
Medical Policy



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***Current Policy Effective Date: 11/1/26**
(See policy history boxes for previous effective dates)

Title: Skin and Tissue Substitutes

Description

Skin substitutes, including bioengineered skin, bioengineered soft tissue, human skin equivalents, and artificial skin, are applied to wounds to facilitate healing by replicating key properties of natural skin. While they mimic certain characteristics of human skin, they do not replace the function of a skin graft and are not intended as a substitute for autologous skin transplantation. They are derived from various sources, including human tissue, other species (e.g., bovine, porcine), synthetic materials, or a combination of any of the above.

Medical Policy Statement

The use of skin and tissue substitutes is established when specified criteria are met.

Inclusionary and Exclusionary Guidelines

U.S. Food & Drug Administration (FDA) approval alone is not sufficient to establish medical necessity; product-specific evidence must demonstrate the product's safety, effectiveness, and a clinically meaningful improvement in net health outcomes.

Inclusions:

The use of skin and tissue substitutes has been scientifically validated and may be considered medically necessary for the following indications, provided the specified criteria are met:

BREAST RECONSTRUCTION FOLLOWING CANCER TREATMENT (POST-MASTECTOMY):

ONE of the criteria 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.

and

ONE of the following products are used:

- AlloDerm®
- AlloMend®
- Cortiva® [AlloMax™]
- DermACELL™
- DermaMatrix™
- FlexHD®
- FlexHD® Pliable™

DIABETIC FOOT ULCERS: chronic, non-infected, or full-thickness

ALL of the following criteria are met:

- Physician documentation of medical management for clinically documented type 1 or type 2 diabetes
- Failure to achieve at least 50% ulcer area reduction with a minimum of 4 weeks of documented compliance with standard of care^a (SOC) treatment.
- The wound is a non-infected full thickness neuropathic diabetic foot ulcer and at least 1.0 cm² in size due to clinically documented diabetic neuropathy.
- The ulcer extends through the dermis but does not involve the tendon, muscle, capsule, or exposed bone.
- There is adequate arterial blood supply to support tissue growth.
- The foot is free of Charcot's arthropathy.

and

ONE of the following products are used:

- AlloPatch HD®
- Apligraf®
- DermACELL®
- Derma-Gide®
- GraftJacket®
- Integra® Dermal Regeneration Template (DRT)
- Kerecis® Omega3
- Kerecis® Omega3 Marigen
- Oasis® Wound Matrix
- PriMatrix®
- TheraSkin®

^a SOC treatment includes, but is not limited to mechanical offloading, infection control, limb elevation, debridement of necrotic tissue, management of systemic disease and medications, nutrition assessment, tissue perfusion and oxygenation, education regarding care of the foot, including callus nails, and fitting of shoes, as well as counseling on the risk of continued tobacco use. In addition, maintenance of a moist ulcer environment through appropriate dressings facilitates development of healthy granulation tissue and epithelialization and potentiates complete healing at an ulcer site.

CHRONIC VENOUS INSUFFICIENCY LOWER EXTREMITY ULCERS:

ALL of the following criteria are met:

- Physician documentation of medical management for clinically documented chronic lower extremity venous insufficiency.
- Failure to achieve at least 50% ulcer area reduction with a minimum of 4 weeks of documented compliance with SOC treatment^a
- The wound is a non-infected full thickness venous stasis ulcer and at least 1.0 cm² in size due to clinically documented venous insufficiency.
- The ulcer extends through the dermis but does not involve the tendon, muscle, capsule, or exposed bone.
- There is adequate arterial blood supply to support tissue growth.

and

ONE of the following products are used:

- Apligraf®
- Oasis Wound Matrix

DYSTROPHIC EPIDERMOLYSIS BULLOSA:

OrCel™ when **ALL** of the following are met:

- Used to treat mitten-hand deformity
- Standard wound therapy has failed

- The product has been provided in accordance with the humanitarian device exemption [HDE] specifications of the U.S. Food and Drug Administration
- Limited to a one time only application

SECOND- OR THIRD-DEGREE BURNS:

ALL of the following criteria are met:

- The wound must be thoroughly debrided to remove necrotic tissue, bacteria, and other debris.
- The wound must be hemostatic, with minimal bleeding, to ensure optimal take of the skin graft.
- The wound must be free of infections or have a controlled infection, as evidenced by negative cultures or a significant reduction in bacterial load.
- The presence of healthy granulation tissue is essential for skin substitute take and integration.

and

ONE of the following products are used:

- Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area $\geq 30\%$ when provided in accordance with the HDE specifications of the FDA)
- Integra® DRT
- Transcyte®

Exclusions:

- All other uses of bioengineered skin and soft tissue substitutes or indications not outlined in the criteria above.
- Use of skin substitutes in individuals with inadequate control of underlying conditions or exacerbating factors including but not limited to any of the following:
 - Wounds with exposed bone, tendon, or fascia.
 - HbA1c $> 12\%$
 - Active Charcot arthropathy of the ulcer extremity for indications aside from diabetic foot ulcers.
- Repeat application of a skin substitute graft when previous treatment has failed to produce measurable clinical improvement. Indicators of unsuccessful treatment include, but are not limited to:
 - Increase in wound size or depth;
 - No measurable reduction in wound dimensions;
 - Absence of objective evidence of healing; or
 - Recurrence of an ulcer at the same anatomical location within 12 months of the initial treatment.
- Wounds with active infection, untreated ischemia, necrotic tissue, or inadequate wound bed preparation.
- Use of skin or tissue substitute products for reconstruction or wound management following Mohs micrographic surgery

- Use of skin substitute or tissue-based products for surgical repair of hernias or reinforcement of parastomal defects
- Use of skin or tissue substitute products for the treatment of musculoskeletal pain, injuries, joint disorders, tendon or ligament conditions, osteoarthritis, or other non-wound musculoskeletal indications.

CPT/HCPCS Level II Codes

Established codes:

15150	15151	15152	15155	15156	15157
15271	15272	15273	15274	15275	15276
15277	15278	15777	A2019	A6011	A6023
Q4101	Q4102	Q4105 ^a	Q4107	Q4110	Q4116
Q4121	Q4122	Q4128	Q4158	Q4182	Q4203
Q4431 ^b	Q4432 ^c	Q4433 ^c			

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

15011	15012	15013	15014	15015	15016
15017	15018	A2001	A2002	A2004	A2005
A2006	A2007	A2008	A2009	A2010	A2011
A2012	A2013	A2014	A2015	A2016	A2017
A2018	A2020	A2021	A2022	A2023	A2024
A2025	A2026	A2027	A2028	A2029	A2030
A2031	A2032	A2033	A2034	A2035	A2036
A2037	A2038	A2039	A2040	A2041	A2042
A2043	A2044	A2045	A4100	C1832	C8002
C9250	C9363	C9399	G0681	G0682	G0683
G0684	Q4103	Q4104	Q4108	Q4111	Q4112
Q4113	Q4114	Q4115	Q4117	Q4118	Q4123
Q4124	Q4125	Q4126	Q4127	Q4130	Q4134
Q4135	Q4136	Q4141	Q4142	Q4143	Q4146
Q4147	Q4149	Q4152	Q4161	Q4164	Q4165
Q4166	Q4167	Q4175	Q4179	Q4180	Q4193
Q4195	Q4196	Q4197	Q4200	Q4202	Q4220
Q4222	Q4226	Q4238	Q4345	Q4431	Q4433

J3590	1044T	1045T	1046T	1047T	1048T
1049T					

- ^a Covered for Integra® dermal regeneration template (DRT); Not covered for Integra Omnigraft dermal regeneration matrix (DRM)
- ^b Covered only for burns and epidermolysis bullosa when criteria are met
- ^c Covered when criteria are met

Notes:

- 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.
- BCBSM/BCN may consider certain services investigational and thus, not reasonable and necessary. The term "investigational" is not meant to imply the procedure or device has not received approval by the Food and Drug Administration (FDA). Rather, the use of this term simply means the procedure or device does not meet the health plan's objective: evidence-based technology assessment based on authoritative evidence, which then leads to improved net health outcomes.

Background

SKIN AND SOFT TISSUE SUBSTITUTES

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

In 2020, the Agency for Healthcare Research and Quality (AHRQ) published an updated technology assessment for Skin and Tissue Substitutes for the Treatment of Chronic Wounds for CMS (AHRQ, 2020). The assessment concluded that clinical evidence for most skin substitutes is lacking, making it difficult to determine their clinical efficacy. Skin and tissue substitutes are considered a useful therapeutic option when they are supported by scientific evidence, do not cause harm, and demonstrate successful outcomes for individuals meeting specified inclusion criteria.

