Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/23**
(See policy history boxes for previous effective dates)

Title: Skin and Tissue Substitutes

Description/Background

Bioengineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman tissue (xenograph), 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.

SKIN AND SOFT TISSUE SUBSTITUTES

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

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

Applications

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

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

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

Tissue-engineered skin represents a new approach to wound healing. A number of skin substitute products are available commercially; others are under development or awaiting approval from the United States Food and Drug Administration (FDA).

The following products are derived from human tissue (**may not be all-inclusive**) and therefore subject to the rules and regulations for banked human tissue developed by the American Association of Tissue Banks (AATB):

- Alloderm®
- AlloMax™
- AllopatchHD™
- AlloSkin®
- Arthroflex™
- BellaCell HD or SureDerm®
- Coll-e-Derm
- Cortiva™
- Cymetra®
- DermACELL™
- FlexHD®
- FlowerDerm®
- GammaGraft®
- GraftJacket®
- IntéguPly®
- Matrix™ HD
- MemoDerm™
- MyOwn Skin™
- NeoForm™
- Progenamatrix™
- Purpos® Dermis
- SimpliDerm®
- SkinTE™
- Theraskin®

Devices, Kits and Systems used for Autologous Cell Preparation
Devices, kits and systems have been designed for the treatment of wound beds including:

Ac5® Advanced Wound System is a self-assembling wound care matrix which uses a peptide solution that creates a nanofiber scaffold structure. Once the peptide and sterile water are mixed in a syringe, the solution is applied to the wound bed.

The Recell® Autologus Cell Harvesting device enables active delivery of an individuals own living cells. A small piece of the individuals skin is submersed in a heated proprietary enzymatic formulation which targets and disrupts protein-to-protein interactions, priming the cells for mechanical isolation. Once the individual cells are isolated and the cell suspension is filtered, the regenerative epidermal suspension is ready to be sprayed onto the wound bed. The spray includes keratinocytes, fibroblasts, and melanocytes.

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

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

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

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

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:
1. The HCT/P is minimally manipulated;
2. The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4. Either: i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

a) Is for autologous use; b) Is for allogeneic use in a first-degree or second-degree blood relative; or c) Is for reproductive use."

- AlloDerm® (LifeCell Corp.) is an ADM (allograft) tissue-replacement product created from native human skin and processed so that the basement membrane and cellular matrix remain intact. Originally, AlloDerm® required refrigeration and rehydration before use. It is currently available in a ready-to-use product stored at room temperature. An injectable micronized form of AlloDerm® (Cymetra) is available.
- Cortiva® (previously marketed as AlloMax™ Surgical Graft and before that NeoForm™) is an acellular non-cross-linked human dermis allograft.
- AlloPatch® (Musculoskeletal Transplant Foundation) is an acellular human dermis allograft derived from the reticular layer of the dermis and marketed for wound care. This product is also marketed as FlexHD® for postmastectomy breast reconstruction.
- FlexHD® and the newer formulation FlexHD® Pliable™ (Musculoskeletal Transplant Foundation) are acellular hydrated reticular dermis allograft derived from donated human skin.
- DermACELL™ (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL® and PRESERVON®.
- DermaMatrix™ (Synthes) is a freeze-dried ADM derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation.
- DermaPure™ (Tissue Regenix Wound Care) is a single-layer decellularized human dermal allograft for the treatment of acute and chronic wounds.
- Graftjacket® Regenerative Tissue Matrix (also called Graftjacket Skin Substitute; KCI) is an acellular regenerative tissue matrix that has been processed from human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells while preserving dermal structure. Graftjacket Xpress® is an injectable product.

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

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

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

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

FDA product codes: FTM, OXF.

Xenogeneic Products

Apis® is fully absorbable, biodegradable and manufactured using a porcine collagen derivative, Manuka honey and hydroxyapatite. It was cleared for marketing (2019) by the FDA 510(k) process for the management of full and partial thickness wounds, pressure ulcers (stages I-IV), venous stasis ulcers, diabetic ulcers, abrasion, surface wounds, traumatic wounds (healing by secondary intention), donor site wounds, and surgical wounds.

Atlas Wound Matrix is a sterile, decellularized fenestrated or non-fenestrated processed porcine collagen dermal material. It was cleared for marketing (2009) by the FDA 510(k) process for the management of partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds.

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.

Geistlich Derma-Gide is derived from porcine tissue (mostly collagen Type I) and is processed using proprietary technologies to remove bacteria and inactive viruses. It was cleared for marketing by the FDA 510(k) process (2018) for the management of partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post Moh’s surgery, post laser surgery, podiatric, wound dehiscence), and trauma skin wounds (abrasions, laceration, second degree burns, skin tears).

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

InnovaMatrix™ (also known as InnovaMatrix AC) and InnovaMatrix™ FS are decellularized extracellular matrix topical wound coverings derived from porcine placental tissue. The only modification made to InnovaMatrix FS since the InnovaMatrix clearance is the addition of fenestrations. Both devices have been cleared for marketing (InnovaMatrix AC – 2020; InnovaMatrix FS - 2021) by the FDA 510(k) process for the management of wounds including: partial- and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second degree burns and skin tears) and draining wounds.

Integra® Matrix Wound Dressing (previously known as Avagen) is an advanced wound dressing comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. The biodegradable matrix provides a scaffold for cellular invasion and capillary growth. It was cleared for marketing by the FDA through the 510(k) process in 2002. The wound dressings are indicated in the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds (donor sited grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree bums, and skin tears) and draining wounds. The device is intended for one-time use.

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

Kerecis™ Omega3 Wound (Kerecis; previously known as MeriGen) is an ADM derived from fish skin. It has a high content of omega 3 fatty acids and is intended for use in partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (abrasions, lacerations, second-degree burns, skin tears), surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), and draining wounds.

Kerecis Limited MariGen Wound Extra is processed fish dermal matrix composed of fish collagen. MariGen Wound Extra is indicated for the management of wounds, including: Partial and full-thickness wounds, Pressure ulcers, Venous ulcers, Chronic vascular ulcers, Diabetic ulcers, Trauma wounds (second degree burn, abrasions, lacerations, skin tears), Surgical wounds (donor sites/grafts, post-Mohs surgery, post laser surgery, podiatric, wound dehiscence), and Draining wounds.

Note: Kerecis has multiple U.S. wound, surgical and burn products. Not all are FDA approved (i.e., Wounds: Marigen Standard, Marigen Micro, Marigen Expanse, Marigen Shield; Burns: Graftguide Standard, Graftguide Micro, Graftguide Mano; Surgical: Surgiclose Standard, Surgiclose Micro, Surgibind Standard)

MicroMatrix® is composed of porcine-derived extracellular matrix scaffolds, specifically known as urinary bladder matrix. It was cleared for marketing (2016) by the FDA 510(k) process for the management of topical wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunnel/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds. The device is intended for one-time use.

NeoMatriX® is fabricated from the dermal extracellular matrix of axolotl. NeoMatriX® Wound Matrix is intended for management of wounds including: Partial and full-thickness wounds, Pressure ulcers, Venous ulcers, Diabetic ulcers, Chronic vascular ulcers, Tunneled/undermined wounds, Surgical wounds (donor sites/grafts, Moh’s surgery, post-laser surgery, podiatric, and wound dehiscence), Trauma wounds (abrasions, lacerations, partial

thickness burns, and skin tears), and Draining wounds. The device is intended for one-time use.

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

Ologen™ Collagen Matrix is a biodegradable material composed of collagen. It is derived from porcine hide and the matrix structure has a porous configuration made of ≥90% cross-linked lyophilized porcine collagen and ≤10% glycosaminoglycans. It was cleared for marketing (2018) by the FDA 510(k) process for the management of wounds including: surgical wounds, trauma wounds, draining wounds, second degree burns, partial and full-thickness wounds, pressure ulcers, venous ulcers, vascular ulcers, diabetic ulcers, oral wounds and sores.

PELNAC™ Bilayer Wound Matrix (aka TheraGenesis® Bilayer Wound Matrix) is a collagen-based wound matrix that consists of two layers which include a porcine collagen sponge layer and a silicone film layer. It was cleared for marketing (2020) by the FDA 510(k) process for the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds. Product code KGN.

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; a subsidiary of Integra Life Sciences) 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.

Puracol Plus Ag Collagen Wound Dressing (Medline Industries, Inc) was cleared for marketing by the FDA through the 510(k) process. It is intended to treat full thickness and partial thickness wounds, pressure ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, first and second degree bums, donor sites and other bleeding surface wounds, abrasions, trauma wounds healing by secondary intention, dehisced wounds, surgical wounds, and dehisced surgical wounds.

