Medicare Advantage Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Skin and Tissue Substitutes – Medicare Advantage

Medicare Advantage Plan
☒ Medicare Plus Blue℠
☒ BCN Advantage℠

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Description

Skin substitutes (i.e., bioengineered skin, bioengineered soft tissue, human skin equivalent, or artificial skin) are used to replace or support damaged or lost skin or soft tissue. They are commonly used in wound healing, burns, and reconstructive surgery (e.g., breast reconstruction post mastectomy for cancer).

Policy Guidelines

Blue Cross Blue Shield of Michigan (BCBSM) and Blue Care Network of Michigan (BCN) adhere to guidance from the Centers for Medicare and Medicaid Services (CMS), including when performing organization determinations for Medicare Advantage plan members. CMS Medicare statutes, regulations, manuals, National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs) and other sub-regulatory guidance provide the clinical guidelines for coverage determinations, payment integrity functions, and all other uses by CMS regulations. When CMS Medicare guidance is not fully established, CMS permits BCBSM/BCN to utilize “internal coverage criteria”, such as independent criteria, health plan policy research, LCD/LCAs outside the services area or research from independent medical research repositories (i.e., Hayes) for coverage policies 42 CFR § 422.101. BCBSM/BCN internal medical coverage policies are developed and based on current evidence in widely accepted treatment guidelines or clinical literature; in addition, they address how clinical benefits may or may not outweigh member harm.

The following is applicable for this medical policy:

After searching the Medicare Coverage Database and other sources of conditions of coverage, it was determined that CMS guidance is not fully developed, related to codes found in this medical policy. BCBSM/BCN internal policy coverage criteria will be applied. This service may be medically necessary when the criteria are met.

Skin and Tissue Substitute Service	Guidance	
Porcine Based Skin Substitute	**Pub 100-3 Medicare National Coverage Determination (NCD) 270.5:** Porcine Skin and Gradient Pressure Dressing	
Amniotic and Placental Derived Product Injections and/or Applications for Musculoskeletal (Non-Wound) Indications	**Local Coverage Determinations (LCD)** WPS: L39624, A59434 CGS: L39575, A59374 First Coast: L39877, A59764 NGS: L39139, A58893 Noridian JE: L39116, A58865 Noridian JF: L39118, A58867 Novitas: L39879, A59766 Palmetto: L39128, A58883	**Note**: for uses of these products or indications not addressed by the Local Coverage Determination, refer to the Inclusionary, Exclusionary, and Limitation Guidelines section of the policy below for coverage guidance
Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers	**BCBSM/BCNA Skin and Tissue Substitutes – Medicare Advantage**: see the Inclusionary, Exclusionary, and Limitation Guidelines section of the policy below for coverage guidance	
For all other use of Skin and Tissue Substitute products	**BCBSM/BCNA Skin and Tissue Substitutes – Medicare Advantage:** see the Inclusionary, Exclusionary, and Limitation Guidelines section of the policy below for coverage guidance	

The above information is current as of the review date for this policy. However, the coverage issues and policies maintained by CMS are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. Please refer to the Medicare Coverage Database website at https://www.cms.gov/medicare-coverage-database/search.aspx for the most current applicable NCD, LCD, LCA, and CMS Online Manual System Transmittals.

CMS Medicare Administrative Contractors (MAC) Jurisdictions

Part A and Part B Medicare Administrative Contractor (MAC) Jurisdiction	
Wisconsin Physicians Service Insurance Corporation (WPS)	IA, IN, KS, MI, MO, NE
CGS Administrators, LLC	KY, OH
First Coast Service Options, Inc	FL, PR, US VI
National Government Services, Inc (NGS)	CT, IL, MA, ME, MN, NH, NY, RI, VT, WI,
Noridian Healthcare Solutions, LLC, Jurisdiction JE	CA, HI, NV, American Samoa, Guam, Northern Mariana Islands
Noridian Healthcare Solutions, LLC, Jurisdiction JF	AK, AZ, ID, MT, ND, OR, SD, UT, WA, WY
Novitas Solutions, Inc	AR, CO, DC, DE, LA, MD, MS, NJ, NM, OK, PA, TX,

Palmetto GBA	AL, GA, TN NC, SC, VA, WV
DME MAC Jurisdictions	
CGS Administrators, LLC, Jurisdictions JB and JC	AL, AR, CO, FL, GA, IL, IN, KY, LA, MI, MN, MS, NM, NC, OH, OK, Puerto Rico, SC, TN, TX, VA, Virgin Island, WI, WV
Noridian Healthcare Solutions, LLC, Jurisdictions JA and JD	AK, American Soamoa, AZ, CA, CT, DE, DC, Guam, HI, ID, IA, KS, MA, MD, ME, MO, MT, ND, NE, NH, NJ, NV, NY, Northern Mariana Islands, OR, PA, RI, SD, UT, VT, WA, WY

Important Reminder

BCBSM and BCN follow CMS Medicare coverage guidance to limit coverage to items and services that are reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member. Medicare Advantage Medical Policies list the criteria BCBSM and BCN use to decide which medical services are considered “reasonable and necessary” when Medicare coverage rules are not fully developed. Individual member benefit plan documents, such as the Evidence of Coverage and Annual Notice of Change, as well as applicable laws govern benefit coverage, including any inclusion, exclusion, and/or other restrictions.

Medicare Advantage Medical policies are created when permitted by applicable laws, reviewed regularly, and may be revised periodically. BCBSM/BCN Medical Policies are proprietary and should not be copied or disseminated without the express, prior written approval of BCBSM. All providers are required to review applicable BCBSM reimbursement policies prior to claim submission and bill for covered services in accordance with those policies. Additionally, providers contracted with BCBSM or BCN’s Medicare Advantage network(s) should review the provider manual for any additional claim submission requirements. Providers not contracted with BCBSM or BCN’s Medicare Advantage network may be required to submit documentation supporting billed claims, including but not limited to applicable medical records.

Note: U.S. Food and Drug Administration (FDA) approval for a specific indication or the issuance of a CPT code is not sufficient for a procedure to be considered medically reasonable and necessary. Similarly, the presence of a procedure/device code or payment amount for the service in the Medicare fee schedule does not necessarily indicate coverage. If a service is deemed not reasonable and necessary, to treat illness or injury for any reason (including lack of safety and efficacy because it is an experimental procedure, etc.), the procedure is considered not covered.

Disclaimer: This medical policy is not an authorization, certification, explanation of benefits, or a contract for the services, devices, or drugs that is referenced in the medical policy. Medical policies do not constitute medical advice and do not guarantee any results or outcomes or guarantee payment. The medical policy is not intended to replace independent medical judgment for treatment of individuals. Treating physicians and health care providers are solely responsible for determining what care to provide to their patients. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test, or procedure over another.