Skin and tissue substitutes, also referred to as bioengineered skin and soft tissue, human skin equivalents, and artificial skin, are used to facilitate wound healing by mimicking the properties of natural skin. These substitutes do not replace the function of a skin graft and are not intended as a substitute for autologous skin transplantation. However, skin substitutes may offer several advantages that include protecting the skin from excessive fluid loss, preventing infection, providing a stable framework to support the growth of new dermal tissue, and promoting the production of cytokines and growth factors that aid in the healing process.(1)

They can be used in the treatment of chronic wounds that have not improved with standard treatment after four weeks. In addition, skin substitutes can be used in post-surgical situations where skin coverage is limited, such as breast reconstruction. They can also be used to treat second- and third-degree burns, certain skin conditions like bullous diseases that involve large areas of skin breakdown, and ocular surface disorders. Furthermore, skin substitutes are being explored for use in the repair of other soft tissues including rotator cuff repair, oral and facial surgery, hernias, and other conditions.

There are 2 main types of skin and tissue substitutes: acellular and cellular.

Acellular products, often referred to as acellular dermal matrix (ADM) are derived from humans (decellularized cadaveric dermis), animals (porcine or bovine tissue), or synthetic materials. The tissues are processed to remove all donor cells and antigenic materials thereby reducing risk of rejection. They provide a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin, which allows easy access by host cells and blood vessels to migrate into during the healing process. Acellular skin substitutes are the most common commercially available products for treating non-healing, chronic wounds. They usually are easy to store and have a long shelf life because they do not contain living cells. However, they have some disadvantages, including the risk of rejection if cell remnants are not sufficiently removed during processing, poor barrier function, and the risk of infectious disease transmission.(2)

Cellular skin substitutes, also known as human cells, tissues, and cellular and tissue-based products (HCT/Ps), on the other hand, contain living, viable cells, such as fibroblasts and keratinocytes, within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species. Skin substitutes may also be composed of dermal cells, epidermal cells, or a combination of dermal and epidermal cells, and may provide growth factors, cytokines, and matrix proteins to stimulate healing. They are more complex in nature than acellular products. They require more specific storage and have a shorter shelf life because they contain living cells. While human-based products undergo stringent processing, the risk of bacterial or viral infection remains. Additionally, there are concerns about the potential for the derived microenvironment to promote tumorigenesis, metastasis, inflammatory, or autoimmune disease evolution due to the unknown mechanisms of changes that take place at the extracellular matrix (ECM) level.(3)

Acellular Dermal Matrix Products

Allograft ADM products derived from donated cadaveric human skin tissue are supplied by tissue banks compliant with standards of the American Association of Tissue Banks and FDA guidelines.(4) 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.

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

AlloPatch® (Musculoskeletal Transplant Foundation) is an acellular human dermis allograft derived from the reticular layer of the dermis and marketed for wound care. This product is also marketed as FlexHD® for postmastectomy breast reconstruction.

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

FlexHD® and the newer formulation FlexHD® Pliable™ (Musculoskeletal Transplant Foundation) are acellular hydrated reticular dermis allograft derived from donated human skin.

DermACELL™ (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL® and PRESERVON®. DermaMatrix™ (Synthes) is a freeze-dried ADM derived from donated human skin tissue.

DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation.

DermaPure™ (Tissue Regenix Wound Care) is a single layer decellularized human dermal allograft for the treatment of acute and chronic wounds.

GraftJacket® Regenerative Tissue Matrix (also called GraftJacket Skin Substitute; KCI) is an acellular regenerative tissue matrix that has been processed from human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells while preserving dermal structure. GraftJacket Xpress® is an injectable product.

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

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

Xenogeneic Products

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

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

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

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

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

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

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

SurgiMend® PRS (TEI Biosciences, a subsidiary of Integra Life Sciences) is a xenogeneic ADM processed from fetal and neonatal bovine dermis.

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

Living Cell Therapy

Apligraf® (Organogenesis) is a bi-layered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts.

Apligraf® is supplied as needed, in 1 size, with a shelf-life of 10 days. 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 foot ulcers nonresponsive to standard wound therapy.

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

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

Autologous Cell Harvesting Device

Recell® (Avita Medical) was initially approved by the FDA in September 2018 under the premarket approval (PMA) process (PMA BP170122). It is an autologous cell harvesting device indicated for the treatment of acute partial-thickness thermal burn wound when used by an appropriately licensed healthcare professional at the patient's point of care to prepare autologous RES Regenerative Epidermal Suspension. The initial indication was for use in patients 18 years of age and older in combination with meshed autografting. Subsequently, indications were expanded to include direct application to acute partial-thickness thermal burn wounds in patients 18 years of age and older or application in combination with meshed autografting for acute full-thickness thermal burn wounds in pediatric as well as adult patients and for and full-thickness skin defects after traumatic avulsion (e.g., degloving) or surgical excision (e.g., necrotizing tissue infection) or resection (e.g., skin cancer) in patients 15 years of age and older.(5)

Biosynthetic Products

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

Integra® Dermal Regeneration Template (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.

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

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

Nerve Wraps

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

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

Evidence-Based Guidelines for SOC Therapy for Chronic Wounds

Frykberg (2015) expounded on the basic tenets of chronic wound treatment that the AHRQ technical brief (2020) aligned with. (6) SOC therapy for chronic wounds includes:

- Wound cleansing and debridement
- Management of infection with antibiotic therapy

- Correction of ischemia in the wound area
- Maintenance of moisture balance with wound dressing
- Compression for venous leg ulcers
- Offloading for diabetic foot ulcers
- Management of systemic disease and medications
- Nutrition assessment
- Education regarding care of the foot, including callus nails, and fitting of shoes, as well as counseling on the risk of continued tobacco use.

It is essential to achieve routine medical management of diabetes and a hemoglobin A1c level of less than 12% to maximize complete healing of the wound. For wounds that have not responded to SOC treatment within four to six weeks, advanced treatment with skin substitutes

Optimizing the Use of Skin Substitutes in Chronic Wound Management

Skin substitute products offer a versatile therapeutic option for a range of noninfected chronic wounds, including diabetic neuropathic ulcers and vascular insufficiency ulcers that have not responded to conventional wound care protocols. A chronic wound is defined as a lesion that fails to achieve expected closure within the typical healing window generally for 30 days to three months when accounting for the patients age, comorbid conditions, and wound etiology.

Successful resolution of chronic wounds hinges on several interrelated factors:

- Adequate perfusion and nutrition: Sufficient blood flow and systemic nutrients are essential for granulation tissue formation and epithelialization.
- Infection control: Preventing bacterial colonization and managing any existing infection are critical to avoid delayed healing.
- Moist wound environment: Maintaining optimal moisture promotes cellular migration, proliferation, and matrix deposition.
- Debridement of nonviable tissue: Removal of necrotic tissue creates a clean wound bed that allows new cells to populate the defect.

Despite adherence to standard wound care practices, a substantial proportion of chronic wounds remain refractory, resulting in prolonged morbidity and heightened mortality risk. Nonhealing lower extremity ulcers, for example, predispose patients to secondary infection, sepsis, limb loss, and death. Incorporating skin substitutes into the treatment algorithm can address these gaps by providing a biologically active scaffold that supports tissue regeneration, enhances vascularization, and protects against microbial invasion, thereby improving healing rates and mitigating secondary complications.

Summary of Evidence

Breast Reconstruction

For individuals who are undergoing breast reconstruction and receive allogeneic acellular dermal matrix (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 an improvement in the net health outcome.

Diabetic Lower-Extremity Ulcers

For individuals who have diabetic lower-extremity ulcers who receive AlloPatch, Apligraf, DermACell, Derma-Gide, Graftjacket, Integra® Dermal Regeneration Template (DRT), Keretic Omega3, Keretic Omega3 Marigen, Oasis Wound Matrix, PriMatrix, or TheraSkin, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, and quality of life. RCTs reporting complete wound healing outcomes with at least 12 weeks of follow-up have demonstrated their efficacy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have diabetic lower-extremity ulcers who receive other ADM products 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 Cytal, compared with current SOC or other advanced wound therapies. Two large RCT's have been published and are registered and reported as completed but have not been published. 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 and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, and quality of life. Notably, RCTs have demonstrated the efficacy of Apligraf living cell therapy and xenogeneic Oasis Wound Matrix over the SOC. The evidence is sufficient to determine that technology results in an improvement in the net health outcome.

For individuals who have lower-extremity ulcers due to venous insufficiency who receive other bioengineered skin substitutes, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Additional studies with larger number of subjects is needed to evaluate their effect vs the current SOC. 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 individuals with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. Outcomes have been reported in a small series (e.g., 5 patients). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Deep Dermal Burns

For individuals who have deep dermal burns who receive bioengineered skin substitutes (i.e., Epicel, Integra® DRT or Transcyte), the evidence includes a case series and RCTs. Relevant outcomes are 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® DRT and TransCyte for the treatment of burns. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Tendon Repair

For individuals who are undergoing tendon repair who receive Graftjacket, the evidence includes 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 studies 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.

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. The following is a summary of the key literature to date.

