronic nonhealing diabetic foot ulcers in 2004. Control patients received conventional therapy with débridement, wound gel with gauze dressing, and off-loading. Graftjacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the Graftjacket group.

Preliminary 1-month results showed that, after a single treatment, ulcers treated with Graftjacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs 15%), width (50% vs 23%), area (73% vs 34%), and depth (89% vs 25%). With follow-up to 4 weeks, no data were reported on the proportion with complete closure or the mean time to heal. All grafts were incorporated into the host tissue.

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

In 2015, Reyzelman and Bazarov 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)³² with 28 patients (total N=154 patients). The time to heal was estimated for the 2004 study by Brigido, based on the average wound reduction per week. The estimated difference in time to heal was considerably larger for Brigido's 2004 study (-4.30 weeks) than for the other 2 studies that measured the difference in time to heal (-1.58 weeks and -1.10 weeks). Analysis of the proportion of wounds that healed included Brigido (2006) and Reyzelman (2009). The odds ratio (OR) in the smaller study by Brigido was considerably larger with a lack of precision in the estimate (OR=15.0; 95% CI, 2.26 to 99.64), and the combined odds ratio (3.75; 95% CI, 1.72 to 8.19) was not significant when analyzed using a random-effects model. Potential sources of bias, noted by Reyzelman and Bazarov, included publication and reporting biases, study selection biases, incomplete data selection, post hoc manipulation of data, and subjective choice of analytic methods. Overall, results of these studies do not provide convincing evidence that Graftjacket is more effective than SOC for healing diabetic foot ulcers. Additional trials with a larger number of subjects are needed to determine whether Graftjacket Regenerative Tissue Matrix improves health outcomes in this population.

DermACELL vs Graftjacket Regenerative Tissue Matrix

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

Integra Dermal Regeneration Template

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

Oasis Wound Matrix vs Regranex Gel

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

treatment to current SOC.

PriMatrix

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

In 2011, Karr published a retrospective comparison of PriMatrix and Apligraf in 40 diabetic foot ulcers.³⁷ The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. The criteria were: diabetic foot ulcers of 4 weeks in duration; ulcer to at least 1 cm² in diameter and to the depth of subcutaneous tissue; healthy tissue at the ulcer; adequate arterial perfusion to heal; and ability to off-load the diabetic ulcer. The time to complete healing for PriMatrix was 38 days with 1.5 applications compared with 87 days with 2 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to compare the efficacy of PriMatrix to current SOC or advanced wound therapies.

Section Summary: Diabetic Lower-Extremity Ulcers

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

Apligraf

Falanga et al reported a multicenter randomized trial of Apligraf living cell therapy in 1998.³⁸ A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or to compression therapy and treatment with Apligraf. Apligraf was applied up to a maximum of 5 (mean, 3.3) times per patient during the initial 3 weeks. The primary end points were the percentage of patients with complete healing by 6 months after initiation of treatment and the time required for complete healing. At 6-month follow-up, the percentage of patients healed was higher with Apligraf (63% vs 49%), and the median time to complete wound closure was shorter (61 days vs 181 days). Treatment with Apligraf was superior to compression therapy in healing larger (>1000 mm²) and deeper ulcers and ulcers of more than 6 months in duration. There were no symptoms or signs of rejection, and the occurrence of AEs was similar in both groups. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (Graftskin), in conjunction with good local wound care, met TEC criteria for the treatment of venous ulcers that fail to respond to conservative management.²⁰

Dermagraft

Dermagraft living cell therapy has been approved by FDA for repair of diabetic foot ulcers. Use of Dermagraft for venous ulcers is an off-label indication. In 2013, Harding et al reported an open-label multicenter RCT that compared Dermagraft plus compression therapy (n=186) to

compression therapy alone (n=180).³⁹ The trial had numerous inclusion/exclusion criteria that restricted the population to patients who had nonhealing ulcers with compression therapy but had capacity to heal. ITT analysis revealed no significant difference between the 2 groups in the primary outcome measure, the proportion of patients with completely healed ulcers by 12 weeks (34% Dermagraft vs 31% control). Prespecified subgroup analysis revealed a significant improvement in the percentage of wounds healed for ulcers of 12 months or less in duration (52% vs 37%) and for ulcers of 10 cm or less in diameter (47% vs 39%). There were no significant differences in the secondary outcomes of time to healing, complete healing by week 24, and percent reduction in ulcer area.