Pursuant to Section 1557 and Section 504, Blue Cross does not discriminate on the basis of race, color, national origin, age, disability, or sex (including sex characteristics, intersex traits; pregnancy or related conditions; sexual orientation; gender identity, and sex stereotypes). This includes our rules, benefit designs and medical policies.

DESCRIPTION/BACKGROUND

Skin substitutes (i.e., bioengineered skin, bioengineered soft tissue, human skin equivalent, or artificial skin) are applied to wounds to promote wound healing by mimicking specific normal skin properties to promote wound healing. However, they do not function like human skin that is grafted onto a wound; they are not a substitute for skin graft [1]. They are considered an advanced therapy that may be recommended after a wound fails to decrease in size after 4 weeks of standard-of-care (SOC) therapy. Some of their promoted advance functions may include protecting the integument from fluid loss, preventing infection, providing a stable scaffold that promotes synthesis of new dermal tissue, and the support of cytokines and growth factors development [2].

Available bioengineered skin substitutes are numerous and diverse. They can be derived from human tissue, non-human tissue, synthetic materials, or a combination of any of the above. They can include amniotic products which may be derived from amnion, chorion, amniotic fluid, and umbilical cord. The substitutes can be used as either temporary or permanent wound coverings and can be either single layer or bilayer composed of epidermal and/or dermal cells. There are multiple complex classification systems, but Davison-Kotler et al. proposed that cellularity is the most important discriminator since cells increases the rejection risk and manufacturing complexity. With this approach, skin substitutes are first divided into acellular or cellular groups [3].

Acellular skin substitutes are made from natural biological materials which includes decellularized human cadaver dermis, human amniotic membranes, and animal tissue. They contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. The construction of the matrix allows easy access by host cells during the healing process. These are most common commercially available skin substitute products for the treatment non-healing, chronic wounds. The disadvantage of natural products is the rejection risk if cell remnants are not sufficiently removed during processing. Acellular skin substitutes also have poor barrier function and contain the risk of infectious disease transmission [4].

Cellular products can promote the regeneration of natural skin because they contain living cells such as fibroblasts and keratinocytes within a matrix. Keratinocytes are essential for the re-epithelialization process and provide barriers against the skin and environment. They can contain either somatic cells or stem cells [4]. Although human based products undergo a stringent processing, the risk for bacterial or viral infection remains. It is also important to note that because of the of unknowns surrounding the mechanism of changes that take place at the extracellular matrix (ECM) level, there exists concerns for the derived microenvironment promoting tumorigenesis, metastasis, inflammatory or autoimmune disease evolution [5]

Grafting techniques utilized to apply skin substitutes include autografting (i.e., tissue transplanted from one part of the body to another), allografting (i.e., transplant from one individual to another of the same species), and xenografting (i.e., a graft from one species such as bovine or porcine to another unlike species)

Applications

There are many potential applications for artificial skin and soft tissue products. One large category is non-infected chronic wounds, which potentially encompasses diabetic neuropathic ulcers and vascular insufficiency ulcers. A chronic wound is defined as a wound that does not heal in the time expected based on the patient's age, comorbidities, and wound etiology. A wound that has not healed within 30 days to three months is considered chronic. Successful healing of chronic wounds depends on critical factors such as proper blood flow and nutrition to ensure tissue growth, infection control, maintenance of a moist environment, and removal of dead tissue to allow space for new cells and tissue to fill the wound void [6]. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, nonhealing lower-extremity wounds represent an ongoing risk for secondary infection, sepsis, limb amputation, and death. Skin substitutes may have the potential to improve rates of healing and reduce secondary complications.

SOC therapy for chronic wounds includes wound cleansing and debridement, management of infection with antibiotic therapy, correct ischemia in the wound area, maintain moisture balance with wound dressing, compression for venous leg ulcers, and offloading for diabetic foot ulcers [3]. It is essential that routine medical management of diabetes and the presence of a hemoglobin A1c of less than 12% be achieved to maximize complete healing of the wound. For wounds that have not responded to standard of care treatment in four to six weeks, advanced treatment with skin substitutes may be indicated if the chronic wound is free of infection, coagulum, sinus tracts, tunnels, cellulitis, eschar, and necrotic tissue. There should also be no exposure of joints, tendons, ligaments, or bone. Adequate blood supply to the affected areas should be evidenced by a palpable pedal pulse or an ankle-brachial index (ABI) of > 0.70 [6].

Acellular dermal skin substitute products can be useful in breast reconstruction post mastectomy for cancer when skin coverage is inadequate for the procedure performed especially in the setting of tissue expander and breast implant reconstruction. Patients should be in overall good health and have no underlying condition that would restrict blood flow or interfere with the normal healing process (e.g., uncontrolled diabetes, hypertension). These matrixes may be indicated when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required, as may be the case in a very thin patient; if there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis; or if there is a need to re-establish the inframammary fold and lateral mammary fold landmarks. When used in appropriate candidates, these skin substitutes are proposed to improve control over placement of the inframammary fold and final breast contour, enhance use of available mastectomy skin, reduce the number of expanders fills necessary, reduce time

to complete expansion and eventual implant exchange, potential improved management of a threatened implant, reduce the need for explanation and the potential for reduction in the incidence of capsular contracture. However, there are ongoing concerns regarding the increased risk of seroma and infection, a higher risk of an implant having to be removed, and tissue flap death [7].

Other situations in which bioengineered skin products might substitute for living skin grafts include second- and third-degree burns (e.g., auto- and allografts) and certain primary dermatologic conditions that involve large areas of skin breakdown (e.g., bullous diseases). acellular dermal matrix (ADM) products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and other conditions.

Definitions

- **ADM**: Acellular dermal matrix
- **Autologous**: An Autologous graft is tissue that is derived from the same individual.
- **Allogeneic/Allografts:** An allograft is a tissue that is transplanted from one person to another.
- **Chronic Wound:** A chronic wound is one that does not progress through the usual phases of healing and therefore fails to heal in a timely manner [6].
- **Composite Skin Substitute Product**: A product derived from a mix of materials of various origins.
- **CTP**: Cellular and/or tissue-based products
- **HCT/P**: Human cells, tissues, and cellular and tissue-based products
- **Synthetic Skin Substitute**: A product derived from man-made materials.
- **Wound dressing or coverings**: Applications applied to wounds as a selective barrier to clean, cover and protect wounds from the surrounding environment to promote optimal environment for wound healing.
- **Xenograft**: Skin from another species (e.g., cows, pigs, horses, fish, etc.).