Potential Harm

The potential harm of skin substitutes is challenged by lack of high-quality studies and long-term data. The risk of human-based products includes infections being transmitted from the donor tissue to the recipient. Most products undergo stringent processing to reduce this risk, but bacterial and viral transmission risk remains. The duration of cells delivered and effect in the wound basement membrane is not fully understood.(7) Some types of grafts are at risk of graft rejection and there is variability in cosmetic results. Adherence to underlying tissues may vary based on hydrophilic surface properties of the graft which may impact effectiveness. Concerns have arisen regarding specific constituent molecules within the matrix with the potential to elicit adverse responses in host tissues. The mechanism of changes in the extracellular matrix (ECM) through cell-matrix interactions and ECM remodeling is not fully understood, eliciting concern for the derived microenvironment promoting tumorigenesis, metastasis, inflammatory or autoimmune disease evolution.(8) Very few studies explore long term safety of skin substitute grafts/cellular tissue type products (CTP) so true risk associated with these products remains unclear.

BREAST RECONSTRUCTION

Davilla et al (2013) 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.(9) 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.

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 (10).

Section Summary: Breast Reconstruction

The literature on the use of ADM's for breast reconstruction consists primarily of retrospective, uncontrolled series and systematic reviews. A meta-analysis found that reconstructions with ADM resulted in higher complications (i.e., seroma, infection, necrosis) than SOC which does not include the use of ADM's. Although the FDA has

issued safety communications regarding the use of certain acellular dermal matrix products in implant-based breast reconstruction, available systematic reviews, randomized controlled trials, and comparative studies demonstrate that selected ADM products may provide clinical benefit in appropriately selected individuals undergoing post-mastectomy breast reconstruction when additional soft-tissue support or implant coverage is required. Coverage is therefore limited to specific products and indications supported by evidence of clinical utility and favorable net health outcomes.

DIABETIC FOOT ULCERS

Tissue substitutes are special dressings that help heal diabetic foot ulcers (DFU). They work like scaffolds, giving cells a place to move and grow, which may promote faster wound healing. These dressings also may act as a protective barrier, lowering the chance of infection, and may help keep the wound environment conducive to healing by preventing excessive dryness or moisture. Some tissue substitutes contain growth factors or are made to trigger the body's own healing response, speeding up tissue repair. There are many types of these products, some are made from synthetic materials, while others are bioengineered skin. The choice depends on what the wound needs and the overall treatment plan.

The 2020 AHRQ technical brief found no convincing evidence that any skin-substitute device is clinically superior for chronic wounds, and it highlights major gaps in long-term safety and effectiveness data.⁽¹⁾ The review screened systematic reviews/meta-analyses, RCTs, and prospective non-randomized comparative studies of 76 commercially available skin substitutes (89 % acellular dermal matrices [ADMs] derived from human placental or animal tissue). Sixteen distinct products were evaluated in three systematic reviews and 22 RCTs; 21 ongoing RCTs are testing nine additional ADMs. Some key findings include that 85% of ADM studies reported faster healing versus standard care, yet only 6 of 38 published trials reported outcomes beyond 12 weeks, and none provided robust data on recurrence, amputation, or infection-related hospitalization. Of six head-to-head trials, five showed no statistically significant differences at ≥ 12 weeks, indicating that the current evidence cannot establish product superiority. It was also noted that Inclusion criteria varied widely (wound size 0.5–100 cm²; most common 1–25 cm²; wound duration ≥ 4 weeks to 52 weeks), limiting cross-study synthesis. It was also found that funding bias was also noted as 20 of the 22 RCTs were industry-sponsored, raising concerns about selective reporting.

A multicenter randomized controlled trial by Driver et al (2015), known as the Foot Ulcer New Dermal Replacement Study (FOUNDER), evaluated the safety and efficacy of Integra® DRT in 307 individuals with chronic neuropathic diabetic foot ulcers across 32 U.S. centers.⁽¹¹⁾ Following a 2-week run-in period with standard wound care, individuals whose ulcers demonstrated less than 30% healing were randomized to receive either DRT (n=154) or standard care alone (n=153). At 16 weeks, complete wound closure was achieved in 51% of individuals treated with DRT compared with 32% of individuals receiving standard care (p=0.001). Among ulcers that healed, the median time to complete closure was 43 days in the DRT group versus 78 days in the standard care group. In addition, wound area reduction occurred at a significantly faster

rate in the DRT-treated group (7.2% per week versus 4.8% per week). The study concluded that treatment with DRT significantly increased healing rates, accelerated wound closure, improved quality-of-life measures, and was associated with fewer adverse events compared with standard diabetic foot ulcer management.

Banerjee et al (2024) systematic review and meta-analysis evaluated the effectiveness of cellular, acellular, and matrix-like products in management of DFU based on RCTs.(12) The authors acknowledge that the different treatment approaches, surgical technique patient demographic, and compliance with SOC are so variable between different RCT it is not possible to compare products against each other.

Section Summary: Diabetic Foot Ulcers

Systematic reviews of skin substitute grafts and cellular tissue products (CTPs) are hindered by several challenges. These reviews often combine data from different products, wound types, and patient populations, which can lead to significant variability and make it difficult to draw conclusions. Additionally, the SOC (SOC) and management strategies used in these studies are often not well-defined, and many of the included studies have methodological limitations, such as small sample sizes, short follow-up periods, and a high risk of bias. As a result, the overall quality of the evidence is low, and it is uncertain whether the observed effects are due to the skin substitute/CTP interventions. However, for patients with diabetic lower extremity ulcers who meet specific criteria, there is evidence from randomized controlled trials (RCTs) that certain skin substitute products, including AlloPatch HD®, DermACELL®, Derma-Gide®, GraftJacket®, Integra® DRT, Kerecis® Omega3, Kerecis® Omega3 Marigen, Oasis® Wound Matrix, PriMatrix®, and Theraskin®, may promote faster healing compared to standard care. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome when criteria are met.

LOWER EXTREMITY VENOUS INSUFFICIENCY ULCERS

The 2020 Agency for Healthcare Research and Quality (AHRQ) technical brief and a subsequent evidence-analysis report from symplr (formerly Hayes, Inc.) on skin-substitute therapies for adult venous leg ulcers reached similar conclusions.(1,13) Both documents characterized the overall evidence base as low-quality, indicating that the addition of either acellular or cellular skin substitutes to SOC (SOC) may enhance ulcer healing, yet many critical questions remain unanswered. Moreover, the comparative data for one skin substitute versus another—as adjuncts to SOC—were deemed “very low” in quality.

Key methodological shortcomings identified across the studies include:

- Sparse product-specific data – few trials evaluated each individual substitute.
- Design limitations – most studies lacked blinding, did not perform a priori power calculations, and enrolled small cohorts, resulting in insufficient statistical power to detect inter-group differences.
- Follow-up issues – high loss-to-follow-up rates and short observation periods limited assessment of long-term outcomes.

- Inconsistent comparators – studies rarely examined the same head-to-head comparisons, undermining the consistency and robustness of the evidence for any given product.

Safety reporting was also limited; few studies provided adverse-event data.

Nonetheless, the available safety information suggests that skin-substitute applications are generally well tolerated, and any complications that have been reported appear to be manageable. For patients with venous stasis lower-extremity ulcers who satisfy predefined inclusion criteria, RCTs demonstrated that the following skin substitute products, Apligraf®, and Oasis® Wound Matrix, may promote faster healing relative to SOC for lower-extremity ulcers due to venous insufficiency. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome when criteria are met.

Section Summary: Skin Substitute Graft for Venous Leg Ulcers

Due to the heterogeneity of randomized controlled trials, poor study designs, small sample sizes, lack of comparators or standardization of practices, lack of long-term efficacy and safety data, and high risk of bias in the current body of literature, there is insufficient evidence to demonstrate efficacy of most skin substitutes in DFU/VLU healing. Moreover, this evidence is challenged by a low level of certainty in the estimated wound-healing effect attributable to these products. Many products have been marketed as substantial equivalents without establishing their role in ulcer healing. Potential risks with these products are not adequately addressed due to lack of long-term safety. Lastly, clinical outcomes have rarely been reported beyond 12 weeks in the current literature, raising additional concern for the durability of the estimated therapeutic benefit(s).

DYSTROPHIC EPIDERMOLYSIS BULLOSA

Tissue substitutes are employed in managing Epidermolysis Bullosa (EB), a genetic condition causing fragile, blistering skin. They are purported to provide benefits including protecting the underlying skin from further trauma and infection, promoting more efficient wound healing by providing a scaffold for cell growth and aiding in the regeneration of tissue, reduced pain, and maintaining a moist wound environment for healing which can help prevent scab formation and subsequent blistering. They may also reduce scar formation which helps maintain skin function and appearance. While primarily therapeutic, tissue substitutes may also help achieve a more normal skin appearance and functionality and can improve the quality of life by reducing the frequency of wound dressing changes, promoting better healing, and minimizing complications associated with chronic wounds. Individuals with dystrophic epidermolysis bullosa who receive OrCel, the evidence includes a case series. OrCel was approved under a humanitarian drug exemption (HDE) for use in individuals with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. OrCel® is an absorbable bi-layered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. Outcomes have been reported in a small series (e.g., 5 patients). The

evidence is sufficient to determine that the OrCel results in an improvement in the net health outcome when used within a Humanitarian Device Exemption.