PuraPly® Antimicrobrial (PuraPly AM) is a bilayered fenestrated sheet of porcine intestinal collagen coated with the broad spectrum antimicrobial agent 0.1 % Polyhexamethylene Biguanide hydrochloride. It is intended for the management of both acute and chronic wounds; and as an effective barrier to resist microbial colonization within the wound dressing and reduce microbes penetrating through the dressing. Product code: FRO

PuraPly Micronized Wound Matrix (PuraPly MZ) consists of micronized porcine collagen intended for the management of wounds. PuraPly® Micronized Wound Matrix is supplied as a dry powder of particle size of ≤ 1000µm. PuraPly MZ received FDA clearance (2022) via the 510(k) process. It is intended for single patient use in the management of wounds including Partial and full-thickness wounds; Pressure ulcers; Venous ulcers; Diabetic ulcers; Chronic

vascular ulcers; Tunneled/undermined wounds; Surgical wounds (e.g., donor sites/grafts, post-Mohs; surgery, post-laser surgery, Podiatric wound, and wound dehiscence); Trauma wounds (e.g., abrasions, lacerations, and skin tears); Partial thickness burns; and Draining wounds.

Note: There are multiple PuraPly products, not all are FDA approved (i.e. PuraPly XT)

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.

SurgiMend® PRS (TEI Biosciences) is a xenogeneic ADM processed from fetal and neonatal bovine dermis. It was cleared for marketing (2017) by the FDA 510(k) process to reinforce soft tissue where weakness exists and for surgical repair of damaged or ruptured soft tissue membranes. SurgiMend® Meshed is specifically indicated for plastic and reconstructive surgery.

Symphony™ is a sterile, single use wound dressing manufactured by incorporating a layer of glycosaminoglycans between sheets of ovine forestomach-derived extracellular collagen matrix. It was cleared for marketing (2020) by the FDA 510(k) process for the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), draining wounds

XCelliStem wound powder is an extracellular matrix composed of porcine collagen. It was cleared for marketing (2018) by the FDA 510(k) process for the management of partial and full-thickness wounds, pressure ulcers, diabetic ulcers, venous ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh’s surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears), and draining wounds. The device is intended for one-time use.

FDA Product code: KGN unless otherwise specified.

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 one size, with a shelf-life of 10 days. In 1998, it was approved by the FDA for use in conjunction with compression therapy for the treatment of noninfected, partial- and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower-extremity ulcers nonresponsive to standard wound therapy. FDA product code: FTM.

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

TheraSkin® (Soluble Systems) is a cryopreserved split-thickness human skin allograft composed of living fibroblasts and keratinocytes and an extracellular matrix in epidermal and dermal layers. TheraSkin® is derived from human skin allograft supplied by tissue banks

compliant with the American Association of Tissue Banks and FDA guidelines. It is considered a minimally processed human cell, tissue, and cellular- and tissue-based product by the FDA.

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

Omeza® Collagen Matrix is an anhydrous matrix comprised of hydrolyzed fish collagen infused with cod liver oil and other plant-derived oils and waxes. Omeza received FDA approval for one-time use in the management of wounds including partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds/surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, superficial partial thickness burns, skin tears), and draining wounds. FDA product code: FRO

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 the FDA premarket approval for healing donor site wounds in burn victims and under a humanitarian device exemption (HDE) for use in patients with recessive dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites. FDA product code: ODS.

Biosynthetic Products

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

PermeaDerm is and FDA approved biosyntheric wound covering product comprised of an adherent and transparent monofilament nylon knitted fabric that is bonded to a thin, silicone membrane, which contains physical slits that are configured to create pores (similar to human skin). FDA code: FRO

- PermeaDerm B (burns) is indicated for use in partial thickness burns, donor sites and coverage of meshed autograft.
- PermeaDerm CW (chronic wounds) is indicated for use with chronic wounds including partial thickness wounds, pressure sores, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's, post-laser surgery, podiatric, wound dehiscence, trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds
- PermeaDerm G (glove) is indicated for use in debrided partial thickness hand burns.

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

Synthetic Products

BTM Wound dressing (NovoSorb BTM [Biodegradable Temporizing Matrix]) is a man-made synthetic polymer composed of a synthetic foam with a polyurethane sealing membrane. It was cleared for marketing by the FDA 510(k) process (2015) for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic and vascular ulcers, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. The device is intended for one-time use.

Microlyte™ Ag wound dressing is a sterile, single use unsupported synthetic absorbent polyvinyl alcohol hydrogel sheet with a polymeric surface coating containing ionic and metallic silver. It was cleared for marketing by the FDA 510(k) process (2016) for the management of partial and full thickness wounds including pressure ulcers, venous stasis ulcers, diabetic ulcers, first and second degree burns, abrasions and lacerations, donor sites and surgical wounds. It may be used over debrided and grafted partial thickness wounds.

Mirragen™ Advanced Wound Matrix is composed solely of biocompatible and resorbable borate glass fibers and particulate. It was cleared for marketing (2016) by the FDA 510(k) process for the management of wound types which include: Partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, first- and second-degree burns, skin tears) and draining wounds. Product code: FRO

Phoenix Wound Matrix is a 3D electrospun synthetic polymer matrix. It was cleared for marketing by the FDA 510(k) process (2018) for the management of partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second degree burns, skin tears) and draining wounds.

Restrata® is made from synthetic biocompatible materials and was designed to include a fibrous structure with high porosity, similar to native extracellular matrix. Restrata® is a porous matrix with a defined rate of resorption that provides a scaffold for cellular infiltration and vascularization before completely degrading via hydrolysis. It was cleared for marketing by the

FDA 510(k) process (2020) for the management of partial and full thickness wounds, pressure sores/ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wound (e.g., donor site/ grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, dehisced wounds), trauma wounds (e.g., abrasions, lacerations, partial thickness burns, skin tears), and draining wounds.

SupraSDRM Bioidegradable Matrix Wound Dressing is fabricated from a tri-polymer of polylactide, trimethylene carbonate, ε-caprolactone and polyvinyl alcohol that can be used either alone or in conjunction with a petroleum jelly and/or gauze wound and burn dressing. It was cleared for marketing by the FDA 510(k) process (2017) for the management of partial and full thickness wounds, pressure (stage I and IV) and venous ulcers, ulcers caused by mixed vascular etiologies, venous stasis and diabetic ulcers, 1st and 2nd degree burns, partial thickness burns, cuts and abrasions, acute wounds, trauma wounds, surgical wounds, superficial wounds, grafted wounds and donor sites.

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. FDA 510(k) approval was granted in 2009. Product code: FRO

Devices, Kits and Systems used for Autologous Cell Preparation
Recell Autologous Cell Harvesting Device is a mechanical and enzymatic autologous skin processor for preparing cell suspension, for burn wounds and non-thermal skin defects, with a spray-on applicator. FDA PMA approval was granted in 2023 for pediatric and adult patients for full-thickness skin defects after traumatic avulsion (e.g., degloving) or surgical excision (e.g., necrotizing tissue infection) or resection (e.g., skin cancer) in patients 15 years of age and older. Device code: QCZ

Medical Policy Statement

The safety and effectiveness of skin and tissue substitutes approved by the United States Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services have been established for individuals meeting specified selection criteria. They may be useful therapeutic options when indicated.

Human tissue products are subject to the rules and regulations of banked human tissue by the American Association of Tissue Banks (AATB) and have been established for individuals meeting specified selection criteria. They may be useful therapeutic options when indicated.

Note:
- *Non-human tissues qualify for FDA approval.*
- *Human tissues are governed by the American Tissue Bank and do not qualify for FDA approval.*

Inclusionary and Exclusionary Guidelines

Inclusions:
The following skin and tissue substitutes are considered established when used according to the FDA approval[a]. This list may not be all-inclusive:

- Apligraft®
- Apis®
- Atlas Wound Matrix
- Biobrane®
- Bio-conneKt® Wound Care Matrix
- BTM Wound Dressing (aka NovoSorb® BTM)
- Cytal® Burn Matrix
- Cytal® MicroMatrix™
- Cytal™ Wound Matrix (formerly MatriStem)
- Cytal® Wound Sheet
- Derma-Gide (aka Geistlich Derma-Gide™)
- Dermagraft®
- Endoform Dermal Template™
- Epicel® has FDA Humanitarian Device Approval
- E-Z Derm™
- Helicoll™
- Hyalomatrix®
- InnovaMatrix™ (also known as InnovaMatrix AC)
- InnovaMatrix™ FS
- Integra® Bilayer Matrix
- Integra® Dermal Regeneration Template
- Integra® Flowable Wound Matrix
- Intregra® Matrix Wound Dressing (formerly known as Avagen)
- Keratec Wound Dressings (Kermatrix®)
    - Keratec Keragel
    - Keraderm
    - Kerafoam
- Kerecis Limited MariGen Wound Extra
- Kerecis™ Omega3 Wound (formerly known as MeriGen)
- MediSkin®
- Microlyte® Ag
- MicroMatrix®
- Mirragen™
- NeoMatriX® Wound Matrix
- Oasis® Burn Matrix
- Oasis® Ultra Tri-Layer Wound Matrix
- Oasis® Wound Matrix
- Ologen™ Collagen Matrix
- Omeza® Collagen Matrix
- OrCel®
- PELNAC™ Bilayer Wound Matrix
- Permacol™ (Covidien)
- PermeaDerm B
- PermeaDerm C
- PermeaDerm Glove