REGULATORY STATUS

Skin and tissue substitutes are regulated by the FDA as either medical devices (classified as wound dressings) or as human cells, tissue, and cellular and tissue-based products (HCT/Ps) under section 361 of the Public Health Services Act. They are regulated under one of four categories, depending on the product's origin and composition:

1. HCT/Ps: Human-derived products are regulated as HCT/Ps by the American Association of Tissue Banks (ATTB) and the FDA guidelines under section 361 of the Public Health Service Act for the manufacture HCT/Ps. Donated skin that requires minimal processing and is not significantly changed in structure from its natural form is classified by the FDA as banked human tissue, is not considered a medical device, and does not require PMA or 510(k) approval. AATB oversees a voluntary accreditation program, and the FDA focuses on preventing the transmission of communicable diseases by requiring donor screening and testing. Establishments that manufacture HCT/Ps must register with the FDA and list each cell or tissue produced. An example of a banked human tissue product is AlloDerm, an acellular dermal matrix.
2. Premarket Approval (PMA): Human- and human/animal-derived products regulated through PMA. Products that are classified by the FDA as an interactive wound and burn dressing are approved under the PMA. These devices may be used as a long-term skin substitute or a temporary synthetic skin substitute. They promote healing by interacting directly or indirectly with the body tissues. Examples of these devices include Apligraf® and Dermagraft®.
3. 510(k): Animal-derived products and synthetic products regulated under the 510(k) process. These wound care devices' primary purpose is to protect the wound and provide a scaffold for healing. They may or may not be integrated into the body tissue. Some devices are rejected by the body after approximately ten days to several weeks and removed prior to definitive wound therapy or skin grafting. Integra™ Bilayer Matrix Wound Dressing (BMWD) and Oasis® Wound Matrix are examples of these devices.
4. Humanitarian Device Exemption (HDE): Humanitarian Use Device (HUD) obtained through an HDE.

NOTE: Non-human tissues may qualify for FDA approval. Whereas human tissues are governed by the AATB and do not qualify for FDA approval.

In 2020, FDA updated their clarification of HCT/Ps. HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. According to the FDA, HCT/P must meet all the following criteria:

1) The HCT/P is minimally manipulated.
2) The HCT/P is intended for homologous use only, as reflected in labeling, advertising, or other indications of the manufacturer's objective intent.
3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P.
4) Either:
    (a) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

(b) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:

1. Is for autologous use; or
2. Is for allogeneic use in a first-degree or second-degree blood relative; or
3. Is for reproductive use.

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" [8]

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."

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 [9]. 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 for 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” [9].

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 [9].

COVERAGE DETERMINATION

BCBSM/BCN follows CMS Medicare coverage guidance to limit coverage to items and services that are reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member.

U.S. Food and Drug Administration (FDA) approval for a specific indication or the issuance of a CPT code is not sufficient for a procedure to be considered medically reasonable and necessary. Similarly, the presence of a procedure/device code or payment amount for the service in the Medicare fee schedule does not necessarily indicate coverage. If a service is deemed not reasonable and necessary, to treat illness or injury for any reason (including lack of safety and efficacy because it is an experimental procedure, etc.), the procedure is considered not covered.

Skin and tissue substitutes obtain the United States Food and Drug Administration (FDA) approval through PMA, 510(k), and HDE for being considered safe and efficacious to bring to the market. However, a skin substitute which is unproven by valid scientific literature is considered not reasonable and necessary due to insufficient evidence of efficacy. In 2020, the Agency for Healthcare Research and Quality (AHRQ) published an update of their previous technology assessment for Skin and Tissue Substitutes for the Treatment of Chronic Wounds for CMS [3]. They concluded that clinical evidence for most skin substitutes is lacking and with the lack of clinical evidence, it is difficult to formulate conclusions on their clinical efficacy. Skin and tissue substitutes are established as a useful therapeutic option when they are supported by science, do not cause harm, and demonstrate successful outcomes for individuals meeting specified inclusion criteria.

HCT/Ps are subject to the rules and regulations of banked human tissue by the AATB and have been established as a potential useful therapeutic option for individuals meeting specified inclusion criteria.

Inclusionary, Exclusionary, and Limitation Guidelines

Inclusion Guidelines

The use of skin and tissue substitutes have been scientifically validated and therefore may be medically necessary when criteria met for the following indications:

1. Breast Reconstruction Post Mastectomy for Cancer
2. Diabetic Foot Ulcers
3. Venous Leg Ulcers
4. Dystrophic epidermolysis bullosa
5. Second- or third-degree burns

There is insufficient evidence to support the efficacy of bioengineered Skin and Tissue Substitute to improve on health outcomes for all other indications and is therefore all other use not listed above is considered investigational and therefore not reasonable and necessary.

All use of skin and soft tissue substitutes may be subjected to the Plan Medical Director Review

Clinical Inclusion Criteria

Use of skin and tissue substitute may be considered medically necessary when **ALL** the following are met:

1. The skin substitute product must satisfy at least **ONE** of the following:
    - AATB Approval: The skin substitute product must meet all applicable regulation and standards established by the American Association of Tissue Banks for procuring and processing human cells, tissues, and cellular or tissue-based products (HCT/Ps), or
    - FDA Approval: The skin substitute product must meet all product specific FDA requirements.
2. And **ALL** the following are met:
    - Documentation noting the member is a non-smoker, or has completed or is currently in smoking cessation therapy; and
    - Wound characteristics and treatment plan are documented including ALL the following:
        - Partial- or full-thickness skin defect, clean, and free of necrotic debris, exudate, or infection and
        - Tissue approximation would cause excessive tension or functional loss; and
        - No involvement of tendon, muscle, joint capsule, or exposed bone or sinus tracts; and
        - No wound infection

3. And the skin substitute product must be used in **ONE** of the following specific indications:

   A. **Breast Reconstruction** - The following allogeneic ADM products may be considered medically necessary for breast reconstructive surgery following cancer treatment:
      - AlloDerm®
      - AlloMend®
      - Cortiva®, [AlloMax™]
      - DermACELL™
      - DermaMatrix™
      - FlexHD®
      - FlexHD® Pliable™
      - Graftjacket®

      AND if one of the following is met:
      - There is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required OR
      - There is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis OR
      - The inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed.