Section Summary: Dystrophic Epidermolysis Bullosa

Although evidence is limited and consists primarily of case series and FDA HDE data, the available evidence is considered sufficient to support use of OrCel in the narrowly defined FDA-authorized indication for dystrophic epidermolysis bullosa undergoing hand reconstruction surgery.

DEEP DERMAL BURNS

Epicel

Epicel is a tissue engineered skin substitute created from a small biopsy of the patients' own epidermal keratinocytes. The cells are expanded in a specialized laboratory culture system for 3 to 4 weeks, producing a thin, flexible sheet of autologous epidermis that can be grafted onto burn wounds. Because the graft is derived from the patient's own tissue, it eliminates the risk of immunologic rejection and disease transmission. In 1998, it received Humanitarian Device Exemption (HDE) from the FDA for individuals with extensive full thickness burns lacking sufficient donor skin. Carsin et al (2000) provided a case series of 30 severely burned patients where Epicel was applied to a mean 37% of total body surface area (TBSA) and achieved permanent coverage of 26% TBSA, essentially matching the 25% coverage obtained with conventional split thickness autografts, while the cohort demonstrated a 90% survival rate, supporting its use when donor skin is limited.(14)

Integra Dermal Regeneration Template (DRT)

Integra® DRT is a bilayer skin substitute consisting of a porous bovine collagen glycosaminoglycan matrix that serves as a dermal scaffold, covered by a silicone epidermal layer that protects the wound while neovascularization occurs. In burn care, Integra has been studied extensively: Lagus et al (2013) comparative trial involving ten patients demonstrated that, despite variations in the wound healing process among Integra, cellulose sponge, and split thickness skin grafts, the histological, functional, and cosmetic 36 outcomes were similar after one year.(15) In a randomized trial, Branski et al (2007) enrolled 20 children with an average burn covering 73% of total body surface area.(16) Compared with standard autograft allograft care, the Integra group showed no significant differences in burn size, mortality, or length of stay. A multicenter post approval study evaluating the safety and effectiveness of Integra template in 216 burn patients was reported in 2003 by Heimbach et al.(17) The findings included an average epidermal autograft take rate of 87.7% and a median rate of 98%. The study found an incidence of invasive infection of 3.1% and a superficial infection rate of 13.2%. Hicks et al (2019) completed a systematic review of 72 studies (1,084 patients) and confirmed overall take rates of 86% for acute burns and 95% for reconstruction, with split thickness graft take rates around 90% and an overall complication rate of 13% (infection up to 18%).(18) Together these data indicate that Integra provides reliable dermal regeneration, comparable scar outcomes, and potential functional benefits, especially in

pediatric and extensive burn populations, albeit with a notable infection risk that requires monitoring.

TransCyte

TransCyte, a synthetic dermal substitute, also shows strong clinical support. In a randomized trial of 33 patients,(19) TransCyte promoted the fastest re-epithelialization and required fewer overall dressings than Biobrane or Silvazine. Patients who received Silvazine or Biobrane require more autografting than those treated with TransCyte. Noordenbos et al (1999) reported on a paired wound sites prospective RCT that compared silver sulfadiazine and TransCyte in 14 patients.(20) The study's findings included a demonstration of faster healing and less hypertrophic scarring with TransCyte versus silver sulfadiazine and an additional noncomparative series of 18 patients reported excellent wound healing with no infections.

Section Summary: Deep Dermal Burns

Collectively, these studies substantiate the use of Epicel, Integra, and TransCyte as evidence based skin substitute options for second- and third-degree burns, each offering distinct advantages in coverage, dermal regeneration, healing speed, and scar quality. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Recell®

Recell® is an autologous cell harvesting device indicated for the treatment of acute partial thickness thermal burn wound when used by an appropriately licensed healthcare professional at the patient's point of care to prepare autologous RES Regenerative Epidermal Suspension. There are 2 RCTs that have evaluated Recell for deep dermal burns. In both studies, 2 similar areas with a burn injury in the same individual were randomized to the control or treatment intervention (i.e., all participants received both treatments). The studies differed in their populations, interventions, and outcome measures. In the earlier study, published by Holmes et al (2018) participants all had deep partial thickness burns,(21) while in the 2019 study the population included individuals with mixed-depth, full thickness burns (22). The 2018 trial was a head-to-head comparison of Recell alone versus skin grafting alone, and the 2019 trial compared Recell in combination with skin grafting. In the earlier study, the primary effective endpoints were the incidence of wound closure at 4 weeks and the incidence of complete donor site healing at 1 week. In the 2019 trial, the co-primary effectiveness endpoints were noninferiority of the incidence of Recell -treated site closure by week 8 when compared to the control, and the superiority of the 37% relative reduction in donor skin for the Recell treatment when compared with the control.

Section Summary: Recell Device

Although ReCell has received FDA Premarket Approval (PMA), FDA approval alone does not establish clinical utility or medical necessity. Available studies suggest that ReCell may achieve wound closure rates comparable to standard care; however, the evidence base is limited by small sample sizes, heterogeneous burn populations, variability in treatment protocols, and inconsistent outcome measures. In addition, there

is insufficient long-term comparative evidence demonstrating sustained clinical benefit or superiority over established treatment approaches. Therefore, the evidence is insufficient to conclude that ReCell results in an improvement in net health outcomes, and additional randomized controlled trials are needed.

Table 1: Evidence for Covered Products

Skin Substitutes/CTP	Literature	Risk-of-bias Assessment
BREAST RECONSTRUCTION		
Alloderm®	• RCT (n=70) reported no difference between groups pain, rate of expansion, or adverse events.(13) • RCT (n=30) reported absence of objective clinical differences other than vessel density in AlloMax biopsies was slightly higher than AlloDerm biopsies.(14) • RCT (n=111) AlloDerm vs DermaMatrix, Stage II outcomes demonstrate a significant but acceptable complication profile with obesity directly associated with complications.(15) • RCT (n=55) AlloDerm vs DermACELL. Both demonstrated high success rate for reconstruction with AlloDerm higher rate of seromas and lower incorporation rate.(16) • RCT (n=302) AlloDerm vs Cortiva. No difference in reconstructive failure rates or complications with seroma formation more prevalent in AlloDerm.(17) • RCT (n=55) AlloDerm vs DermACELL. Both demonstrated high success rate for reconstruction with AlloDerm higher rate of seromas and lower incorporation rate.(16) • RCT (n=81) AlloDerm RTU vs DermACELL. No significant difference in minor and major complications.(18)	• Low risk
Allomend®		• Some concern with limited power due to n=30.
Cortiva®, [Allomax™]		• Some concerns with lack of total submuscular group and differences in demographics between the groups
Dermacell™		• Low risk
Dermamatrix™		• Low risk
FlexHD®/ FlexHD® Pliable™		• Some concerns with sample size
	• Some concerns with sample size and single-center study design	
DIABETIC FOOT ULCER		
Allopatch HD/ Allopatch Pliable/ Matrix HD/ FlexHD	• RCT (n=40) reported wound healing at 12 weeks of 80% for AlloPatch and 20% for SOC, an additional 40 patients enrolled and reported similar results.(34)	• High risk due to missing data outcomes
Apligraf®	• RCT (n=208) reported wound closure at 12 weeks of 56% for Apligraf and 38% for SOC (20)	• High risk due to lack of validation of outcome measurements

	• RCT (n=72) reported wound closure at 12 weeks of 55.2% for Apligraf and 34.3% for SOC (21) • RCT (n=82) reported wound healing at 12 weeks of 51.5% for Apligraf and 26.3% for SOC (22)	• Unable to complete due to pooling data from 2 different studies into one paper • High risk due to lack of validation of outcome measures
Dermacell, AWM, Porous	• RCT (n=168) reported healing rate at 16 weeks was 67.9% in DermACELL arm, 48.1% in SOC arm 47.8% in the GraftJacket arm (23,24) • Prospective study (n=61) of large complex wounds treated with DermACELL with 24.6% closure at 16 weeks (25)	• Some concerns due to randomization • NA
Derma-Gide	• RCT (n=40) reported wound closure at 12 weeks of 85% of Derma-Gide group and 30% of SOC group (interim analysis).(26) • RCT (n=105) reported wound closure at 12 weeks of 83% of Derma-Gide group and 45% of SOC group.(27) • Retrospective case series and bench report.(28,29,30)	• Some concerns due to randomization • Some concerns due to randomization • N/A
Graftjacket	• RCT (n=40) reported on wound healing at 12 weeks with a 67.4% reduction with Graftjacket and 34% with SOC (34) • RCT (n=28) reported wound closure at 16 weeks of 85.71% in Graftjacket arm and 28.57% in SOC.(35) • RCT (n=86) reported on mean wound healing time of 12 weeks was 30.4% with Graftjacket and 53.9% with SOC.(36) • RCT (n=168) reported wound closure at 16 weeks of 67.9% for DermACELL, 47.8% for Graftjacket, and 48.1% for SOC.(23,24) • These studies were included in a meta-analysis and Graftjacket in another (37,38)	• High risk due to unclear randomization, potential deviations from intended intervention (no ITT), lack of validation of outcome measurements, and statistical plan not described. • High risk due to unclear randomization, potential deviations from intended intervention (no ITT), lack of validation of outcome measurements, and statistical plan not described. • High risk due to unclear randomization, lack of validation of outcome measurements • Low risk • NA
Integra® DRT	• RCT (n=307) reported wound closure at 16 weeks of 51% in	• High risk due to missing outcome data