- Phoenix™ Wound Matrix
- PriMatrix™ Dermal Repair Scaffold
- Puracol® and Puracol® Plus Collagen Wound Dressings
- PuraPly Antimicrobial Wound Matrix (PuraPly AM; formerly known as FortaDerm AM)
- PuraPly Micronized Wound Matrix (PuraPly MZ; formerly known as FortaDerm)
- Restrata®
- Strattice™
- Suprathel®
- SupraSDRM Biodegradable Matrix Wound Dressing
- SurgiMend®
- Symphony™
- Talymed™
- TenoGlide™
- TransCyte®
- XCelliStem® Wound Powder

[a] *Cross reference FDA approved products in the inclusion with the information in the Regulatory section (above) for details related to coverage.*

Breast reconstructive surgery using allogeneic acellular dermal matrix products[b] (including each of the following: AlloDerm®, AlloMend®, Cortiva®, [AlloMax™], DermACELL™, DermaMatrix™, FlexHD®, FlexHD® Pliable™, Graftjacket®) are considered established when ONE of the following are met:
- There is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required
- There is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis
- The inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed.

Note: Various acellular dermal matrix products used in breast reconstruction have similar efficacy. The products listed are those that have been identified for use in breast reconstruction. Additional acellular dermal matrix products may become available for this indication.

Treatment of chronic, noninfected, full-thickness diabetic lower extremity ulcers is established when using the following tissue engineered skin substitutes:
- AlloPatch®[b]
- Apligraft®[c]
- Dermagraft®[c]
- GraftJacket® Regenerative Tissue Matrix-Ulcer Repair
- Integra®, Omnigraft™ Dermal Regeneration Matrix (also known as Omnigraft™) and Integra Flowable Wound Matrix
- Theraskin®

Treatment of chronic, noninfected, partial- or full-thickness lower-extremity skin ulcers due to venous insufficiency, which have not adequately responded following a one-month period of conventional user therapy is established when using the following tissue-engineered skin substitutes:
- Aplifraf®[c]

- Oasis™ Wound Matrix[d]
- Theraskin®

OrCel™ is considered established when ALL of the following criteria are met:
- Used for the treatment of dystrophic epidermolysis bullosa
- Used for the treatment of mitten-hand deformity
- Standard would therapy has failed
- Provided in accordance with the humanitarian device exemption [HDE] specifications of the U.S. Food and Drug Administration

The following skin and tissue product(s)/substitute(s) are considered established for use in the treatment of second- and third-degree burns:
- Alloderm
- Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area ≥30% when provided in accordance with the HDE specifications of the FDA)[e]
- Integra® Dermal Regeneration Template[c].

[b] Banked human tissue.
[c] FDA premarket approval.
[d] FDA 510(k) clearance.
[e] FDA-approved under an HDE.

Exclusions:
All other uses of bioengineered skin and soft tissue substitutes listed above unless they meet ONE of the following criteria:
- FDA approval and provided in accordance with the FDA guidelines
- Covered by Centers for Medicare & Medicaid Services

All other skin and soft tissue substitutes, including, but not limited to:
- ACell® UBM Hydrated/Lyophilized Wound Dressing
- AlloSkin™
- AlloSkin™ RT
- Aongen™ Collagen Matrix
- Architect® ECM, PX, FX
- ArthroFlex™ (Flex Graft)
- AxoGuard® Nerve Protector (AxoGen)
- BellaCell HD or SureDerm®
- CollaCare®
- CollaCare® Dental
- Collagen Wound Dressing (Oasis Research)
- CollaGUARD®
- CollaMend™
- CollaWound™
- Coll-e-Derm
- Collexa®
- Collieva®
- Conexa™
- Coreleader Colla-Pad

- CorMatrix®
- Cymetra™ (Micronized AlloDerm™)
- Dermadapt™ Wound Dressing
- DermaPure™
- DermaSpan™
- DressSkin
- Durepair Regeneration Matrix®
- *ENDURA*Gen™
- Excellagen
- ExpressGraft™
- FlexiGraft®
- FlowerDerm®
- GammaGraft
- hMatrix®
- IntéguPly®
- Kerecis omega3 marigen
- Keroxx™
- MatriDerm®
- Matrix HD™
- MemoDerm™
- Microderm® biologic wound matrix
- Miroderm®
- MyOwn Skin™
- NeoForm™
- Progenamatrix™
- PuraPly XT
- Puros® Dermis
- RegenePro™
- Repliform®
- Repriza™
- SkinTE™
- SlimpliDerm®
- StrataGraft®
- TenSIX™ Acellular Dermal Matrix
- TissueMend
- TheraForm™ Standard/Sheet
- TruSkin™
- Veritas® Collagen Matrix
- XCM Biologic® Tissue Matrix
- XenMatrix™ AB.

Systems, kits, or devices used to prepare or construct skin or tissue substitutes including:
- Ac5 advanced wound system
- Recell® Autologous Cell Harvesting Device

CPT/HCPCS Level II Codes ***(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)***

Established codes:

15271	15272	15273	15274	15275	15276
15277	15278	15777	A2001	A2002	A2004
A2005	A2006	A2007	A2008	A2009	A2010
A2011	A2012	A2013	A2014	A2015	A2016
A2017	A2018	A2021	A4100	A6010	A6011
A6021	A6022	A6023	Q4100	Q4101	Q4102
Q4103	Q4104	Q4105	Q4106	Q4107	Q4108
Q4110	Q4113	Q4114	Q4116	Q4117	Q4118
Q4121	Q4122	Q4124	Q4127	Q4128	Q4130
Q4135	Q4136	Q4147	Q4149	Q4158	Q4161
Q4164	Q4165	Q4166	Q4182	Q4195	Q4196
Q4203					

Other codes (investigational, not medically necessary, etc.):

A2019	A2020	C1832	Q4111	Q4112	Q4115
Q4123	Q4125	Q4126	Q4134	Q4141	Q4142
Q4143	Q4146	Q4152	Q4167	Q4175	Q4176
Q4177	Q4178	Q4179	Q4180	Q4193	Q4197
Q4200	Q4202	Q4220	Q4222	Q4226	Q4238

Note: The code(s) above may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

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

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

BREAST RECONSTRUCTION

Review of Evidence

The literature on ADM for breast reconstruction consists primarily of retrospective, uncontrolled series and systematic reviews of these studies.

A 2013 study used data from the American College of Surgeon's National Surgical Quality Improvement Program to compare ADM-assisted tissue expander breast reconstruction (n=1717) to submuscular tissue expander breast reconstruction (n=7442) after mastectomy.(5) Complication rates did not differ significantly between the ADM-assisted (5.5%) and the submuscular tissue expander groups (5.3%; p=0.68). Rates of reconstruction-related complications, major complications, and 30-day reoperation did not differ significantly between cohorts.

Systematic Reviews

A meta-analysis by Lee and Mun (2016) included 23 studies (total N=6199 cases) on implant-based breast reconstruction that were published between February 2011 and December 2014.(6) The analysis included an RCT and three 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 injections 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

Adapted from Lee and Mun (2016).[5]
ADM: acellular dermal matrix; *NS*: not significant.

AlloDerm

Randomized Controlled Trials

McCarthy et al (2012) reported on a multicenter, blinded RCT of AlloDerm in two-stage expander/implant reconstruction.(7) Seventy patients were randomized to AlloDerm ADM-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. The trial was adequately powered to detect clinically significant differences in immediate postoperative pain but underpowered to detect the secondary 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, although the total number of adverse events was small.

Comparisons Between Products

AlloDerm vs AlloMax

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

AlloDerm vs DermaMatrix

Mendenhall et al (2017) conducted an RCT that compared AlloDerm with DermaMatrix in 111 patients (173 breasts).(9) There were no significant differences in overall rates of complications (AlloDerm, 15.4%; DermaMatrix, 18.3%; p=0.8) or implant loss (AlloDerm, 2.2%; DermaMatrix, 3.7%; p=0.5) between the two ADMs.

AlloDerm vs FlexHD

A retrospective review by Liu et al (2014) compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts).(10) Eighty-one percent of the sample was immediate reconstruction: 165 used AlloDerm and 97 used FlexHD. Mean follow-up was 6.4 months. Compared with breast reconstruction without the use of AlloDerm or FlexHD, ADM had a higher rate of delayed healing (20.2% vs 10.3%), although this finding might have been related to differences in fill volumes. In univariate analysis, there were no significant differences in complications (return to operating room, surgical site infection, seroma, hematoma, delayed healing, implant loss) between AlloDerm and FlexHD. In multivariate analysis, there were no significant differences between AlloDerm and FlexHD for the return to the operating room, surgical site infection, seroma, or delayed healing. Independent risk factors for implant loss included the use of FlexHD, single-stage reconstruction, and smoking.