Oasis Wound Matrix

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

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

In a 2010 trial, Romanelli et al compared Oasis to a moist wound dressing (SOC) in 23 patients with mixed arteriovenous ulcers and 27 patients with venous ulcers.⁴² The trial was described as randomized, but the method of randomization was not described. After the 8-week study period, patients were followed monthly for 6 months to assess wound closure. Complete wound closure was achieved in 80% of the

Oasis-treated ulcers at 8 weeks compared with 65% of the SOC group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks compared with 8.3 weeks for the SOC group. Treatment with Oasis also increased the time to dressing change (5.2 days vs 2.1 days) and the

percentage of granulation tissue formed (65% vs 38%).

PriMatrix

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

Section Summary: Lower-Extremity Ulcers due to Venous Insufficiency

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

Dystrophic Epidermolysis

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

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

Deep Dermal Burns

Epicel

Epicel is FDA approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a total body surface area (TBSA) of 30% or more. It is unlikely that RCTs will be

conducted to evaluate whether Epicel improves health outcomes for this condition. One 2000 case series described the treatment of 30 severely burned patients with Epicel. The cultured epithelial autografts were applied to a mean of 37% of TBSA. Epicel achieved permanent coverage of a mean of 26% of TBSA, an area similar to that covered by conventional autografts (mean, 25%). Survival was 90% in these severely burned patients.

Integra Dermal Regeneration Template

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

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

In 2003, Heimbach et al reported a multicenter (13 U.S. burn care facilities) postapproval study involving 222 burn injury patients (36.5% TBSA; range, 1%-95%) who were treated with Integra Dermal Regeneration Template. 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%.

OrCel

There is limited evidence to support the efficacy of OrCel compared with SOC for the treatment of split-thickness donor sites. In 2003, Still et al examined the safety and efficacy of bilayered OrCel to facilitate wound closure of split-thickness donor sites in 82 severely burned patients. Each patient had 2 designated donor sites that were randomized to receive a single treatment of OrCel or standard dressing (Biobrane-L). The healing time for OrCel sites was significantly shorter than for sites treated with a standard dressing, enabling earlier recropping. OrCel sites also exhibited a

nonsignificant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

TransCyte

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

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

TransCyte is no longer commercially available.

OTHER

In addition to indications previously reviewed, off-label uses of bioengineered skin substitutes have included pressure ulcers, inflammatory ulcers (eg, pyoderma gangrenosum, vasculitis), scleroderma digital ulcers, postkeloid removal wounds, genetic conditions, and variety of other conditions. Products that have been FDA approved/cleared for 1 indication (eg, lower-extremity ulcers) have also used off-label in place of other FDA approved/cleared products (eg, for burns). No controlled trials were identified for these indications.

Summary of Evidence

Breast Reconstruction

For individuals who are undergoing breast reconstruction who receive allogeneic acellular dermal matrix (ADM) products, the evidence includes a randomized controlled trial (RCT) and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. A recent systematic review found no difference in overall complication rates with ADM allograft compared to standard procedures for breast reconstruction. Reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM. However, capsular contracture and

malposition of implants may be reduced. Thus, in cases where there is limited tissue coverage, including but not limited to when the use of ADM allows a single-stage reconstruction, the available evidence may be considered sufficient to permit conclusions about health outcomes that may inform patient decision making about reconstruction options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Tendon Repair

For individuals who are undergoing tendon repair who receive Graftjacket ADM, the evidence includes 1 RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. One RCT identified found improved outcomes with Graftjacket ADM allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of patients is needed to evaluate consistency of the effect. The evidence is insufficient to determine the effects of the technology on health outcomes.

Surgical Repair of Hernias or Parastomal Reinforcement

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

Diabetic Lower-Extremity Ulcers

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

For individuals who have diabetic lower-extremity ulcers who receive other ADM products, cryopreserved skin allograft, or xenogenic skin substitutes, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Additional study with a larger number of subjects is needed to compare the effect of other human ADM products, cryopreserved skin allograft (TheraSkin) and xenogenic skin substitutes (eg, Oasis Wound Matrix, PriMatrix) to the standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

Lower-Extremity Ulcers due to Venous Insufficiency

For individuals who have lower-extremity ulcers due to venous insufficiency who receive Apligraf

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

For individuals who have lower-extremity ulcers due to venous insufficiency who receive bioengineered skin substitutes other than Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. In a moderately large RCT, Dermagraft was not shown to be more effective than controls for the primary or secondary end points in the entire population and was only slightly more effective than controls (an 8%-15% increase in healing) in subgroups of patients with ulcer durations of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of the xenogenic PriMatrix skin substitute versus the current standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

Dystrophic Epidermolysis Bullosa

For individuals who have dystrophic epidermolysis bullosa who receive OrCel, the evidence includes case series. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. OrCel was approved under a humanitarian drug exemption for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. Outcomes have been reported in small series (eg, 5 patients). The evidence is insufficient to determine the effects of the technology on health outcomes.