	Integra group and 32% in SOC group.(39)	
Kerecis Omega3/ Kerecis Omega3, Margin Shield	• RCT (n=49) reported wound closure at 12 weeks of 67% for Kerecis and 32% for SOC.(40) • RCT (n=102) reported 56.9% wound closure by 12 weeks in Kerecis group and 31.4% in the SOC group. (41) • RCT (n=255) wound closure by 16 weeks of 44% in Kerecis group and 26% in SOC.(42)	• High risk of bias due to missing outcome data • Some concerns due to randomization. • N/A
Oasis Wound Matrix	• RCT (n=26) reported no difference in closure time for Dermagraft (84.6% or Oasis Wound Matrix (76.9%).(43) • RCT (n=73) reported wound healing at 12 weeks of 49% for Oasis wound matrix and 28% for Regranex gel.(44)	• Some concerns due to no validation of wound measurements • Some concerns due to lack of validation of outcome measurements
Primatrix	• RCT (n=161) reported wound closure at 12 weeks of 59.5% for PriMatrix arm and 35.4% for SOC arm.(45) • Prospective trial (n=55) The mean number of applications for these healed wounds was 2.0 ± 1.4, with 59.1% healing with a single application of PriMatrix and 22.9% healing with 2 applications.(46) • Retrospective comparison (n=68) patients with 2 treatments of PriMatrix healed faster than those with 2 treatments of Apligraf.(47) • Retrospective medical record review (n=34) mean healing time for DFU was 105 days with average 2.6 PriMatrix applications.(48)	• High risk due to lack of blinding and analysis of outcome measures • NA • Retrospective in nature • Retrospective in nature
Theraskin	• RCT (n=100) reported on wound healing at 12 weeks was 76% for TheraSkin and 36% for SOC.(49)	• Some concerns with lack of investigator blinding and lack of strength with comparison of comorbidities.
VENOUS STASIS LOWER EXTREMITY ULCER		
Apligraf®	• RCT (n=275) reported wound closure at 6 months of 63% for Apligraf and 49% for SOC.(50) • RCT (n=120) reported wound closure at 24 weeks of 47% for Apligraf and 19% SOC. (51)	• Some concerns due to potential deviations from intended intervention (no ITT) • High risk because it was unclear if allocation was concealed, data in text and table do not match, unclear if all outcome data was reported and lack of validation

	• RCT (n=31) reported wound healing at 12 weeks of 93.3% for Theraskin and 75% for Apligraf.(52)	• of outcome measures in unblinded study • High risk due to potential deviations from intended intervention (no ITT), and lack of validation of outcome measures in unblinded study, did not enroll planned sample size
Oasis Wound Matrix	• RCT (n=48) reported wound closure at 8 weeks of 80% for Oasis wound matrix and 65% for SOC.(54) • RCT (n=120) reported wound healing at 12 weeks of 55% in Oasis group and 34% in SOC.(55) • RCT (n=89) reported wound closure at 12 weeks with 47.1% for Dermagraft, 73.7% for Oasis and 57.9% for SOC.(56) • RCT (n=84) reported wound closure at 12 weeks of 71% Oasis and 46% SOC.(57)	• Some concerns due to randomization process • High risk due to missing outcome data, lack of validation of outcome measurements • High risk of bias due to per protocol analysis only • High risk due to per-protocol analysis, missing outcome data and uncertain method for outcome
DYSTROPHIC EPIDERMOLYSIS BULLOSA		
Orcel™	The FDA has granted a HDE for Orcel™	
2ND OR 3RD DEGREE BURNS		
Epitel®	The FDA has granted a HDE for Epitel®	
Integra® DRT	• RCT (n=20) reported improvement in scarring in terms of height, thickness, vascularity, and pigmentation.(Branski et al, 2007) • Single arm clinical trial (n=84). 96% of treated sites achieve >90% take by post up day 14. Markedly improved scar quality at 6 months.(Heimbach et al, 2003) • Additional Literature: systematic review (n=1132) (31 studies included) high variability in outcomes but satisfactory cosmetic results and improvement in range of motion.(Hicks et al, 2019)	• High risk due to lack of blinding, small sample size, single-center design, limited age range (2-12), potential selection bias, and industry involvement not disclosed. • Level III. Concerns with lack of randomized comparator • Level III (prospective cohort) with limited

Transcyte®	• RCT (n=14) paired wound sites on 14 patients compared silver sulfadiazine with TransCyte. Wounds treated with TransCyte healed faster and with less hypertrophic scarring. Non-comparison eval was completed on additional 18 patients with excellent wound healing and absence of infection.(Noordenbos et al, 1999) • RCT (n=21) Compared treatment of patients with facial flash burns with TranCyte and standard topical antibiotic care. TransCyte significantly improved healing rate of facial burns compared to bacitracin ointment. (Demling and DeSanti, 1999)	• Some concerns with sample size and single-center study design • Some concerns with sample size and single-center study design
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Products not specifically listed as established are considered investigational due to insufficient evidence demonstrating improved net health outcomes. FDA clearance, approval, HCT/P status, or CMS reimbursement classification alone do not establish medical necessity. Coverage determinations are based on the totality of evidence supporting safety, effectiveness, durability of response, and clinically meaningful outcomes for the intended indication.

Table 2: Evidence for Non-Covered Products. This list may not be all inclusive.

Skin Substitutes	Evidence (Published, peer reviewed literature)	Comments
Abiomend Membrand and Abiomend Hydromembrand	No literature identified	Insufficient evidence
AC5 Advanced Wound System (AC5)	No literature identified	Insufficient evidence
Acesso DL, Acesso TL	No literature identified	Insufficient evidence
Activate Matrix	No literature identified	Insufficient evidence
Alloderm	Few published studies	Insufficient evidence
Allogen, Per Cc	Few published studies	Insufficient evidence
Alloskin, Alloskin AC	Few published studies	Insufficient evidence
Apis	Few published studies	Insufficient evidence
Architect ECM PX FX	Few published studies	Insufficient evidence
Arthroflex	Few published studies	Insufficient evidence
Ascent, 0.5 Mg	Few published studies	Insufficient evidence
Axobiomembrane	Few published studies	Insufficient evidence
AxoloTL Ambient or AxoloTL Cryo, 0.1mg	Few published studies	Insufficient evidence
AxoloTL Graft or AxoloTL Dualgraft	Few published studies	Insufficient evidence
Barrera SL or Barrera DL	Few published studies	Insufficient evidence
Bellacell HD Or Surederm	Few published studies	Insufficient evidence
Bio-Connekt Wound Matrix	Few published studies	Insufficient evidence