   B. **Diabetic Foot Ulcers**: The following skin substitute graft products may be considered medically necessary for the treatment of chronic full-thickness diabetic foot ulcers that have not adequately responded to 4 weeks of standard care with documented compliance [6]:
      - Affinity
      - AmnioBand® Membrane or Guardian
      - Apligraf®
      - DermACELL®
      - Dermagraft®
      - EpiCord®
      - EpiFix
      - FlexHD® or AlloPatch HD®
      - Grafix Prime, Grafix PL Prime, Stravix and StravixPL
      - GraftJacket
      - Integra® Omnigraft™ Dermal Regeneration Matrix (AKA Omnigraft)
      - Oasis® Tri-layer Wound
      - Oasis® Wound Matrix
      - PriMatrix®

- TheraSkin®

AND when all the following criteria are met:

- There is adequate circulation to the affected area.
- There is no sign of clinical infection in the ulcer.
- The plan member has adequate glycemic control.
- The plan member is willing and able to maintain the required schedule of dressing changes and offloading, and
- The plan member is a non-smoker or has refrained for at least 6 weeks prior to planned treatment with skin substitutes or has received counseling on the effects of smoking on wound healing and surgical outcomes and treatment for smoking cessation.

C. **Venous Insufficiency Lower Extremity Ulcers:** The following skin substitute graft products may be considered medically necessary for the treatment of chronic partial and full-thickness venous leg ulcers that have not adequately responded to 4 weeks of standard care with documented compliance [6]:

- Amnioband or Guardian
- Apligraf
- DermACELL
- EpiCord
- EpiFix
- Grafix or Stravix
- Oasis Wound Matrix
- PriMatrix®
- TheraSkin®

AND when all the following criteria are met:

- There is adequate circulation to the affected area.
- There is no sign of clinical infection in the ulcer.
- The plan member has adequate glycemic control.
- The plan member is willing and able to maintain the required schedule of dressing changes and compression, and
- The plan member is a non-smoker or has refrained for at least 6 weeks prior to planned treatment with skin substitutes or has received counseling on the effects of smoking on wound healing and surgical outcomes and treatment for smoking cessation.

D. **Dystrophic Epidermolysis Bullosa** - Treatment of dystrophic epidermolysis bullosa using the following tissue-engineered skin substitute may be considered Medically Necessary.

- OrCel™ (for the treatment of mitten-hand deformity when standard wound therapy has failed and when provided in

accordance with the humanitarian device exemption [HDE] specifications of the U.S. Food and Drug Administration [FDA]).

E. **Second- Or Third-Degree Burns** - Treatment of second- and third-degree burns using the following tissue-engineered skin substitutes may be considered Medically Necessary:
    - Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area ≥30% when provided in accordance with the HDE specifications of the FDA)
    - Integra® Dermal Regeneration Template
    - Transcyte®

Exclusion Guidelines

All other uses of bioengineered skin and soft tissue substitutes **NOT** listed above is considered investigational and therefore not reasonable and necessary. There is insufficient evidence to support the efficacy of Skin and Tissue Substitute to assess and improve on health outcomes.

Skin substitutes are **NOT** considered reasonable and necessary in patients with inadequate control of underlying conditions or exacerbating factors including but not limited to any of the following:

- Use of skin substitutes in wounds with signs of clinical infection.
- Use of skin substitutes when there is not adequate circulation to the affected area.
- Use of skin substitutes in wounds with exposed bone, tendon, or fascia.
- Use of skin substitutes in plan members with HbA1c >12%
- Use of skin substitutes in plan members with active Charcot arthropathy of the ulcer extremity for indications aside from diabetic foot ulcers.

Limitations: (per ulcer episode of care)

The following are considered **NOT** reasonable and necessary [3, 6, 10, 11, 12, 13]:

1. Greater than four applications of a skin substitute graft/CTP within the episode of skin replacement therapy (defined as 12 weeks from the first application of a skin substitute graft/CTP). In exceptional cases in which 4 applications is not sufficient for adequate wound healing, additional applications may be considered with documentation that includes progression of wound closure under current treatment plan and medical necessity for additional applications subject to Plan Medical Director review [13].
2. Application of a skin substitute graft/CTP beyond 12-weeks per episode within the episode of skin replacement therapy. In exceptional cases in which 12 weeks is not sufficient for adequate wound healing, additional duration of care may be considered

with documentation demonstrating progression of wound closure under current treatment plan and benefit expected from additional applications subject to Plan Medical Director review.

3. Repeat applications of skin substitute graft/CTP when a previous application was unsuccessful. Unsuccessful treatment is defined as increase in size or depth of an ulcer, no measurable change from baseline, and no sign of improvement or indication that improvement is likely (such as granulation, epithelialization, or progress towards closure). Unsuccessful therapy also includes reoccurrence of the ulcer in the same location within 12 months from initial application.
4. Application of skin substitute graft/CTP in patients with inadequate control of underlying conditions or exacerbating factors, or other contraindications (e.g., uncontrolled diabetes, active infection, progressive necrosis, active Charcot arthropathy of the ulcer extremity, active vasculitis, or ischemia) [6].
5. Use of surgical preparation services (e.g., debridement), in conjunction with routine, simple or repeat skin replacement surgery with a skin substitute graft/CTP).
6. Excessive wastage (discarded amount). The skin substitute graft/CTP must be used in an efficient manner utilizing the most appropriate size product available at the time of treatment. It is expected that use of product, size and preparation should conform to that most closely fitting the wound with the least amount of wastage.
7. All liquid or gel skin substitute products or CTPs for ulcer [14].
8. Placement of skin substitute graft/CTP on infected, ischemic, or necrotic wound bed [12] [15].

PROVIDER QUALIFICATIONS

Services provided within the LCD coverage indications will be considered reasonable and necessary when all aspects of care are within the scope of practice of the provider's professional licensure. All procedures must be performed by appropriately trained providers in the appropriate setting.

Notice: Services performed for any given diagnosis must meet all the indications and limitations stated in this policy, the general requirements for medical necessity as stated in CMS payment policy manuals, all existing CMS national coverage determinations, and all Medicare payment rules.

CODING INFORMATION

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure. This list of codes may not be all-inclusive since the American Medical Association (AMA) and CMS code updates may occur more frequently than policy updates. Deleted codes and codes which are not effective at the time service is rendered may not be eligible for reimbursement.

CPT/HCPCS LEVEL II CODES

Current Procedural Terminology (CPT) defines skin substitute grafts to include non-autologous skin (dermal or epidermal, cellular, or acellular) grafts (e.g., homograft, allograft), non-human skin substitute grafts (i.e., xenograft), and biological products that form a sheet scaffolding for skin growth. CPT does not include non-graft wound dressings (e.g., gel, powder, ointment, liquid) or injectable skin substitutes in the skin substitute graft codes.

HCPCS codes included in this list are FDA approved/ meeting necessary regulatory requirements for CTPs for chronic ulcer treatment as of publication. Each product has specific designated approved usage. This is not an all-inclusive list of CTPs as new products and HCPCS codes will be considered for coverage if meeting the regulatory requirements and criteria. Therefore, any HCPCS code that is not included in this list will not be separately reimbursed.