AlloDerm vs FlexHD Pliable and DermACELL

Chang and Liu (2017) reported on a prospective comparison of FlexHD Pliable (32 breasts), AlloDerm (22 breasts), and DermACELL (20 breasts) in breast reconstruction.(11) The choice of ADM was based on different years when each ADM was available for use at the investigators' institution; patient demographics were comparable between groups. The pieces of ADM used were all the same size (8 × 16 cm) to eliminate an effect of size on outcomes. The time to drain removal was longer with AlloDerm (26 days) than with FlexHD (20 days) or DermACELL (15 days; p=0.001). Complications were low (4 in the Flex Pliable group, two in the AlloDerm group, one in the DermACELL group), with no significant differences between groups. At the time of exchange for a permanent implant or free flap reconstruction, all grafts had completely incorporated into the mastectomy skin flaps. No patients developed complications requiring removal of the ADM.

Pittman et al (2017) reported a retrospective pilot study of the use of AlloDerm (50 breasts) and DermACELL (50 breasts).(12) The choice of ADM was based on products available during different years and patient demographics were similar between the 2 groups. Patients in the DermACELL group had a significantly lower incidence of "red breast syndrome" (0% vs 26%,

p=0.001) and fewer days until drain removal (15.8 days vs 20.6 days, p=0.017). There were no significant differences in the rates of other complications.

Strattice

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

Table 2. Summary of Key RCT Characteristics

Author	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*
Dikmans et al (2017)[12]	EU	8	2013-2015	Women intending to undergo skin-sparing mastectomy and immediate IBBR	59 patients (91 breasts) undergoing 1-stage IBBR with ADM	62 women (92 breasts) undergoing 2-stage IBBR

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

Table 3. Summary of Key RCT Outcomes

Study	Surgical Complications	Severe Adverse Events	Reoperation	Removal of Implant, ADM, or Both
Dikmans et al (2017)[12]				
1-stage with ADM, n (%)	27 (46)	26 (29)	22 (37)	24 (26)
2-stage with ADM, n (%)	11 (18)	5 (5)	9 (15)	4 (5)
OR (95% CI)	3.81 (2.67 to 5.43)		3.38 (2.10 to 5.45)	8.80 (8.24 to 9.40)
p	<0.001		<0.001	<0.001

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

Section Summary: Breast Reconstruction

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

TENDON REPAIR

Review of Evidence

Graftjacket

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

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

Section Summary: Tendon Repair

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

SURGICAL REPAIR OF HERNIAS OR PARASTOMAL REINFORCEMENT

Review of Evidence

Systemic Reviews

A 2013 systematic review evaluated the clinical effectiveness of acellular collagen-based scaffolds for the repair of incisional hernias.(16) The bioprosthetic materials could be harvested from bovine pericardium, human cadaveric dermis, porcine small intestine mucosa, porcine dermal collagen, or bovine dermal collagen. Products included in the search were Surgisis, Tutomesh, Veritas, AlloDerm, FlexHD, AlloMax, CollaMend, Permacol, Strattice, FortaGen, ACell, DermaMatrix, XenMatrix, and SurgiMend. Sixty publications with 1212 repairs were identified and included in the review, although meta-analysis could not be

performed. There were four level III studies (two AlloDerm, two Permacol); the remainder were level IV or V. The largest number of publications were on AlloDerm (n=27) and Permacol (n=18). No publications on incisional hernia repair were identified for AlloMax, FortaGen, DermaMatrix, or ACell. The overall incidence of a surgical site occurrence (e.g., postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, mechanical failure) was 82.6% for porcine small intestine mucosa, 50.7% for xenogeneic dermis, 48.3% for human dermis, and 6.3% for xenogeneic pericardium. No comparative data were identified that could establish superiority to permanent synthetic meshes.

AlloDerm as an Overlay

Espinosa-de-los-Monteros et al (2007) retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases.(17) They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

Comparisons Between Products

AlloDerm vs Surgisis Gold

Gupta et al (2006) compared the efficacy and complications associated with use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair.(18) The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine submucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7 to 10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in 8 (24%) hernia recurrences. Fifteen (45%) of the AlloDerm patients developed a diastasis or bulging at the repair site. Seroma formation was only a problem in two patients.

AlloDerm vs FlexHD

A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery.(19) From 2005 to 2007, AlloDerm was used to repair large (>200 cm^2) symptomatic complicated ventral hernias that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD was used to repair large, complicated ventral hernias in patients meeting the same criteria (n=40). The two groups were comparable at baseline. At one year follow-up, all AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, true recurrence) requiring a second repair. Eleven (31%) patients in the FlexHD group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

FlexHD vs Strattice

Roth et al (2017) reported on a prospective study assessing clinical and quality of life outcomes following complex hernia repair with a human (FlexHD) or porcine (Strattice) ADM.(20) The study was funded by the Musculoskeletal Transplant Foundation, which prepares and supplies FlexHD. Patients were enrolled if they had a hernia at least six cm in the transverse dimension, active or prior infection of the abdominal wall, and/or enterocutaneous fistula requiring mesh removal. Eighteen (51%) of the 35 patients had undergone a previous hernia repair. After abdominal wall repair with the ADM, 20 (57%)

patients had a surgical site occurrence, and nearly one-third had hospital readmission. The type of biologic material did not impact hernia outcomes. There was no comparison with synthetic mesh in this study, limiting interpretation.

Strattice vs Synthetic Mesh

Bellows et al (2014) reported early results of an industry-sponsored multicenter RCT that compared Strattice (non-cross-linked porcine ADM, n=84) with a standard synthetic mesh (n=88) for the repair of inguinal hernias.(21) The trial was designed by the surgeons and was patient- and assessor-blinded to reduce risk of bias. Blinding continued through two years of follow-up. The primary outcome was resumption of activities of daily living at one year. Secondary outcomes included complications, recurrences, or chronic pain (i.e., pain that did not disappear by three months post-surgery). At three-month follow-up, there were no significant differences in either the occurrence or type of wound events (relative risk, 0.98; 95% CI, 0.52 to 1.86). Pain was reduced from one to three days postoperative in the group treated with Strattice, but at three month follow-up pain scores did not differ significantly between groups.

Strattice Versus 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.(22) Patients were randomized to standard stoma construction with no reinforcement (n=58) or stoma construction with Strattice as parastomal reinforcement (n=55). At 24-month follow-up (n=75), the incidence of parastomal hernias was similar for the two groups (13.2% of controls, 12.2% of study group).

Adverse Events

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

Section Summary: Surgical Repair of Hernias or Parastomal Reinforcement

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

DIABETIC LOWER-EXTREMITY ULCERS

Review of Evidence

Systematic Reviews

A 2016 Cochrane review evaluated skin substitutes for the treatment of diabetic foot ulcers.(24) Seventeen trials (N=1655) were included in the meta-analysis. Most trials identified were industry-sponsored, and an asymmetric funnel plot indicated publication bias. Pooled results of published trials found that skin substitutes increased the likelihood of achieving complete ulcer closure compared with standard of care (SOC) alone (relative risk, 1.55; 95% CI, 1.30 to 1.85). Use of skin substitutes also led to a statistically significant reduction in amputations (relative risk, 0.43; 95% CI, 0.23 to 0.81), although the absolute risk difference was small. Analysis by individual products found a statistically significant benefit on ulcer closure for Apligraf, EpiFix, and Hyalograft-3D. The products that did not show a statistically significant benefit for ulcer closure were Dermagraft, Graftjacket, Kaloderm, and OrCel.

Martinson and Martinson (2016) conducted an industry-sponsored analysis of Medicare claims data (13,193 treatment episodes) to compare efficacy and cost of skin substitutes for the management of diabetic foot ulcers.(25) Included in the analysis were treatment episodes with Apligraf (37%), Dermagraft (42%), Oasis (19%), and Cytal (MatriStem, 2%). The mean number of applications was 3.24 for Apligraf, 4.48 for Oasis, 5.53 for Cytal, and 5.96 for Dermagraft. All comparisons were statistically significant. Healing at 90 days was modestly but statistically higher for Oasis (63%) and Cytal (62%) than for Apligraf (58%) or Dermagraft (58%). Amputation rates were similar after treatment with the four products, ranging from 1.3% for Oasis to 2.1% for Cytal.