BioNextPATCH	No literature identified	
Bioskin	Few published studies	Insufficient evidence
Bioskin Flow	Few published studies	Insufficient evidence
BioWound, BioWound Plus, BioWound Xplus	Few published studies	Insufficient evidence
CarePATCH	Few published studies	Insufficient evidence
Celera Dual Layer Or Celera Dual Membrane	No literature identified	
Clarix Regenerative Cord/Clarix 100 Quick Peel	Few published studies	Insufficient evidence
Clarix Flo	Few published studies	Insufficient evidence
Cocoon Membrane	Few published studies	Insufficient evidence
Coll-E-Derm	Few published studies	Insufficient evidence
Complete AA, Complete ACA, Complete SL, Complete FT	Few published studies	Insufficient evidence
Conexa	Few published studies	Insufficient evidence
Corecyte, for topical use only, per 0.5cc	Few published studies	Insufficient evidence
Coretext or Protex, per cc	Few published studies	Insufficient evidence
CorMatrix	Few published studies	Insufficient evidence
Corplex P	Few published studies	Insufficient evidence
Corplex P, per cc	Few published studies	Insufficient evidence
Cryo-Cord	Few published studies	Insufficient evidence
Cymetra, Injectable, 1 cc	Few published studies	Insufficient evidence
Cytal (Formerly MatriStem)	Few published studies	Insufficient evidence
Dermabind DL, Dermabind CH, Dermabind SL	Few published studies	Insufficient evidence
Dermabind TL or Amniobind	No literature identified	Insufficient evidence
Dermapure	Few published studies	Insufficient evidence
DermaSpan	Few published studies	Insufficient evidence
Derm-Maxx	Few published studies	Insufficient evidence
Dual Layer Impax Membrane	Few published studies	Insufficient evidence
Emerge Matrix	No literature identified	Insufficient evidence
Enverse	No literature identified	Insufficient evidence
Epieffect	Few published studies	Insufficient evidence
Esano A, Esano AAA, Esano AC, Esano ACA	Few published studies	Insufficient evidence
Excellagen, 0.1 cc	Few published studies	Insufficient evidence
EZ-Derm	Few published studies	Insufficient evidence
Fluid Flow or Fluid GF, 1 cc	Few published studies	Insufficient evidence
Gammagraft	Few published studies	Insufficient evidence
Grafix Core, GrafixPL Core	Few published studies	Insufficient evidence
Grafix Plus	No literature identified	Insufficient evidence
Graftjacket Xpress, Injectable, 1 cc	No literature identified	Insufficient evidence
Helicoll	Few published studies	Insufficient evidence
HMatrix	Few published studies	Insufficient evidence
Human Health Factor 10 Amniotic Patch (HHF10-P)	No literature identified	Insufficient evidence
Hyalomatrix	Few published studies	Insufficient evidence
Innovaburn or Innovamatrix XL	Few published studies	Insufficient evidence
Innovamatrix AC, Innovamatrix FS	Few published studies	Insufficient evidence
Innovamatrix PD 1mg	No literature identified	Insufficient evidence
InteguPly	Few published studies	Insufficient evidence

Integra® Omnigraft™ Dermal Regeneration Matrix (DRM)	Few published studies	Insufficient evidence
Keramatrix or Kerasorb	Few published studies	Insufficient evidence
Keroxx (2.5g/cc), 1 cc	Few published studies	Insufficient evidence
Lamellas XT, Lamellas	No literature identified	Insufficient evidence
Matriderm	Few published studies	Insufficient evidence
Matrion	Few published studies	Insufficient evidence
MatriStem Micromatrix, 1 mg, MatriStem Wound Matrix, MatriStem Burn Matrix	Several studies all with limitations	Insufficient evidence
Mediskin	Few published studies	Insufficient evidence
Membrane Graft or Membrane Wrap	Few published studies	Insufficient evidence
Membrane Wrap-Hydro	Few published studies	Insufficient evidence
MemoDerm, DermaSpan, TranZgraft, or InteguPly	Few published studies	Insufficient evidence
MLG-Complete	No literature identified	Insufficient evidence
Microlyte, Matrix	Few published studies	Insufficient evidence
Miro3d	No literature identified	Insufficient evidence
Miroderm	Few published studies	Insufficient evidence
Mirragen Adv Wound Matrix	Few published studies	Insufficient evidence
MyOwn Skin	Few published studies	Insufficient evidence
Neomatrix	Few published studies	Insufficient evidence
Neostim TL, Neostim Membrane, Neostim DL	No literature identified	Insufficient evidence
Novachor	Few published studies	Insufficient evidence
Novafix, Novafix DL	Few published studies	Insufficient evidence
Novosorb Synpath Dermal Matrix	Few published studies	Insufficient evidence
Nudyn DL or Nudyn DL Mesh, Nudyn SL or Nudyn SLW	Few published studies	Insufficient evidence
Oasis Burn Matrix	No literature identified	Insufficient evidence
Oasis Tri-Layer Wound	Few published studies	Insufficient evidence
Omeza Collagen Matrix, per 100 mg	Few published studies	Insufficient evidence
Orion	Few published studies	Insufficient evidence
PermeaDerm B, PermeaDerm C	Few published studies	Insufficient evidence
Phoenix Wound Matrix	Few published studies	Insufficient evidence
Polycyte, for topical use only, per 0.5cc	Few published studies	Insufficient evidence
Porcine Implant, Permacol	Literature in hernia repair	Insufficient evidence
Procenta, per 200 mg	Few published studies	Insufficient evidence
Progenamatrix	Few published studies	Insufficient evidence
ProMatrX	Few published studies	Insufficient evidence
Puraply, Puraply XT	Few published studies	Insufficient evidence
Puraply, AM	Few published studies	Insufficient evidence
Rebound Matrix	No literature identified	Insufficient evidence
Recell	Few published studies	Insufficient evidence
Reguard, for topical use	No literature identified	Insufficient evidence
Relese	No literature identified	Insufficient evidence
Ripriza	Literature in plastic surgery	Insufficient evidence
Resolve Matrix	No literature identified	Insufficient evidence
Restrata	Few published studies	Insufficient evidence
Revitalon	Few published studies	Insufficient evidence

Sanopellis	No literature identified	Insufficient evidence
Signature Apatch	No literature identified	Insufficient evidence
Skin TE	Few published studies	Insufficient evidence
StrataGraft		Insufficient evidence
Strattice TM	Few published studies.	Insufficient evidence
Supra SDRM	Few published studies	Insufficient evidence
Suprathel	Several studies all with limitations	Insufficient evidence
Surederm	Few published studies	Insufficient evidence
Surfactor or Nudyn, per 0.5cc	Few published studies	Insufficient evidence
Surgicord	Few published studies	Insufficient evidence
Surgigraft, Surgraft TL, Surgraft FT, Surgraft XT, Surgigraft-Dual	Few published studies	Insufficient evidence
SurgiMend Collagen Matrix, per 0.5 sq cm	Literature in breast surgery	Insufficient evidence
Surgraft	Few published studies	Insufficient evidence
Symphony	Few published studies	Insufficient evidence
Tag	Few published studies	Insufficient evidence
Talymed	Few published studies	Insufficient evidence
Tensix	Case reports	Insufficient evidence
Theragenesis	Few published studies	Insufficient evidence
Therion	Few published studies	Insufficient evidence
Transcyte	Literature in burns	Insufficient evidence
TranZgraft	Few published studies	Insufficient evidence
TruSkin	No literature identified	Insufficient evidence
Unite Biomatrix	Few published studies	Insufficient evidence
Via Matrix	No literature identified	Insufficient evidence
Vim	No literature identified	Insufficient evidence
Woundplus Membrane or E-Graft	Few published studies	Insufficient evidence
Xcellerate	Few published studies	Insufficient evidence
Xcellistem, 1 mg	Few published studies	Insufficient evidence
XCM Biologic Tissue Matrix	Literature for chest wall defects	Insufficient evidence

APPLICATION CHANGES

Establishing application limits is challenging and reflects the shortcomings of the current evidence including lack of standardized protocol, missing data on frequency of application, and lack of studies directed at this specific area. Many reports do not include information on consistent outcome measures, co-morbidities, or other risk factors that may impact application frequency. This is further complicated as products have set parameters for weekly application changes, despite lack of evidence to support this labeling, so the true number of application necessary for the product may not be known. Some products remain in place with 1-2 applications per episode of care. Other products are reapplied weekly or biweekly, and some studies report changes only when there has been a slow progression of healing. Because the labeled use for the products is left to manufacturer discretion and not based on evidence, this creates a dilemma on understanding what factors should be considered regarding if and when to reapply products and what application frequency is optimal for wound healing. Objective evidence of progressive wound healing should be documented to continue treatment with a skin or tissue substitute.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

International Working Group on the Diabetic Foot (IWGDF)

For topically applied treatments, the IWGDF advises against the use of bioengineered skin products compared to SOC.

The IWGDF considered the available evidence to be of low quality, and their recommendation was weak (e.g., based on the quality of evidence, balance between benefits and harms, patient values and preferences, and cost or resource utilization).(23)

IWGDF updated its systematic review and evidence-based guideline on interventions to enhance healing of diabetes-related foot ulcers in 2023, with continued relevance in 2024, which demonstrates low quality evidence for skin substitute products. The IWGDF/EWMA has published 21-point checklist of reporting standards of studies and papers representing markers of good quality research in DFU which may aid future investigators for high quality study designs.(24)

Journal of Wound Care International Consensus Document

A consensus document was published by the Journal of Wound Care which included an international panel of experts and the recommendations scrutinized by an expert review board.(25) This project was sponsored by multiple manufacturers of skin substitute graft/CTPs products, and their evidence reviewed was not conducted through systematic review although they provide an excellent summary of systematic reviews and meta-analyses that have been conducted on cellular, acellular and matrix-like products. Recommendations include:

- Use on wounds of all etiologies after failure to respond to SOC when risk factors and co-morbidities are optimized.
- The time period the product is left in place needs to be individualized based on assessment of the individual, the wound and the manufacturer's recommendations for use.
- If closure has not progressed, new treatment goals should be established.
- There needs to be ongoing support for research to better understand the physiological effect and modes of action of skin substitute grafts, and "research studies need to have longer follow-up periods to determine the full patient and cost benefits..."
 - This level of evidence is critical to obtain universal acceptance and availability of the products".