The above medical necessity criteria MUST be met for the following codes to be covered

BREAST RECONSTRUCTIVE SURGERY

Group 1 Codes: Breast Reconstruction following Mastectomy for Cancer

The following codes may be medically necessary when criteria met and reported with an ICD-10-CM Diagnostic Code from group 2 Codes in the following table for Breast Reconstruction.

Codes	Code Description
Q4100	Skin substitute, not otherwise specified**for use with Allomax™, AlloMend®, Cortiva® DermaMatrix™,
Q4107	GraftJacket®, Per SQ CM
Q4116	AlloDerm, Per SQ CM
Q4122	DermACELL, DermACELL AWM or DermACELL AWM Porous, Per SQ CM
Q4128	FlexHD, FlexHD® Pliable™, AlloPatchHD, or Matrix HD, Per SQ CM

Group 2 Codes: Breast Reconstruction following Mastectomy for Cancer

A CPT/HCPCS code from the Group 1 Codes above must be reported with an ICD-10-CM Diagnosis code from the Group 2 Codes in the table below for Breast Reconstruction

ICD-10 Codes:	Description
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast

C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast

C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast
F64.0	Transsexualism
F64.1	Gender identity disorder in adolescence and adulthood
F64.2	Gender identity disorder of childhood
F64.8	Other identity disorders
F64.9	Gender identity disorder, unspecified

DIABETIC FOOT ULCER

Group 1 Codes: Diabetic Foot Ulcer

The following codes may be medically necessary when criteria met and reported with an ICD-10-CM Diagnostic Code from group 2 Codes in the following table for Diabetic Foot Ulcer.

Codes	Code Description
Q4159	Affinity
Q4151	AmnioBand® Membrane or Guardian
Q4101	Apligraf®
Q4122	DermACELL®
Q4106	Dermagraft®
Q4187	EpiCord®
Q4186	EpiFix®
Q4128	FlexHD® or AlloPatch HD®
Q4133	Grafix Prime, Grafix PL Prime, Stravix and StravixPL
Q4107	GraftJacket®
Q4105	Integra® Omnigraft™ Dermal Regeneration Matrix (AKA Omnigraft)
Q4124	Oasis® Tri-layer Wound
Q4102	Oasis® Wound Matrix
Q4110	PriMatrix®
Q4121	TheraSkin®

Group 2 Codes: Diabetic Foot Ulcer

A CPT/HCPCS code from the Group 1 Codes above must be reported with an ICD-10-CM Diagnosis code from the Group 2 Codes in the table below for Diabetic Foot Ulcer

ICD-10 Codes:	Description
I83.011	Varicose veins of right lower extremity with ulcer of thigh
I83.012	Varicose veins of right lower extremity with ulcer of calf
I83.013	Varicose veins of right lower extremity with ulcer of ankle
I83.014	Varicose veins of right lower extremity with ulcer of heel and midfoot
I83.015	Varicose veins of right lower extremity with ulcer other part of foot
I83.018	Varicose veins of right lower extremity with ulcer other part of lower leg
I83.021	Varicose veins of left lower extremity with ulcer of thigh
I83.022	Varicose veins of left lower extremity with ulcer of calf
I83.023	Varicose veins of left lower extremity with ulcer of ankle

I83.024	Varicose veins of left lower extremity with ulcer of heel and midfoot
I83.025	Varicose veins of left lower extremity with ulcer other part of foot
I83.028	Varicose veins of left lower extremity with ulcer other part of lower leg
I83.211	Varicose veins of right lower extremity with both ulcer of thigh and inflammation
I83.212	Varicose veins of right lower extremity with both ulcer of calf and inflammation
I83.213	Varicose veins of right lower extremity with both ulcer of ankle and inflammation
I83.214	Varicose veins of right lower extremity with both ulcer of heel and midfoot and inflammation
I83.215	Varicose veins of right lower extremity with both ulcer other part of foot and inflammation
I83.218	Varicose veins of right lower extremity with both ulcer of other part of lower extremity and inflammation
I83.221	Varicose veins of left lower extremity with both ulcer of thigh and inflammation
I83.222	Varicose veins of left lower extremity with both ulcer of calf and inflammation
I83.223	Varicose veins of left lower extremity with both ulcer of ankle and inflammation
I83.224	Varicose veins of left lower extremity with both ulcer of heel and midfoot and inflammation
I83.225	Varicose veins of left lower extremity with both ulcer other part of foot and inflammation
I83.228	Varicose veins of left lower extremity with both ulcer of other part of lower extremity and inflammation
I87.011	Postthrombotic syndrome with ulcer of right lower extremity
I87.012	Postthrombotic syndrome with ulcer of left lower extremity
I87.013	Postthrombotic syndrome with ulcer of bilateral lower extremity
I87.031	Postthrombotic syndrome with ulcer and inflammation of right lower extremity
I87.032	Postthrombotic syndrome with ulcer and inflammation of left lower extremity
I87.033	Postthrombotic syndrome with ulcer and inflammation of bilateral lower extremity
I87.311	Chronic venous hypertension (idiopathic) with ulcer of right lower extremity
I87.312	Chronic venous hypertension (idiopathic) with ulcer of left lower extremity
I87.313	Chronic venous hypertension (idiopathic) with ulcer of bilateral lower extremity
I87.331	Chronic venous hypertension (idiopathic) with ulcer and inflammation of right lower extremity
I87.332	Chronic venous hypertension (idiopathic) with ulcer and inflammation of left lower extremity
I87.333	Chronic venous hypertension (idiopathic) with ulcer and inflammation of bilateral lower extremity
L97.111	Non-pressure chronic ulcer of right thigh limited to breakdown of skin
L97.112	Non-pressure chronic ulcer of right thigh with fat layer exposed
L97.121	Non-pressure chronic ulcer of left thigh limited to breakdown of skin
L97.122	Non-pressure chronic ulcer of left thigh with fat layer exposed
L97.211	Non-pressure chronic ulcer of right calf limited to breakdown of skin
L97.212	Non-pressure chronic ulcer of right calf with fat layer exposed
L97.221	Non-pressure chronic ulcer of left calf limited to breakdown of skin
L97.222	Non-pressure chronic ulcer of left calf with fat layer exposed
L97.311	Non-pressure chronic ulcer of right ankle limited to breakdown of skin