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

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

Apligraf

Veves et al (2001) reported on a randomized prospective trial on the effectiveness of Apligraf (previously called Graftskin), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers.(27) The trial involved 24 centers in the United States; 208 patients were randomized to ulcer treatment with Apligraf (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical débridement and adequate foot off-loading, was provided in both groups. Apligraf was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of five 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, which was significantly lower than the 90 days observed in the control group (p=0.003). The rates of adverse reactions were similar between groups, except osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf group. Trialists concluded that application of Apligraf for a maximum of 4 weeks resulted in higher healing rates than state-of-the-art treatment and was not associated with any significant adverse events. This trial was reviewed in a 2001 TEC Assessment, which concluded that Apligraf, in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.(28)

Steinberg et al (2010) reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of noninfected diabetic foot ulcers.(29) The study design and patient population were similar to the 208-subject U.S. study (previously described), which led to 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 two weeks were enrolled in prospective, multicenter, open-label RCTs that compared Apligraf use plus standard therapy (sharp débridement, standard wound care, off-loading) with standard therapy alone. Pooling of data was performed because of the similarity and consistency of the two studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration, which was significantly longer in the European study (21 months vs 10 months in the U.S. study). Reported adverse events by 12 weeks were comparable across treatment groups in the two

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 ulcers.

Kirsner et al (2010) analyzed 2517 patients with diabetic neuropathic foot ulcers treated between 2001 and 2004.(30) This retrospective analysis used a wound care database; the patients received advanced biologic therapy, specifically, Apligraf (446 patients), Regranex, or Procuren. The analysis found that advanced biologic therapy was used, on average, within 28 days from the first wound clinic visit and was associated with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biologic therapy were 31% more likely to heal than wounds first treated with topical recombinant growth factor ($p<0.001$) and 40% more likely to heal than those first treated with platelet release ($p=0.01$). Wound size, wound grade, duration of wound, and time to initiation of advanced biologic therapy affected the time to healing.

Dermagraft

A 2003 pivotal multicenter FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft (human-derived fibroblasts cultured on mesh) or control.(31) Over the 12-week study, patients received up to 8 applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91% compared with 78% for the control group. Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious adverse events were attributed to Dermagraft. Ulcer infections developed in 10.4% of the Dermagraft patients compared with 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group (19% vs 32.5%). A 2015 retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft (5.5% vs 12.6%, $p=0.031$).(32) Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

AlloPatch

AlloPatch Pliable human reticular acellular dermis was compared with SOC in an industry-sponsored multicenter trial by Zelen et al (2017-2018).(33,34) The initial trial, with 20 patients per group, was extended to determine the percent healing at 6 weeks with 40 patients per group. Healing was evaluated by the site investigator and confirmed by an independent panel. At six weeks, 68% (27/40) of wounds treated using AlloPatch had healed compared with 15% (6/40) in the SOC-alone group ($p<0.001$). At 12 weeks, 80% (32/40) of patients in the AlloPatch group had healed compared to 30% (12/40) in the control group. Mean time to heal within 12 weeks was 38 days (95% CI: 29-47 days) for the HR-ADM group and 72 days (95% CI: 66-78 days) for the SOC group ($p < 0.001$).

Integra Omnigraft Dermal Regeneration Template or Integra Flowable Wound Matrix

Integra Dermal Regeneration Template is a biosynthetic skin substitute that is FDA-approved for life-threatening thermal injury. The FOUNDER (Foot Ulcer New Dermal Replacement) multicenter study (32 sites) assessed Integra Dermal Regeneration Template (marketed as

Omnigraft) for chronic nonhealing diabetic foot ulcers under an FDA-regulated investigational device exemption.(35) A total of 307 patients with at least 1 chronic diabetic foot ulcer were randomized to treatment with the Integra Template or a control condition (sodium chloride gel 0.9%). Treatment was given for 16 weeks or until wound closure. There was a modest increase in wound closure with the Integra Template (51% vs 32%, p=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 after10 weeks. Trial strengths included adequate power to detect an increase in wound healing of 18%, which was considered to be clinically significant, secondary outcomes of wound closure and time to wound closure by computerized planimetry, and ITT analysis.

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

Table 4. Probability of Wound Healing With IFWM vs SOC

Study	Complete Wound Healing	Rehospitalization	Major Amputation
Campitiello et al (2017)[35]			
IFWM, n (%)	20 (86.95)	2 (6.69)	1 (4.34)
SOC, n (%)	12 (52.17)	10 (43.47)	7 (30.43)
RR (95% CI)	1.67 (1.09 to 2.54)	0.10 (0.01 to 0.72)	0.16 (0.02 to 1.17)
p	0.010	0.001	0.028

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

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

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

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

Graftjacket Regenerative Tissue Matrix

Brigido et al (2004) reported a small (N=40) randomized pilot study comparing Graftjacket with conventional treatment for chronic nonhealing diabetic foot ulcers.(37) Control patients received conventional therapy with 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 one month results showed that, after a single treatment, ulcers treated with Graftjacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs 15%), width (50% vs 23%), area (73% vs 34%), and depth (89% vs 25%), respectively. With

follow-up to four weeks, no data were reported on the proportion with complete closure or the mean time to heal. All grafts were incorporated into the host tissue.

Reyzelman et al (2009) reported an industry-sponsored multicenter randomized study that compared a single application of Graftjacket with SOC in 86 patients with diabetic foot ulcers.(38) Eight patients, six in the study group and two 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 vs 6.8 weeks for the control group. The authors did not report whether this difference was statistically significant. Median time to healing was 4.5 weeks for Graftjacket (range, 1-12 weeks) and 7.0 weeks for control (range, 2-12 weeks). Kaplan-Meier method survivorship analysis for time to complete healing at 12 weeks showed a significantly lower nonhealing rate for the study group (30.4%) than for the control group (53.9%). The authors commented that a single application of Graftjacket, as used in this study, was often sufficient for complete healing. Conclusions drawn from this study are limited by the small study population and differences in ulcer size at baseline. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant.

Reyzelman and Bazarov (2015) (39) reported an industry-sponsored meta-analysis of Graftjacket for diabetic foot ulcers that included the two studies described above and a third RCT by Brigido (2006) (40) with 28 patients (N=154). The time to heal was estimated for the 2004 Brigido study, based on the average wound reduction per week. The estimated difference in time to heal was considerably larger for Brigido's 2004 study (-4.30 weeks) than for the other two studies that measured the difference in time to heal (-1.58 weeks and -1.10 weeks). Analysis of the proportion of wounds that healed included Brigido (2006) and Reyzelman et al (2009). The odds ratio in the smaller study by Brigido was considerably larger, with a lack of precision in the estimate (odds ratio, 15.0; 95% CI, 2.26 to 99.64), and the combined odds (3.75; 95% CI, 1.72 to 8.19) was not significant when analyzed using a random-effects model. Potential sources of bias, noted by Reyzelman and Bazarov, included publication and reporting biases, study selection biases, incomplete data selection, post hoc manipulation of data, and subjective choice of analytic methods. Overall, results of these studies do not provide convincing evidence that Graftjacket is more effective than SOC for healing diabetic foot ulcers.

DermACELL vs Graftjacket Regenerative Tissue Matrix or SOC

DermACELL and Graftjacket are both composed of human ADM. Walters et al (2016) reported on a multicenter randomized comparison of DermACELL, Graftjacket, or SOC (2:1:2 ratio) in 168 patients with diabetic foot ulcers.(41) The study was sponsored by LifeNet Health, a nonprofit organ procurement association and processor for DermACELL. At 16 weeks, the proportion of completely healed ulcers was 67.9% for DermACELL, 47.8% for Graftjacket, and 48.1% for SOC. The 20% difference in completely healed ulcers was statistically significant for DermACELL vs SOC (p=0.039). The mean time to complete wound closure did not differ significantly for DermACELL (8.6 weeks), Graftjacket (8.6 weeks), and SOC (8.7 weeks).

A second report from this study was published in 2017.(42) This analysis compared DermACELL with SOC and did not include the Graftjacket arm. The authors reported that either 1 or 2 applications of DermACELL led to a greater proportion of wounds healed compared with SOC in per protocol analysis (see Table 5), but there was no significant

difference between DermACELL (1 or 2 applications) and SOC when analyzed by intention-to-treat. For the group of patients who received only a single application, the percentage of patients who achieved complete wound healing was significantly higher than SOC at 16 and 24 weeks, but not at 12 weeks. Although reported as an ITT analysis, results were analyzed only for the group who received a single application of DermACELL. This would not typically be considered ITT unless the number of DermACELL applications was prespecified.