National Institute for Health and Care Excellence

In 2023, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems.(26) The Institute

recommended that clinicians “consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service.”

In 2019, NICE published guidance on the ReCell system for treating skin loss, scarring, and depigmentation after burn injury. The guidance recommended that additional research was needed to address the uncertainties regarding the potential benefits of ReCell.(27)

Society for Vascular Surgery/American Podiatric Medical Association/Society for Vascular Medicine (SVS/APMA/SVM)

The SVS/APMA/SVM published a joint evidence-based guideline using Grades of Recommendation Assessment, Development, and Evaluation system for the management of patients with diabetes, including treatment of diabetes related chronic foot ulcers.(28)

These organizations’ recommendations for diabetic foot ulcers failing to demonstrate improvement (> 50% ulcer area reduction) after a minimum of 4 weeks of standard ulcer therapy include:

- Adjunctive ulcer therapy options with negative pressure therapy, biologics (platelet-derived growth factor, living cellular therapy, extracellular matrix products, ...) and hyperbaric oxygen therapy. The choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice (Grade 1B).
- Consideration of living cellular therapy using a bilayer keratinocyte/fibroblast construct or a fibroblast-seeded matrix for treatment of diabetic foot ulcers when the individual is recalcitrant to standard therapy (Grade 2B).
- Consideration of the use of extracellular matrix products employing acellular human dermis or porcine small intestinal submucosal tissue as an adjunctive therapy for diabetic foot ulcers when the individual is recalcitrant to standard therapy (Grade 2C).

Wound Healing Foundation (WHF)

The WHF published the results of a Consensus Panel on Chronic Wounds composed of dermatology, general surgery, vascular surgery, pediatric surgery, plastic surgery, podiatry, nursing, and wound healing research experts in diverse practice settings.(29)

The panel agreed that a chronic wound is designated as a “stalled wound” when it has failed to progress towards healing, following 4 weeks of standard evaluation and management during which identified etiologic factors have been addressed. The importance of treating the underlying condition contributing to the wound development is emphasized as essential for healing. Identified elements in the SOC (SOC) treatment for these wounds include debridement, infection control, moisture management, dressing and protection, compression in venous and lymphatic ulcers, and offloading. Negative pressure wound therapy, grafting and hyperbaric oxygen are identified as advanced or adjunctive treatment modalities. Decision-making depending on the level of evidence for a specific product and wound type is recommended for cellular and tissue-

based products. Unlike autologous skin grafts, the homologous grafts do not persist and act as a template for cell growth; however, advantages include no donor site, application in office or operating room, possible growth factors and immunomodulators, reduction of insensible water loss and preparation of wound bed for autografting. Disadvantages include prolonged or repeat applications which may delay final grafting and definitive wound coverage. However, the consensus panel did not include the evidence level or qualify the strength of this recommendation.

Wound Healing Society (WHS)

The WHS has published updated evidence-based guidelines on the treatment of diabetic ulcers.(30) Regarding the use of skin substitutes, the WHS concluded that level I evidence suggests that cellular and acellular skin equivalents improve the healing of diabetes-related foot ulcers. In these guidelines Level I required at least 2 RCT supporting the intervention of the guidelines. The quality of evidence was not assessed.

- In evidence-based guidelines for venous ulcers, the WHS stated that there is evidence that a bi-layered living human skin equivalent, used in conjunction with compression bandaging, increases the incidence and speed of healing for venous ulcers compared with compression and a simple dressing (Level I evidence). The WHS recommends adequate ulcer bed preparation and control of excess bioburden levels prior to application of a biologically active dressing.

They also noted that cultured epithelial autografts or allografts have not been demonstrated to improve stable healing of venous ulcers (Level I). The WHS also stated that there is Level II evidence that a porcine small intestinal submucosal construct may enhance healing of venous ulcers.(31)

Regulatory Status

The U.S. Food and Drug Administration (FDA) does not refer to any single product or class of products as “skin substitutes”. There are many artificial skin and soft-tissue products that are commercially available or in development. 2020 AHRQ-commissioned Technical Brief lists specific products for chronic wounds.(1)

The FDA classifies these products and defines their regulatory pathway based on the product’s composition and origin (e.g., human animal, synthetic).(75) Skin and tissue substitute products may be regulated through several FDA pathways, depending on product composition, processing, intended use, and risk profile as follows:

- Premarket Approval (PMA) – Human-derived or human/animal-derived products
- 510(k) - Animal-derived products and synthetic products
- 361 HCT/Ps – Minimally manipulated human cells, tissues, and tissue-based products (HCT/P).
- Biological License Application (BLA) – Biological products licensed under Section 351 of the Public Health Service Act is the FDA’s pathway for full approval of biological products, ensuring they are safe, pure, and potent. Approval, safety, and manufacturing details can be found in the FDA’s Purple Book.(75) To lawfully market

a drug that is a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)].

- Humanitarian Device Exemption (HDE) - Permits the use of certain medical devices when there is no comparable device available to treat or diagnose a disease or condition affecting fewer than 8,000 individuals annually.

Premarket Approval (PMA) – Class III Devices

The Premarket Approval (PMA) process, governed by 21 CFR Part 814 (and classified under Part 860), is the FDA's most stringent regulatory pathway for medical devices. This process is reserved for Class III devices, which are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury.

Unlike the 510(k) pathway, which relies on "substantial equivalence" to a predicate device, the PMA requires independent valid scientific evidence to provide reasonable assurance of both safety and effectiveness. This typically involves a rigorous series of pre-clinical and clinical trials. While only a small minority of the products addressed in this document require a PMA, this pathway ensures the highest level of regulatory scrutiny for high-risk innovations.(76)

510(k) Premarketing Notification

The FDA's Premarket Notification [510(k)] pathway, established under Section 510(k) of the Federal Food, Drug, and Cosmetic Act, requires manufacturers to notify the FDA prior to marketing a medical device in the United States. This regulatory pathway is primarily used for Class II (moderate-risk) devices that must demonstrate substantial equivalence to a legally marketed predicate. This process is usually used when manufacturers make small changes to a previously approved device that is thought to improve effectiveness without compromising safety. A device is considered substantially equivalent if it has the same intended use and either identical technological characteristics or different ones that do not raise new questions of safety or effectiveness. This allows for faster and less costly processes than PMA.(77)

In the context of wound care, 510(k)-cleared skin and tissue substitutes are regulated as medical devices rather than banked human tissue. Depending on the product, they may protect the wound from external contaminants, reduce fluid loss, maintain appropriate moisture levels, support granulation tissue formation, and provide a scaffold that facilitates cellular infiltration and tissue remodeling.

Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

361 HCT/Ps are human cells, tissues, and cellular and tissue-based products that meet FDA criteria for regulation solely under Section 361 of the Public Health Service Act. These products are generally minimally manipulated and intended for homologous use and are regulated through establishment registration, donor screening, and tissue safety requirements rather than premarket approval. Products that do not meet these criteria are regulated under Section 351 and/or the Federal Food, Drug, and Cosmetic Act and may require FDA review and approval as biologics, drugs, or medical devices.(78)

Although surgeons commonly use biologic and synthetic mesh products during breast reconstruction procedures, the FDA does not consider breast reconstruction to be the same type of use as the tissue's original function in the body (known as "homologous use"). In addition, the FDA has not specifically cleared or approved any surgical mesh product—whether synthetic, animal-derived, or human-derived—for breast surgery. While some surgical mesh products were previously cleared for general use in plastic and reconstructive surgery, that clearance did not specifically include breast reconstruction. In 2019, the FDA stated that the use of surgical mesh in breast procedures should be considered a new intended use. Because of this, the FDA has stated that using surgical mesh in breast procedures represents a new intended use that may require a higher level of regulatory review and approval rather than the standard 510(k) clearance process.