L97.312	Non-pressure chronic ulcer of right ankle with fat layer exposed
L97.321	Non-pressure chronic ulcer of left ankle limited to breakdown of skin
L97.322	Non-pressure chronic ulcer of left ankle with fat layer exposed
L97.411	Non-pressure chronic ulcer of right heel and midfoot limited to breakdown of skin
L97.412	Non-pressure chronic ulcer of right heel and midfoot with fat layer exposed
L97.421	Non-pressure chronic ulcer of left heel and midfoot limited to breakdown of skin
L97.422	Non-pressure chronic ulcer of left heel and midfoot with fat layer exposed
L97.511	Non-pressure chronic ulcer of other part of right foot limited to breakdown of skin
L97.512	Non-pressure chronic ulcer of other part of right foot with fat layer exposed
L97.521	Non-pressure chronic ulcer of other part of left foot limited to breakdown of skin
L97.522	Non-pressure chronic ulcer of other part of left foot with fat layer exposed
L97.811	Non-pressure chronic ulcer of other part of right lower leg limited to breakdown of skin
L97.812	Non-pressure chronic ulcer of other part of right lower leg with fat layer exposed
L97.821	Non-pressure chronic ulcer of other part of left lower leg limited to breakdown of skin
L97.822	Non-pressure chronic ulcer of other part of left lower leg with fat layer exposed

VENOUS LEG ULCER

Group 1 Codes: Venous Leg Ulcer

The following codes may be medically necessary when criteria met and reported with an ICD-10-CM Diagnostic Code from group 2 Codes in the following table for Venous Leg Ulcer.

Codes	Code Description
Q4101	Apligraf®
Q4102	OASIS® Wound Matrix
Q4110	PriMatrix™
Q4121	TheraSkin®
Q4122	DermACELL™ AWM
Q4133	Grafix®
Q4151	AmnioBand®
Q4187	EpiCord®

Group 2 Codes: Venous Leg Ulcer

A CPT/HCPCS code from the Group 1 Codes above must be reported with an ICD-10-CM Diagnosis code from the Group 2 Codes in the table below for Venous Leg Ulcer

ICD-10 Codes:	Description
I83.011	Varicose veins of right lower extremity with ulcer of thigh
I83.012	Varicose veins of right lower extremity with ulcer of calf
I83.013	Varicose veins of right lower extremity with ulcer of ankle
I83.014	Varicose veins of right lower extremity with ulcer of heel and midfoot
I83.015	Varicose veins of right lower extremity with ulcer other part of foot
I83.018	Varicose veins of right lower extremity with ulcer other part of lower leg
I83.021	Varicose veins of left lower extremity with ulcer of thigh

I83.022	Varicose veins of left lower extremity with ulcer of calf
I83.023	Varicose veins of left lower extremity with ulcer of ankle
I83.024	Varicose veins of left lower extremity with ulcer of heel and midfoot
I83.025	Varicose veins of left lower extremity with ulcer other part of foot
I83.028	Varicose veins of left lower extremity with ulcer other part of lower leg
I83.211	Varicose veins of right lower extremity with both ulcer of thigh and inflammation
I83.212	Varicose veins of right lower extremity with both ulcer of calf and inflammation
I83.213	Varicose veins of right lower extremity with both ulcer of ankle and inflammation
I83.214	Varicose veins of right lower extremity with both ulcer of heel and midfoot and inflammation
I83.215	Varicose veins of right lower extremity with both ulcer other part of foot and inflammation
I83.218	Varicose veins of right lower extremity with both ulcer of other part of lower extremity and inflammation
I83.221	Varicose veins of left lower extremity with both ulcer of thigh and inflammation
I83.222	Varicose veins of left lower extremity with both ulcer of calf and inflammation
I83.223	Varicose veins of left lower extremity with both ulcer of ankle and inflammation
I83.224	Varicose veins of left lower extremity with both ulcer of heel and midfoot and inflammation
I83.225	Varicose veins of left lower extremity with both ulcer other part of foot and inflammation
I83.228	Varicose veins of left lower extremity with both ulcer of other part of lower extremity and inflammation
I87.011	Postthrombotic syndrome with ulcer of right lower extremity
I87.012	Postthrombotic syndrome with ulcer of left lower extremity
I87.013	Postthrombotic syndrome with ulcer of bilateral lower extremity
I87.031	Postthrombotic syndrome with ulcer and inflammation of right lower extremity
I87.032	Postthrombotic syndrome with ulcer and inflammation of left lower extremity
I87.033	Postthrombotic syndrome with ulcer and inflammation of bilateral lower extremity
I87.311	Chronic venous hypertension (idiopathic) with ulcer of right lower extremity
I87.312	Chronic venous hypertension (idiopathic) with ulcer of left lower extremity
I87.313	Chronic venous hypertension (idiopathic) with ulcer of bilateral lower extremity
I87.331	Chronic venous hypertension (idiopathic) with ulcer and inflammation of right lower extremity
I87.332	Chronic venous hypertension (idiopathic) with ulcer and inflammation of left lower extremity
I87.333	Chronic venous hypertension (idiopathic) with ulcer and inflammation of bilateral lower extremity
L97.111	Non-pressure chronic ulcer of right thigh limited to breakdown of skin
L97.112	Non-pressure chronic ulcer of right thigh with fat layer exposed
L97.121	Non-pressure chronic ulcer of left thigh limited to breakdown of skin
L97.122	Non-pressure chronic ulcer of left thigh with fat layer exposed
L97.211	Non-pressure chronic ulcer of right calf limited to breakdown of skin
L97.212	Non-pressure chronic ulcer of right calf with fat layer exposed
L97.221	Non-pressure chronic ulcer of left calf limited to breakdown of skin

L97.222	Non-pressure chronic ulcer of left calf with fat layer exposed
L97.311	Non-pressure chronic ulcer of right ankle limited to breakdown of skin
L97.312	Non-pressure chronic ulcer of right ankle with fat layer exposed
L97.321	Non-pressure chronic ulcer of left ankle limited to breakdown of skin
L97.322	Non-pressure chronic ulcer of left ankle with fat layer exposed
L97.411	Non-pressure chronic ulcer of right heel and midfoot limited to breakdown of skin
L97.412	Non-pressure chronic ulcer of right heel and midfoot with fat layer exposed
L97.421	Non-pressure chronic ulcer of left heel and midfoot limited to breakdown of skin
L97.422	Non-pressure chronic ulcer of left heel and midfoot with fat layer exposed
L97.511	Non-pressure chronic ulcer of other part of right foot limited to breakdown of skin
L97.512	Non-pressure chronic ulcer of other part of right foot with fat layer exposed
L97.521	Non-pressure chronic ulcer of other part of left foot limited to breakdown of skin
L97.522	Non-pressure chronic ulcer of other part of left foot with fat layer exposed
L97.811	Non-pressure chronic ulcer of other part of right lower leg limited to breakdown of skin
L97.812	Non-pressure chronic ulcer of other part of right lower leg with fat layer exposed
L97.821	Non-pressure chronic ulcer of other part of left lower leg limited to breakdown of skin
L97.822	Non-pressure chronic ulcer of other part of left lower leg with fat layer exposed