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

Study	Single Application			One or Two Applications		
	% With Wound Healing at 12 Wk	*% With Wound Healing at 16 Wk*	*% With Wound Healing at 24 Wk*	*% With Wound Healing at 12 Wk*	*% With Wound Healing at 16 Wk*	*% With Wound Healing at 24 Wk*
Cazzell et al (2017)[36.]						
DermACELL, %	65.0%	82.5%	89.7%	NR	67.9%	83.7%
SOC, %	41.1%	48.1%	67.3%	NR	48.1%	67.3%
HR (95% CI)	1.97 (1.1 to 3.5)	2.40 (1.4 to 4.1)	2.11 (1.3 to 3.5)		1.72 (1.04 to 2.83)	1.55 (0.98 to 2.44)
p	0.012	<0.001	<0.001	*NS*	0.028	0.049

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

TheraSkin Versus Standard of Care

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

TheraSkin vs Dermagraft

Sanders et al (2014) reported on a small (N=23) industry-funded randomized comparison of TheraSkin (cryopreserved human skin allograft with living fibroblasts and keratinocytes) and Dermagraft for diabetic foot ulcers.(44) Wound size at baseline ranged from 0.5 to 18.02 cm^2; the average wound size was about 5 cm^2 and was similar for the two 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 two 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).

TheraSkin vs Apligraf

DiDomenico et al (2011) compared TheraSkin with Apligraf for the treatment of diabetic foot ulcers in a small (N=29) RCT.(45) The risk of bias in this study is uncertain, because reporting did not include a description of power analysis, statistical analysis, method of randomization, or blinding. The percentage of wounds closed at 12 weeks was 41.3% in the Apligraf group and 66.7% in the TheraSkin group. Results at 20 weeks were not substantially changed from those at 12 weeks, with 47.1% of wounds closed in the Apligraf group and 66.7% closed in the TheraSkin group. The percentage healed in the Apligraf group was lower than expected based on prior studies. The average number of grafts applied was similar for both groups (1.53 for Apligraf, 1.38 for TheraSkin). The low number of dressing changes may have influenced results, with little change in the percentage of wounds closed between 12 and 20 weeks. An adequately powered trial with blinded evaluation of wound healing and a standard treatment regimen would permit greater certainty on the efficacy of this product.

Cytal (MatriStem) vs Dermagraft

Frykberg et al (2017) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cytal (a porcine urinary bladder-derived extracellular matrix) vs Dermagraft in 56 patients with diabetic foot ulcers.(46) The mean duration of ulcers before treatment was 263 days (range, 30-1095 days). The primary outcome was the percent wound closure with up to eight 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 with two (6.9%) wounds treated with Dermagraft (p=not significant [*NS]*). Quality of life (QOL), 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.

PriMatrix

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

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

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

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

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	*Comparator*

Lantis et al (2021)[47] NCT03010319	US	21	2019-2020	Diabetic foot ulcer for a minimum of 2 weeks, adequate vascular perfusion to the affected extremity	PriMatrix plus standard of care n = 103	Standard of care n = 104

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

Study	Wound Healed at 12 weeks	Median Time to Heal, days (range)	AEs
Lantis et al (2021)[47] NCT03010319			
Number analyzed	207	76	226
Primatrix	47/103 (45.6%)	43 (22 to 93)	Any AE: 44.8%
Standard Care	29/104 (27.9%)	57 (16 to 88)	Any AE: 46.4%
Treatment Effect	HR 2.02 (95% CI 1.3 to 3.2)		
p	.008	0.362	

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

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

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

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

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

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

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4.

Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other

Nonrandomized Studies

Kavros et al (2014) reported a prospective multicenter study of PriMatrix (a xenograft fetal bovine dermal collagen matrix) for the treatment of chronic diabetic foot ulcers in 55 patients.(48) The average duration of ulcers before treatment was 286 days, and the average wound area was 4.34 cm^2. Of the 46 patients who completed the study, 76% healed by 12 weeks with an average of 2 applications of PriMatrix. For the ITT population, 64% of wounds healed by 12 weeks.

Karr (2011) published a retrospective comparison of PriMatrix and Apligraf in 40 diabetic foot ulcers.(49) The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. The criteria were: diabetic foot ulcers of 4 weeks in duration; ulcer of at least 1 cm^2 in diameter and to the depth of subcutaneous tissue; healthy tissue at the ulcer; adequate arterial perfusion to heal; and ability to off-load the diabetic ulcer. The time to complete healing for PriMatrix was 38 days with 1.5 applications compared with 87 days with 2 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to compare the efficacy of PriMatrix with current SOC or advanced wound therapies.

Oasis Wound Matrix vs Regranex Gel

Niezgoda et al (2005) compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix (a porcine acellular wound care product) to Regranex Gel.(50) This industry-sponsored, multicenter RCT was conducted at 9 outpatient wound care clinics and involved 73 patients with at least 1 diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix (n=37) or Regranex Gel (n=36) and 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 I diabetes (33% vs 25%) but showed a significant improvement in patients with Type II 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.

Autologous Grafting on HYAFF Scaffolds

Uccioli et al (2011) reported a multicenter RCT of cultured expanded fibroblasts and keratinocytes grown on a HYAFF scaffold (benzyl ester of hyaluronic acid) compared with paraffin gauze for difficult diabetic foot ulcers.(51) A total of 180 patients were randomized. At 12 weeks, complete ulcer healing was similar for the two groups (24% treated vs 21% controls). At 20 weeks, complete ulcer healing was achieved in a similar proportion of the

treatment group (50%) and the control group (43%, log-rank test = 0.344). Subgroup analysis, adjusted for baseline factors and possibly post-hoc, found a statistically significant benefit of treatment on dorsal ulcers but not plantar ulcers.

Omega3 Wound

Lullove et al (2022) reported results of a RCT of the Omega3 Wound plus standard wound care compared to standard care alone in individuals with diabetic lower extremity skin ulcers (Tables 10). The 2021 publication was an initial report of 49 patients and the 2022 publication was an unscheduled interim analysis of these same 49 participants plus an additional 45 participants.(52,53) One-year follow-up is planned but results have not yet been published. The primary outcome of the trial was healing at 12 weeks. Complete ulcer healing was based on the site investigator's assessment, as evidenced by complete (100%) re-epithelialization without drainage and need of dressing. An independent panel of wound care experts who were blinded to the patient allocation process and the principal investigator's assessment reviewed all study-related decisions made by the site investigators and confirmed healing status. Secondary outcomes were time to heal and wound area reduction by percentage at 12 weeks. Patients underwent a 2-week run-in period prior to randomization. If the ulcer reduced in area by 20% or more after 14 days of standard care, the patient was excluded as a screening failure. If the wound area was reduced by less than 20%, the patient was randomized and enrolled in the study. Among the subset of wounds that did not heal completely by 12 weeks (n = 40), there was a larger percent wound reduction in the intervention group (69.3% vs 44.2%; p =.015).

Study limitations are summarized in Table 11. At 12 weeks, the complete healing rate was significantly higher in the intervention arm (63.0% vs 31.3%), but time to healing was similar between groups for wounds that healed completely.

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

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

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

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

Study	Wound Healed at 12 weeks	Time to Heal	Percent Wound Reduction at 12 Weeks for Wounds that did not Heal	Adverse events
Lullove et al (2021)[52] NCT04133493				
N analyzed	49		34	
Omega3 Wound	63.0% (29/46)		69.3% (SD not reported)	Not reported
Standard Care	31.3% (15/48)	Mean 7 weeks in both groups	44.2% (SD not reported)	Not reported
p	0.0036		.015	

SD: standard deviation

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

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

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

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

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Lullove et al (2021)[52], NCT04133493	3. Allocation concealment not described.	1. Patients and investigator not blinded, although an independent panel confirmed healing.		1. 15/49 (30.6%) patients were excluded from the analysis of wound area reduction at 12 weeks. Per protocol, patients exited from study if their wound had healed less than 50% at 6 weeks and were not included when wound area reduction at 12 weeks was calculated.		3. Confidence intervals not reported

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other

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

Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients who only required a single application of the ADM. Studies are needed to

further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of Graftjacket, TheraSkin, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies.

LOWER-EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

Review of Evidence

Apligraf

Falanga et al (1998) reported on a multicenter randomized trial of Apligraf living cell therapy.(54) 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 three weeks. The primary end points were the percentage of patients with complete healing by six months after initiation of treatment and the time required for complete healing. At six-month follow-up, the percentage of patients healed was higher with Apligraf (63% vs 49%), and the median time to complete wound closure was shorter (61 days vs 181 days). Treatment with Apligraf was superior to compression therapy in healing larger (>1000 mm^2) and deeper ulcers and ulcers of more than 6 months in duration. There were no symptoms or signs of rejection, and the occurrence of adverse events was similar in both groups. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (Graftskin), in conjunction with good local wound care, met TEC criteria for the treatment of venous ulcers that fail to respond to conservative management.(28)

Oasis Wound Matrix

Mostow et al (2005) reported on an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment using Oasis Wound Matrix (xenogeneic collagen scaffold from porcine small intestinal mucosa) with SOC in 120 patients who had chronic ulcers due to venous insufficiency that had not adequately responding to conventional therapy.(55) Healing was assessed weekly for up to 12 weeks, with follow-up performed after six 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 three 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 two comparative studies of the Oasis matrix for mixed arteriovenous ulcers. In a 2007 quasi randomized study, Romanelli et al compared the efficacy of two extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid).(56) Fifty-four patients with mixed arteriovenous leg ulcers were assigned to the two arms based on order of entry into the study; 50 patients completed the study. Patients were followed twice weekly, and dressings changed more than once a week, only when necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis-treated ulcers compared with 46.2% of Hyaloskin-treated ulcers. Oasis treatment significantly increased the time to dressing change (mean, 6.4 days vs 2.4 days), reduced pain on a 10-point scale (3.7 vs 6.2), and improved patient comfort (2.5 vs 6.7).