Deep Dermal Burns

For individuals who have deep dermal burns who receive bioengineered skin substitutes (ie, Epicel, Integra Dermal Regeneration Template), the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, there are few skin substitutes approved, and the evidence is limited for each product. Epicel (living cell therapy) has received Food and Drug Administration approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. Comparative studies have demonstrated improved outcomes for biosynthetic skin substitute Integra Dermal Regeneration Template for the treatment of burns. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2016 Input

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

2014 Input

In response to requests, input was received from 3 physician specialty societies and 4 academic medical centers while this policy was under review in 2014. In addition to questions on medical necessity for different indications, input was specifically requested on the equivalency of products within the different categories (eg, acellular dermal matrix [ADM], living cell therapy, xenogeneic collagen scaffold, amniotic membrane). Five reviewers addressed the use of ADM products for breast reconstruction, and most considered the various ADM products (AlloDerm, AlloMax, DermaMatrix, FlexHD, Graftjacket) to have similar outcomes when used for breast reconstructive surgery, although differences in firmness and stretch of the products were noted. Six reviewers addressed questions on bio-engineered skin and soft tissue substitutes for diabetic and venous lower-extremity ulcers. Responses were mixed, although most reviewers considered living cell therapies to be equivalent for these indications. Most reviewers did not consider xenogeneic ADM products (eg, PriMatrix) or amniotic membrane (eg, EpiFix) to be medically necessary for any indication.

2011 Input

In response to requests, input was received from 3 physician specialty societies and 2 academic medical centers while this policy was under review in 2011. Most reviewers supported the indications and products described in this policy. Clinical input was requested regarding the use of an interpositional spacer after parotidectomy. Support for this indication was mixed. Some reviewers suggested use of other products and/or additional indications; however, the input on these products/indications was not uniform. The reviewers provided references for the additional indications; these were subsequently reviewed.

2008 Input

In response to requests for input on use of AlloDerm in breast reconstruction surgery, input was received from 1 physician specialty society (2 physicians) and 1 academic medical center while this policy was under review in 2008. All reviewers indicated that this procedure should be available for use during breast reconstructive surgery.

Practice Guidelines and Position Statements**American Society of Plastic Surgeons and Wound Healing Society**

A literature review for the 2013 guidelines from the American Society of Plastic Surgeons (ASPS) found that use of acellular dermal matrix (ADM), although increasingly common in postmastectomy expander/implant breast reconstruction, can result in increased risk of complications in the presence of certain risk factors. ASPS noted that cellular dermal matrix is currently used to

increase soft tissue coverage, support the implant pocket, improve contour, and reduce pain with expansion. However, evidence to support these improved surgical outcomes are limited. Some evidence has suggested that use of ADM is associated with increased postoperative complications, specifically related to infection and seroma. Overall, ASPS found that evidence on ADM products in postmastectomy expander/implant breast reconstruction was varied and conflicting, and gave a grade C recommendation based on level III evidence that surgeons should evaluate each clinical case individually and objectively determine the use of ADM.

In 2006, ASPS endorsed guidelines from the Wound Healing Society (WHS) on the treatment of arterial insufficiency ulcers. The guidelines stated that extracellular matrix replacement therapy appears to be promising for mixed ulcers and may have a role as an adjuvant agent in arterial ulcers, but further study is required (level IIIC): “Despite the existence of animal studies, case series, and a small number of random control trials to support biomaterial use for pressure ulcers, diabetic ulcers, and venous ulcers; there are no studies specifically on arterial ulcers. Therefore, studies in arterial ulcers must be conducted before the recommendation can be made.” ASPS also endorsed WHS guidelines on the treatment of venous ulcers in 2006. The guidelines stated that various skin substitutes or biologically active dressings are emerging that provide temporary wound closure and serve as a source of stimuli (eg, growth factors) for healing of venous ulcers. Guideline 7b.1 stated that there is evidence that a bilayered artificial skin (biologically active dressing), used in conjunction with compression bandaging, increases the chance of healing a venous ulcer compared with compression and a simple dressing (level I).