Group 3 Codes: Diabetic Foot Ulcer and Venous Leg Ulcers
The following HCPCS codes are **NON-COVERED** for Diabetic Foot Ulcers and Venous Leg Ulcers:

Code	Description
A2001	INNOVAMATRIX AC, PER SQUARE CENTIMETER
A2002	MIRRAGEN ADVANCED WOUND MATRIX, PER SQUARE CENTIMETER
A2004	XCELLISTEM, 1 MG
A2005	MICROLYTE MATRIX, PER SQUARE CENTIMETER
A2006	NOVOSORB SYNPATH DERMAL MATRIX, PER SQUARE CENTIMETER
A2007	RESTRATA, PER SQUARE CENTIMETER
A2008	THERAGENESIS, PER SQUARE CENTIMETER
A2009	SYMPHONY, PER SQUARE CENTIMETER
A2010	APIS, PER SQUARE CENTIMETER
A2011	SUPRA SDRM, PER SQUARE CENTIMETER
A2012	SUPRATHEL, PER SQUARE CENTIMETER
A2013	INNOVAMATRIX FS, PER SQUARE CENTIMETER
A2014	OMEZA COLLAGEN MATRIX, PER 100 MG
A2015	PHOENIX WOUND MATRIX, PER SQUARE CENTIMETER
A2016	PERMEADERM B, PER SQUARE CENTIMETER
A2018	PERMEADERM C, PER SQUARE CENTIMETER
A2019	KERECIS OMEGA3 MARIGEN SHIELD, PER SQUARE CENTIMETER
A2020	AC5 ADVANCED WOUND SYSTEM (AC5)
A2021	NEOMATRIX, PER SQUARE CENTIMETER
A2022	INNOVABURN OR INNOVAMATRIX XL, PER SQUARE CENTIMETER

Group 3 Codes: Diabetic Foot Ulcer and Venous Leg Ulcers The following HCPCS codes are **NON-COVERED** for Diabetic Foot Ulcers and Venous Leg Ulcers:	
A2023	INNOVAMATRIX PD, 1 MG
A2024	RESOLVE MATRIX, PER SQUARE CENTIMETER
A2025	MIRO3D, PER CUBIC CENTIMETER
A4100	SKIN SUBSTITUTE, FDA CLEARED AS A DEVICE, NOT OTHERWISE SPECIFIED
C9358	DERMAL SUBSTITUTE, NATIVE, NON-DENATURED COLLAGEN, FETAL BOVINE ORIGIN (SURGIMEND COLLAGEN MATRIX), PER 0.5 SQUARE CENTIMETERS
C9360	DERMAL SUBSTITUTE, NATIVE, NON-DENATURED COLLAGEN, NEONATAL BOVINE ORIGIN (SURGIMEND COLLAGEN MATRIX), PER 0.5 SQUARE CENTIMETERS
C9363	SKIN SUBSTITUTE, INTEGRA MESHED BILAYER WOUND MATRIX, PER SQUARE CENTIMETER
C9364	PORCINE IMPLANT, PERMACOL, PER SQUARE CENTIMETER
Q4100	SKIN SUBSTITUTE, NOT OTHERWISE SPECIFIED
Q4103	OASIS BURN MATRIX, PER SQUARE CENTIMETER
Q4104	INTEGRA BILAYER MATRIX WOUND DRESSING (BMWD), PER SQUARE CENTIMETER
Q4108	INTEGRA MATRIX, PER SQUARE CENTIMETER
Q4111	GAMMAGRAFT, PER SQUARE CENTIMETER
Q4112	CYMETRA, INJECTABLE, 1 CC
Q4113	GRAFTJACKET XPRESS, INJECTABLE, 1 CC
Q4114	INTEGRA FLOWABLE WOUND MATRIX, INJECTABLE, 1 CC
Q4115	ALLOSKIN, PER SQUARE CENTIMETER
Q4116	ALLODERM, PER SQUARE CENTIMETER
Q4117	HYALOMATRIX, PER SQUARE CENTIMETER
Q4118	MATRISTEM MICROMATRIX, 1 MG
Q4123	ALLOSKIN RT, PER SQUARE CENTIMETER
Q4125	ARTHROFLEX, PER SQUARE CENTIMETER
Q4126	MEMODERM, DERMASPAN, TRANZGRAFT OR INTEGUPLY, PER SQUARE CENTIMETER
Q4127	TALYMED, PER SQUARE CENTIMETER
Q4130	STRATTICE TM, PER SQUARE CENTIMETER
Q4132	GRAFIX CORE AND GRAFIXPL CORE, PER SQUARE CENTIMETER
Q4134	HMATRIX, PER SQUARE CENTIMETER
Q4135	MEDISKIN, PER SQUARE CENTIMETER
Q4136	EZ-DERM, PER SQUARE CENTIMETER
Q4137	AMNIOEXCEL, AMNIOEXCEL PLUS OR BIODEXCEL, PER SQUARE CENTIMETER
Q4138	BIODFENCE DRYFLEX, PER SQUARE CENTIMETER
Q4139	AMNIOMATRIX OR BIODMATRIX, INJECTABLE, 1 CC
Q4140	BIODFENCE, PER SQUARE CENTIMETER
Q4141	ALLOSKIN AC, PER SQUARE CENTIMETER
Q4142	XCM BIOLOGIC TISSUE MATRIX, PER SQUARE CENTIMETER
Q4143	REPRIZA, PER SQUARE CENTIMETER