Biological Licensed Application (BLA) Pathway

A BLA-licensed product is a biological therapeutic authorized for interstate commerce by the FDA under Section 351 of the Public Health Service (PHS) Act (21 CFR Parts 600-680). These products are classified as biological that may contain living human cells, bioengineered tissue, or active biological components derived from living systems. They are not drugs, medical devices, or minimally manipulated human tissues. Unlike Section 361 HCT/Ps, which are primarily regulated to prevent the transmission of communicable diseases, Section 351 biologics requires the submission of a Biologics License Application (BLA) supported by substantial evidence from human clinical trials proving safety, purity, and potency for specific clinical indications. Due to their complexity and potential for variability, these products are subject to the highest level of regulatory scrutiny, including stringent cGMP manufacturing, batch-to-batch potency testing, and mandatory long-term safety monitoring.(78-80)

Humanitarian Device Exemption (HDE)

In rare instances, certain medical devices intended to be used for humanitarian purposes are evaluated by the FDA through the HDE process. A device approved in this manner is designated as a Humanitarian Use Device (HUD). A HUD designation permits the use of certain medical devices when there is no comparable device available to treat or diagnose a disease or condition affecting fewer than 8,000 individuals annually. Because clinical investigation demonstrating the device's efficacy is not feasible (given the low prevalence of the disease in the population), an HDE grants manufacturers an exemption to the usual premarket approval process and allows marketing of the device only for the FDA-labeled HDE indication(s). Under FDA requirements, an HUD may only be used after institutional review board (IRB) approval has been obtained for the use of the device in accordance with the FDA-labeled indication(s) under the HDE. The FDA's approach to skin and tissue substitutes is product-specific, not class-based. Determining the correct pathway hinges on the material's origin, degree of manipulation, intended (homologous) function, and the risk profile of the device.(81)

CMS Reclassification of Skin and Tissue Substitute Products

Effective January 1, 2026, CMS implemented classification changes for cellular and/or tissue-based products (CTPs).(82) Most skin and tissue-based products are no longer considered biological drugs but are now classified as “incident-to-supplies. The new incident-to-supplies category of skin and tissue substitute products belong to three groups based on their regulatory pathway:

- PMA Products: Devices requiring Premarket Approval.
- 510(k) Products: Devices requiring 510(k) clearance.
- 361 HCT/Ps: Human cells, tissues, and cellular-based products.

Definition: The term “incident-to-supplies” refers to supplies that are furnished as an integral, although incidental, part of the physician’s professional services in the course of diagnosis or treatment of an injury or illness.

Exceptions: Products excluded from the “incident-to-supplies” category are biological skin and tissue products that have an established biological license application (BLA) with the FDA under § 351 of the Public Health Services Act

FDA Updates and Warnings on Regenerative Medicine Therapies

In June 2021, the FDA updated a July 2020 consumer alert on regenerative medicine therapies. These products require FDA licensure/approval to be marketed to consumers. These unapproved products include stem cells, stromal vascular fraction (fat-derived cells), umbilical cord blood and/or cord blood stem cells, amniotic fluid, Wharton’s jelly, ortho biologics, and exosomes. The warning included the statement that “regenerative medicine therapies have not been approved for the treatment of any orthopedic condition, such as osteoarthritis, tendonitis, disc disease, tennis elbow, back pain, hip pain, knee pain, neck pain, or shoulder pain”.(83)

Per the FDA, safety concerns with these products included the following:

- “Blindness,
- Tumor formation,
- Neurological events,
- Bacterial infections including life-threatening blood infections,
- Reactions at the site of collection and administration,
- Unwanted inflammatory or immune response to the cell or therapy,
- Cells moving to another part of the body and turning into an unintended type of tissue or excessively growing in the body (i.e., forming a tumor),
- Failure of the therapy to work as anticipated when approved treatments are available,
- Cross-contamination with bacteria, viruses or mold related to processing (preparation of the product) or the therapy not being tested for infectious diseases such as hepatitis and HIV.”

FDA Safety Communication on ADM Products

In 2021, the FDA issued a safety communication informing healthcare providers and patients that certain ADM products used in implant-based breast reconstruction may

have a higher risk for complications or problems.(79) They go on to state that they have not cleared or approved ADM or mesh for use in breast reconstruction. The FDA's safety communication cited a prospective cohort study evaluating safety outcomes (i.e., reoperation, explantation, infection) from implant-based breast reconstruction surgeries after mastectomy in multiple centers in the United States and Canada that showed significantly higher complication rates in patients with FlexHD and AlloMax ADMs two years after surgery compared to a control group that did not receive an ADM. The FDA pointed to a need for additional, high-quality studies evaluating the safety and efficacy of ADMs. As a result of their analysis, the FDA recommends health care providers to:

- "Discuss the potential benefits and risks of all relevant treatment options with your patients as part of a shared decision-making process.
- Be aware that the FDA has not approved or cleared any ADM products for use in implant-based breast reconstruction. Data analyzed by the FDA and published literature suggest that some ADMs may have higher risk profiles than others.
- Be aware that the FDA does not recommend reoperation or removal of implanted ADM as a preventive measure.
- Report any patient adverse events to the FDA MedWatch program, using the information in the Reporting Problems with Your Device page".

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 benefits.(83)

On December 19, 2024, the FDA issued a warning letter to Integra Life Sciences Corporation stating: "FDA investigators and a microbiologist determined that the above firms manufacture a variety of neurological and neurosurgical devices, including but not limited to, cranial perforators, disposable cottonoid patties and strips as well as collagen based medical devices, that are used for wound care, soft tissue repair and reconstruction surgery. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body."(84)

Devices, Kits and Systems used for Autologous Cell Preparation

Recell® (Avita Medical) was initially approved by the FDA in September 2018 under the premarket approval (PMA) process (PMA BP170122). It is an autologous cell harvesting device indicated for the treatment of acute partial-thickness thermal burn wound when used by an appropriately-licensed healthcare professional at the patient's point of care to prepare autologous RES Regenerative Epidermal Suspension. The initial indication was for use in patients 18 years of age and older in combination with meshed autografting. Subsequently, indications were expanded to include direct application to acute partial-thickness thermal burn wounds in patients 18 years of age and older or application in combination with meshed autografting for acute full-thickness thermal burn wounds in pediatric as well as adult patients and for 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.(88)

FDA product code: QCZ.

Government Regulations

FDA approval is a prerequisite for Medicare coverage but is not the sole determining factor for medical necessity. Having a CPT code or payment amount in the Medicare fee schedule is also not sufficient.

National:

In 2019, CMS reported that it is finalizing the proposal to continue the policy established in calendar year 2018 to assign skin substitutes to the low cost or high-cost group.(84) 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."(85)

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.(86)

Local:

In 2025 WPS released a proposed LCD Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers. L39865 for public comment. It was expected to be effective on January 1, 2026,

however the LCD was pulled and never released. The proposed LCD contained information regarding support or lack thereof regarding certain products.

(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 & Medicaid 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 7/15/26, 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 • Human 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 A2014, A2015, 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
11/1/24	8/20/24		• Routine maintenance (slp) • Vendor managed: N/A • DeNovoSkin, Tutomesh Fenestrated Bovine Pericardium added as EI • ProgenaMatrix (Q4222) moved from EI to EST • mVASC and Restrata MiniMatrix (A2026) added as EST • WPS issued proposed LCD • OviTex® PRS Long Term Resorbable and Ovine Tissue Matrix added as EST – FDA approved
5/1/25			• Policy pulled
11/1/25			• Routine review (slp/fr) • Vendor managed: N/A • Formatting updated • Policy Tabled

7/1/26	6/24/26		• Routine review (slp/fr) • Vendor managed: N/A • Policy sent out post-JUMP for review and approval • Codes adjusted as follows: • Codes changed to/added as EI ○ A2001-2, A2004-18, A2021-29, A2031-39, A4100 ○ C8002, C9250, C9352-56, C9358, C9360, C9361, C9363, C9364, C9399 ○ Q4103, Q4108, Q4113, Q4114, Q4115, Q4117-18, Q4124, Q4127, Q4130, Q4132, Q4135-36, Q4147, Q4149, Q4154, Q4161, Q4164, Q4165, Q4166, Q4195, Q4196, Q4222, Q4238, Q4345 ○ J3590 ○ 15011-15018 • Removed from policy ○ Q4133, Q4151, Q4159, Q4160, Q4186, Q4187 – amniotic products ○ Q4100, Q4106 (deleted per AMA) ○ A6010, A6021, A6022 • Added/Moved from EI to EST ○ A2019 • Aligned Medicare and commercial LOB
11/1/26	8/18/26		• Routine maintenance (slp/fr) • Vendor managed: N/A • Codes added as EI: 1044T-1049T (code update) • Coders added as EST: 15150-52, 15155-57 (replacing deleted code Q4100 for Epicel); code update • Codes moved from EI to EST: Q4431-33 • Q4154 (Biovance); Q4176 (NeoPatch) removed from policy – human placental products • Moved from EST to EI: Q4104

			• Removed: C9352-56, C9358, C9360, C9361, C9364; incidental to the procedure • G0681-84 added as EI (Application codes for FDA products) ○ CMS indicates there is a package payment for the application. Classified as Status N – non-covered service. • Graftjacket removed from breast reconstruction – literature does not support; Remains EST for DFU • Dermagraft (Q4106) removed – code deleted • Integra Omnigraft Dermal Regeneration Matrix (DRM) removed from criteria – literature does not support (part of code Q4105) • Amniotic products removed: Floweramniflo (Q4177); Floweramniopatch (Q4178) Neopatch or Therion (Q4176)
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Next Review Date:

3rd Qtr, 2027

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: SKIN AND TISSUE SUBSTITUTES

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