ASPS also endorsed WHS guidelines on the treatment of diabetic ulcers in 2006. The guidelines stated that healthy living skin cells assist in healing diabetic foot ulcers by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed. Guideline 7.2.2 stated that living skin equivalents may be of benefit in healing diabetic foot ulcers (level I). The 2007 ASPS guidelines on chronic wounds of the lower extremity stated that maintaining a moist environment, while simultaneously removing soluble factors detrimental to wound healing, might logically provide optimal conditions for wound healing. Classic dressings include gauze, foam, hydrocolloid, and hydrogels. Fluid-handling mechanisms include absorption, gelling, retention, and vapor transmission. Bioactive dressings include topical antimicrobials, bioengineered composite skin equivalent, bilaminar dermal regeneration template, and recombinant human growth factor.

National Institute for Health and Care Excellence

In 2015, the U. K.’s National Institute for Health and Care Excellence (NICE) published clinical guidelines on the prevention and management of diabetic foot problems. NICE recommends that clinicians consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service.

American College of Foot and Ankle Surgeons

The 2006 clinical consensus statement [previously called clinical practice guideline] on diabetic foot disorders from the American College of Foot and Ankle Surgeons states that bio-engineered tissues have been shown to significantly increase complete wound closure in venous and diabetic foot

ulcers. Tissue-engineered skin substitutes can function both as biologic dressings and as delivery systems for growth factors and extracellular matrix components through the activity of live human fibroblasts contained in their dermal elements. Currently, two bio-engineered tissues have been approved to treat diabetic foot ulcers in the United States: Apligraf and Dermagraft; both have demonstrated efficacy in RCTs. Apligraf has been shown to significantly reduce the time to complete wound closure in venous and diabetic ulcers. Regenerative tissue matrix (Graftjacket) is used in diabetic foot ulcers, although it had not undergone any RCTs at the time of this guideline. This allograft skin is minimally processed to remove epidermal and dermal cells while preserving the bioactive components and structure of dermis. This results in a framework that supports cellular repopulation and vascularization. Oasis, composed of structural cellular components and growth factors used to promote natural tissue remodeling, completed a randomized trial that showed noninferiority to becaplermin gel in the healing of diabetic foot ulcers. Integra Dermal Regeneration Template, a collagen-chondroitin sponge overlaid with silicone originally developed for burns, has been shown to be ideally suited to chronic and pathologic wounds.

Infectious Diseases Society of America

The 2012 guidelines from the Infectious Diseases Society of America state that for selected diabetic foot wounds that are slow to heal, clinicians might consider using bio-engineered skin equivalents (weak recommendation, moderate evidence) growth factors (weak, moderate), granulocyte colony stimulating factors (weak, moderate), hyperbaric oxygen therapy (strong, moderate), or negative pressure wound therapy (weak, low). It is emphasized that none of these measures have been shown to improve resolution of infection and that they are expensive, not universally available, may require consultation with experts, and reports supporting their utility are mostly flawed.

Agency for Healthcare Research and Quality

A 2012 Technology Assessment from the Agency for Healthcare Research and Quality does not make a formal recommendation for bioengineered skin and soft tissue substitutes. The Assessment notes that autologous tissue grafting is an invasive and painful procedure and often the extent of damaged skin is too large to be covered by autologous tissue graft alone. A variety of skin substitutes and alternatives are designed to replace the damaged epithelial and dermal layers of skin, and many of the conditions and biological factors needed in the healing process may be provided by the substitute skin products.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Since 2014, CMS no longer distinguishes between different skin substitutes and will classify them as either high cost or low cost. CMS will package skin substitutes of the same class into the associated surgical procedures for hospital outpatient departments and ambulatory surgical centers. A separate payment might be made if the item is furnished on a different date of service as the

primary service.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02521623 ^a	SurgiMend® vs. Strattice™ in Direct to Implant Breast Reconstruction- A Prospective Randomized Trial	60	Aug 2017
NCT01987700 ^a	A Randomized, Prospective, Double-blind, Multi-Center Study To Examine And Compare The Outcomes Associated With The Use Of Flex HD®, A Human Acellular Dermal Matrix, And Strattice™, A Porcine Acellular Dermal Matrix Allograft, When Used As A Reinforcing Material In The Repair Of Large Abdominal Wall Hernias By A Component Separation Technique	120	Oct 2017
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	Oct 2019
NCT02322554	The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers	50,000	Jan 2020
Unpublished			
NCT01970163 ^a	A Multicenter, Randomized, Controlled, Open Label Trial of DermACELL in Subjects With Chronic Wounds of the Lower Extremities	202	Mar 2016 (completed)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

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