Romanelli et al (2010) compared Oasis with a moist wound dressing (SOC) in 23 patients with mixed arteriovenous ulcers and 27 patients with venous ulcers.(57) 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 six months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis-treated ulcers at eight weeks compared with 65% of the SOC group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks compared with 8.3 weeks for the SOC group. Treatment with Oasis also increased the time to dressing change (5.2 days vs 2.1 days) and the percentage of granulation tissue formed (65% vs 38%).

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

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

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

Dermagraft

Dermagraft living cell therapy has been approved by FDA for repair of diabetic foot ulcers. Use of Dermagraft for venous ulcers is an off-label indication. Harding et al (2013) reported an open-label multicenter RCT that compared Dermagraft plus compression therapy (n=186) with compression therapy alone (n=180).(58) The trial had numerous inclusion and exclusion criteria that restricted the population to patients who had nonhealing ulcers with compression therapy but had the capacity to heal. ITT analysis revealed no significant difference between the two groups in the primary outcome measure, the proportion of patients with completely healed ulcers by 12 weeks (34% Dermagraft vs 31% control). Prespecified subgroup analysis revealed a significant improvement in the percentage of wounds healed for ulcers of 12 months or less in duration (52% vs 37%) and for ulcers of 10 cm or less in diameter (47% vs 39%). There were no significant differences in the secondary outcomes of time to healing, complete healing by week 24, and percent reduction in ulcer area.

PriMatrix

Karr (2011) published a retrospective comparison of PriMatrix (xenogenic ADM) and Apligraf in 28 venous stasis ulcers.(49) The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Criteria were venous stasis ulcers of 4 weeks in duration, at least 1 cm^2 in diameter, and to a depth of subcutaneous tissue, with healthy tissue at the ulcer edge, adequate arterial perfusion to heal, and ability to tolerate compression therapy. The time to complete healing for PriMatrix was 32 days with 1.3 applications compared with 63 days with 1.7 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to assess the effect of PriMatrix treatment in compared with current SOC.

DermACELL

Cazzell (2019) published an RCT on DermACELL ADM for venous leg ulcers in 18 patients (see Table 6).(59) This was part of a larger study of the acellular dermal matrix for chronic wounds of the lower extremity in 202 patients; the component on diabetic lower extremity ulcers was previously reported by Cazzell et al (2017) and is described above.(42) When including patients who required more than one application of the ADM, the percent of wounds

closed at 24 weeks was 29.4% with DermACELL and 33.3% with SOC, suggesting no benefit DermACELL for the treatment of venous ulcers in this small sub study.

Table 14. Summary of Key RCT Characteristics

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

RCT: randomized controlled trial; SOC: standard of care

TheraSkin Versus Standard of Care

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

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

In a moderately large RCT, Dermagraft was not shown to be more effective than controls in the primary or secondary 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 needed to evaluate the effect of PriMatrix treatment compared with current SOC.

DEEP DERMAL BURNS

Review of Evidence

Epicel

One case series from 2000 has described the treatment of 30 severely burned patients with Epicel.(60) The cultured epithelial autografts were applied to a mean of 37% of total body surface area (TBSA). Epicel achieved permanent coverage of a mean of 26% of TBSA, an area similar to that covered by conventional autografts (mean, 25%). Survival was 90% in these severely burned patients.

Integra Dermal Regeneration Template

A 2013 study compared Integra with split-thickness skin graft and with viscose cellulose sponge (Cellonex), using three 10x5 cm test sites on each of 10 burn patients.(61) 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 three methods resulted in similar clinical appearance, along with similar histologic and immunohistochemical findings.

Branski et al (2007) reported on a randomized trial that compared Integra with a standard autograft-allograft technique in 20 children with an average burn size of 73% TBSA (71% full-thickness burns).(62) 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 for 2 years, and cumulative operating room time required for these procedures. The authors concluded that Integra can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

Heimbach et al (2003) reported on a multicenter (13 U.S. burn care facilities) post-approval study involving 222 burn injury patients (36.5% TBSA; range, 1%-95%) who were treated with Integra Dermal Regeneration Template.(63) Within 2 to 3 weeks, the dermal layer regenerated, and a thin epidermal autograft was placed over the wound. The incidence of infection was 16.3%. Mean take rate (absence of graft failure) of Integra was 76.2%; the median take rate was 98%. The mean take rate of epidermal autograft placed over Integra was 87.7%; the median take rate was 95%.

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

An infection rate of 18% was noted in a systematic review of complication rates in 10 studies that used Integra dermal regeneration template for burns.(65)

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

TransCyte
Earlier studies included a 2001 report by Lukish et al that found improved healing in 20 consecutive cases of pediatric burns greater than 7% TBSA that underwent wound closure using TransCyte compared to the previous 20 consecutive burn cases greater than 7% TBSA that received standard therapy.(68) In 2006, Amani et al found significant improvement in healing in 110 consecutive patients who had deep partial-thickness burns treated with TransCyte as compared to results from the American Burn Association Patient Registry for similar burns.(69)

Section Summary: Deep Dermal Burns
Epicel is FDA-approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a TBSA of 30% or more, with patient survival of 90%. Integra Dermal Regeneration

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

OTHER INDICATIONS

DYSTROPHIC EPIDERMOLYSIS BULLOSA

OrCel was approved under a humanitarian device exemption (HDE) for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. HDE status has been withdrawn for Dermagraft for this indication.

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

Section Summary: Dystrophic Epidermolysis Bullosa

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

Punch Biopsy Wounds

Baldursson et al (2015) reported a double-blinded RCT with 81 patients (162 punch biopsy wounds) that compared Kerecis Omega3 Wound (derived from fish skin) with Oasis SIS ECM (porcine small intestinal submucosa extracellular matrix).(71) The primary outcome (the percentage of wounds healed at 28 days) was similar for the fish skin ADM (95%) and the porcine SIS ECM (96.3%). The rate of healing was faster with Kerecis Omega3 (p=0.041). At 21 days, 72.5% of the fish skin ADM group had healed compared with 56% of the porcine SIS ECM group. Interpretation of this study is limited because it did not include an accepted control condition for this indication.

Split-Thickness Donor Sites

There is limited evidence to support the efficacy of OrCel compared with SOC for the treatment of split-thickness donor sites in burn patients. 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.(72) Each patient had two designated donor sites that were randomized to a single treatment of OrCel or standard dressing (Biobrane-L). The healing time for OrCel sites was significantly shorter than for sites treated with a standard dressing, enabling earlier re-cropping. OrCel sites also exhibited a nonsignificant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

Pressure Ulcers

Brown-Etris et al (2019) reported an RCT of 130 patients with stage III or stage IV pressure ulcers who were treated with Oasis Wound Matrix (extracellular collagen matrix derived from porcine small intestinal submucosa) plus SOC or SOC alone.(73) At 12 weeks, the proportion of wounds healed in the collagen matrix group was 40% compared to 29% in the SOC group. This was not statistically significant (p=0.111). There was a statistical difference in the proportion of patients who achieved 90% wound healing (55% vs. 38% p=0.037), but complete

wound healing is the preferred and most reliable measure. It is possible that longer follow-up may have identified a significant improvement in the percent of wounds healed. The study did include six-month follow-up, but there was high loss to follow-up and an insufficient number of patients at this time point for statistical comparison.

In the propensity matched study by Gurtner et al (2020) described above, Theraskin improved the healing rate of pressure ulcers by 20% (66.7% vs 46.8%).(42)

Miscellaneous
In addition to indications previously reviewed, off-label uses of bioengineered skin substitutes have included pressure ulcers, inflammatory ulcers (e.g., pyoderma gangrenosum, vasculitis), scleroderma digital ulcers, post-keloid removal wounds, genetic conditions, and variety of other conditions.(71) Products that have been FDA-approved or -cleared for one indication (e.g., lower-extremity ulcers) have also been used off-label in place of other FDA-approved or -cleared products (e.g., for burns).(72) No controlled trials were identified for these indications.

SUMMARY OF EVIDENCE

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

Tendon Repair
For individuals who are undergoing tendon repair who receive Graftjacket, the evidence includes RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. The RCT identified found improved outcomes with the Graftjacket ADM allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of patients is needed to evaluate the consistency of the effect. The evidence is insufficient to determine 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, the evidence includes RCTs. Relevant outcomes are 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 (biosynthetic) over the standard of care (SOC). 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 ADM products other than AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients who only required a single application of the ADM. Studies are needed to further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of Graftjacket, TheraSkin, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies. The evidence is insufficient to determine 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 xenogeneic 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 xenogeneic PriMatrix skin substitute vs 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 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 (e.g., five 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 (i.e., Epicel, Integra Dermal Regeneration Template), the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, few skin substitutes have been approved, and the evidence is limited for each product. Epicel (living cell

therapy) has received FDA approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. Comparative studies have demonstrated improved outcomes for biosynthetic skin substitute Integra Dermal Regeneration Template for the treatment of burns. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems.(76) The Institute recommended that clinicians "consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service."

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 6.

Table 15. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04537520[a]	Interventional Multi-Center Post Market Randomized Controlled Open-Label Clinical Trial Comparing Kerecis Omega3 Wound Versus SOC in Hard to Heal Diabetic Foot Wounds	180	Feb 2022
NCT04257370[a]	An Open Label, Randomized Controlled Study to Compare Healing of Severe Diabetic Foot Ulcers and Forefoot Amputations in Diabetics With and Without Moderate Peripheral Arterial Disease Treated With Kerecis Omega3 Wound and SOC vs. SOC Alone	330	Oct 2022
NCT02587403[a]	A Randomized, Prospective Study Comparing Fortiva™ Porcine Dermis vs. Strattice™ Reconstructive Tissue Matrix in Patients Undergoing Complex Open Primary Ventral Hernia Repair	120	Feb 2024
NCT04133493[a]	A Multi-center, Randomized Controlled Clinical Trial Evaluating the Effect ofOmega3 Wound Fish Skin Graft in the Treatment of Diabetic Foot Ulcers	100	Jan 2023

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

Government Regulations

National:

In 2019, CMS reported that it is finalizing the proposal to continue the policy established in CY 2018 to assign skin substitutes to the low cost or high-cost group.(76) In addition, CMS

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

Porcine Skin and Gradient Pressure Dressings Pub 100-3, Ch 4. Rev. 198, 6/29/17; (270.5); Rev. 1, 10/3/03. Longstanding national coverage determination. Effective date has not been posted.

Indications and Limitations of Coverage
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.

Local:

Application of Bioengineered Skin Substitutes (L34593) for services performed on or after 1/1/16 (Retired 3/1/16)

This LCD covers the use of skin substitutes and related products in the treatment of lower extremity ulcer disease. The LCD does not pertain or otherwise apply to the use of any skin substitutes or related products in the treatment of burns, skin cancer, or for true reconstructive surgery.

Indications
Application of bioengineered skin substitutes will be covered when the following conditions are met and documented as appropriate for the individual patient:

1. Presence of neuropathic diabetic foot ulcers for greater than four (4) weeks duration
2. Presence of venous stasis ulcers of greater than (1) one month duration that have failed to respond to documented conservative measures for greater than one (1) month duration
3. Presence of neuropathic diabetic foot ulcers that have failed to respond to documented conservative measures for greater than one (1) month duration. These measures must include appropriate steps to off-load pressure during treatment.
4. Presence of partial or full-thickness ulcers
5. Measurements of the initial ulcer size, the size following cessation of any conservative management and the size at the beginning of skin substitute treatment.

In all cases, the ulcer must be free of infection and underlying osteomyelitis. Documentation must be provided that these conditions have been successfully treated, resolved, prior to instituting skin substitute treatment.

Medicare accepts the Federal Drug Administration's (FDA) classification and description of any bioengineered skin substitute. Application of a Bioengineered Skin Substitute is covered when the following conditions are met and documented as appropriate for the individual patient:

1. Beneficiaries with diabetes under current medical management and controlled with stable HgbA1c level.
2. Venous stasis ulcers that have failed to heal, using conservative measures.
3. Neuropathic diabetic foot ulcers that have failed to heal, using conservative measures.
4. Ulcers that, do not involve tendon, muscle or joint capsule, or have bone exposure, extend through the dermis Unless specifically indicated within the FDA approved package insert.
5. Beneficiaries with adequate arterial blood supply to the foot evidenced by a palpable pulse on the foot (either dorsalis pedis or posterior tibial artery) or an Ankle Brachial Index (ABI) of 0.65 or greater.
6. Neuropathic diabetic foot ulcers that have been treated with appropriate steps to off-load pressure.
7. The ulcer must be free of infection and underlying osteomyelitis.

The following SKIN Substitutes are currently covered under Medicare in an inpatient hospital, outpatient hospital, ambulatory surgical center, or office setting:

Q4101 Skin substitute, apligraf, per square centimeter
Q4102 Skin substitute, oasis wound matrix, per square centimeter
Q4106 Skin substitute, dermagraft, per square centimeter
Q4107 Graftjacket, per square centimeter
Q4110 Skin substitute, primatrix, per square centimeter
Q4121 Theraskin per square centimeter
Q4131 EpiFix per square centimeter

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Amniotic Membrane and Amniotic Fluid

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 5/24/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/01/06	8/30/06	9/18/06	Joint policy established
3/1/07	12/28/06	1/15/07	Policy updated with new FDA-approved items.
5/1/08	2/19/08	5/1/08	Routine maintenance
11/1/09	8/18/09	8/18/09	Maintenance, new codes added
11/1/10	8/17/10	8/17/10	Maintenance, new code added
9/1/11	6/21/11	6/21/11	Policy updated with new codes; J codes removed; added Q4117-Q4121, G0440-G0441, 15330-15336, 15430,15431; nomenclature revised for codes Q4101-Q4115 to remove “skin substitute” from the descriptors; Flex HD® added to list of human derived tissue; added Medicare criteria to Inclusions relative to diabetic wounds.
11/1/12	7/30/12	7/30/12	Policy updated with new codes effective 1/1/12: 15271-15278, C9366-C9369, Q4122- Q4130; Theraskin (Q4121) and GraftJacket (Q4107) added as approved human tissue products; deleted codes 15170-15175, 15330-15336, 15340-15341, 15360-15366,15400-15401,15420-15421, 15430-15431, C9365, G0440, G0441.
11/1/13	8/20/13	9/3/13	Codes added to policy: 15777, Q4126, Q4131-Q4136, A6010-A6011, C9356, C9358, C9360 and C9364; Medical Policy Statement and Inclusion section revised to reflect EpiFix as established.
3/1/15	12/12/14	12/29/14	Routine maintenance; added codes A6021-A6023; updated CMS information
7/1/15	4/24/15	5/8/15	Codes added: Q4137-Q4160
7/1/16	4/19/16	4/19/16	Routine maintenance Added codes: Q4161-Q4165

			Moved codes Q4147 Q4149 and Q4158 under covered codes Removed C codes from policy
3/1/17	12/13/16	12/13/16	• Routine maintenance • Continues to diverge from BCBSA - No similarities • Codes added: Q4166-Q4175 Deleted codes: Q4118-Q4120, Q4129
5/1/17	5/9/17	5/9/17	• Continues to diverge from BCBSA except: - Moved codes Q4132 and Q4133 to "established" section of HCPCS codes for Grafix products to mirror BCBSA determination.
7/1/18	3/20/18	3/12/18	• Routine maintenance • Codes added: C9358 and C9360 • Deleted Unite Biomatrix – no longer available • Codes added Q4176-Q4182 Policy rewrite to cover BCBSA indications, and FDA and CMS approved products
3/1/19	12/11/18		• Routine maintenance Amniotic products and codes removed from policy (Grafix, EpiFix, amnioband, neox, woundEx, palinGen); new policy written
3/1/20	12/17/19		• Routine maintenance • Codes added as investigational: Q4193, Q4197, Q4200, Q4202, Q4220, Q4222, Q2226 • Codes added as Established – FDA approved: Q4195, Q4196, Q4203 Q4172 deleted – per AMA
11/1/20	8/18/20		• Routine maintenance

11/1/21	8/17/21		• Routine maintenance • Products cross checked and added to Incl and Excl based on FDA approval, BCBSA coverage or Medicare coverage.
11/1/22	8/16/22		• Routine maintenance • Inclusions updated with FDA approved products
3/1/23	12/20/22		• Off schedule review for code update: added A2015, A2014, A2016, A2017, A2018 • Nomenclature update to Q4128 (Matrix HD removed) (slp)
11/1/23	8/15/23		• Routine maintenance (slp) • Vendor managed: N/A • Code update – NeoMatrix added as EST (A2021); Kerecis Omega3 Marigen (A2019) and AC5 Advance wound system (A2020) added as EI • Recell and Ac5 added as EI • Clarification added to cross reference FDA approved products with regulatory section for specified uses

Next Review Date: 3rd Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: SKIN AND TISSUE SUBSTITUTES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.