Group 3 Codes: Diabetic Foot Ulcer and Venous Leg Ulcers The following HCPCS codes are **NON-COVERED** for Diabetic Foot Ulcers and Venous Leg Ulcers:	
Q4145	EPIFIX, INJECTABLE, 1 MG
Q4146	TENSIX, PER SQUARE CENTIMETER
Q4147	ARCHITECT, ARCHITECT PX, OR ARCHITECT FX, EXTRACELLULAR MATRIX, PER SQUARE CENTIMETER
Q4148	NEOX CORD 1K, NEOX CORD RT, OR CLARIX CORD 1K, PER SQUARE CENTIMETER
Q4149	EXCELLAGEN, 0.1 CC
Q4150	ALLOWRAP DS OR DRY, PER SQUARE CENTIMETER
Q4152	DERMAPURE, PER SQUARE CENTIMETER
Q4153	DERMAVEST AND PLURIVEST, PER SQUARE CENTIMETER
Q4154	BIOVANCE, PER SQUARE CENTIMETER
Q4155	NEOXFLO OR CLARIXFLO, 1 MG
Q4156	NEOX 100 OR CLARIX 100, PER SQUARE CENTIMETER
Q4157	REVITALON, PER SQUARE CENTIMETER
Q4158	KERECIS OMEGA3, PER SQUARE CENTIMETER
Q4160	NUSHIELD, PER SQUARE CENTIMETER
Q4161	BIO-CONNEKT WOUND MATRIX, PER SQUARE CENTIMETER
Q4162	WOUNDEX FLOW, BIOSKIN FLOW, 0.5 CC
Q4163	WOUNDEX, BIOSKIN, PER SQUARE CENTIMETER
Q4164	HELICOLL, PER SQUARE CENTIMETER
Q4165	KERAMATRIX OR KERASORB, PER SQUARE CENTIMETER
Q4166	CYTAL, PER SQUARE CENTIMETER
Q4167	TRUSKIN, PER SQUARE CENTIMETER
Q4168	AMNIOBAND, 1 MG
Q4169	ARTACENT WOUND, PER SQUARE CENTIMETER
Q4170	CYGNUS, PER SQUARE CENTIMETER
Q4171	INTERFYL, 1 MG
Q4173	PALINGEN OR PALINGEN XPLUS, PER SQUARE CENTIMETER
Q4174	PALINGEN OR PROMATRX, 0.36 MG PER 0.25 CC
Q4175	MIRODERM, PER SQUARE CENTIMETER
Q4176	NEOPATCH OR THERION, PER SQUARE CENTIMETER
Q4177	FLOWERAMNIOFLO, 0.1 CC
Q4178	FLOWERAMNIOPATCH, PER SQUARE CENTIMETER
Q4179	FLOWERDERM, PER SQUARE CENTIMETER
Q4180	REVITA, PER SQUARE CENTIMETER
Q4181	AMNIO WOUND, PER SQUARE CENTIMETER
Q4182	TRANSCYTE, PER SQUARE CENTIMETER
Q4183	SURGIGRAFT, PER SQUARE CENTIMETER
Q4184	CELLESTA OR CELLESTA DUO, PER SQUARE CENTIMETER
Q4185	CELLESTA FLOWABLE AMNION (25 MG PER CC); PER 0.5 CC
Q4188	AMNIOARMOR, PER SQUARE CENTIMETER
Q4189	ARTACENT AC, 1 MG

Group 3 Codes: Diabetic Foot Ulcer and Venous Leg Ulcers The following HCPCS codes are **NON-COVERED** for Diabetic Foot Ulcers and Venous Leg Ulcers:	
Q4190	ARTACENT AC, PER SQUARE CENTIMETER
Q4191	RESTORIGIN, PER SQUARE CENTIMETER
Q4192	RESTORIGIN, 1 CC
Q4193	COLL-E-DERM, PER SQUARE CENTIMETER
Q4194	NOVACHOR, PER SQUARE CENTIMETER
Q4195	PURAPLY, PER SQUARE CENTIMETER
Q4196	PURAPLY AM, PER SQUARE CENTIMETER
Q4197	PURAPLY XT, PER SQUARE CENTIMETER
Q4198	GENESIS AMNIOTIC MEMBRANE, PER SQUARE CENTIMETER
Q4199	CYGNUS MATRIX, PER SQUARE CENTIMETER
Q4200	SKIN TE, PER SQUARE CENTIMETER
Q4201	MATRION, PER SQUARE CENTIMETER
Q4202	KEROXX (2.5G/CC), 1CC
Q4203	DERMA-GIDE, PER SQUARE CENTIMETER
Q4204	XWRAP, PER SQUARE CENTIMETER
Q4205	MEMBRANE GRAFT OR MEMBRANE WRAP, PER SQUARE CENTIMETER
Q4206	FLUID FLOW OR FLUID GF, 1 CC
Q4208	NOVAFIX, PER SQUARE CENTIMETER
Q4209	SURGRAFT, PER SQUARE CENTIMETER
Q4210	AXOLOTL GRAFT OR AXOLOTL DUALGRAFT, PER SQUARE CENTIMETER
Q4211	AMNION BIO OR AXOBIOMEMBRANE, PER SQUARE CENTIMETER
Q4212	ALLOGEN, PER CC
Q4213	ASCENT, 0.5 MG
Q4214	CELLESTA CORD, PER SQUARE CENTIMETER
Q4215	AXOLOTL AMBIENT OR AXOLOTL CRYO, 0.1 MG
Q4216	ARTACENT CORD, PER SQUARE CENTIMETER
Q4217	WOUNDFIX, BIOWOUND, WOUNDFIX PLUS, BIOWOUND PLUS, WOUNDFIX XPLUS OR BIOWOUND XPLUS, PER SQUARE CENTIMETER
Q4218	SURGICORD, PER SQUARE CENTIMETER
Q4219	SURGIGRAFT-DUAL, PER SQUARE CENTIMETER
Q4220	BELLACELL HD OR SUREDERM, PER SQUARE CENTIMETER
Q4221	AMNIOWRAP2, PER SQUARE CENTIMETER
Q4222	PROGENAMATRIX, PER SQUARE CENTIMETER
Q4225	AMNIOBIND OR DERMABIND TL, PER SQUARE CENTIMETER
Q4226	MYOWN SKIN, INCLUDES HARVESTING AND PREPARATION PROCEDURES, PER SQUARE CENTIMETER
Q4227	AMNIOCORE, PER SQUARE CENTIMETER
Q4229	COGENEX AMNIOTIC MEMBRANE, PER SQUARE CENTIMETER
Q4230	COGENEX FLOWABLE AMNION, PER 0.5 CC
Q4231	CORPLEX P, PER CC
Q4232	CORPLEX, PER SQUARE CENTIMETER
Q4233	SURFACTOR OR NUDYN, PER 0.5 CC

Group 3 Codes: Diabetic Foot Ulcer and Venous Leg Ulcers The following HCPCS codes are **NON-COVERED** for Diabetic Foot Ulcers and Venous Leg Ulcers:	
Q4234	XCELLERATE, PER SQUARE CENTIMETER
Q4235	AMNIOREPAIR OR ALTIPLY, PER SQUARE CENTIMETER
Q4236	CAREPATCH, PER SQUARE CENTIMETER
Q4237	CRYO-CORD, PER SQUARE CENTIMETER
Q4238	DERM-MAXX, PER SQUARE CENTIMETER
Q4239	AMNIO-MAXX OR AMNIO-MAXX LITE, PER SQUARE CENTIMETER
Q4240	CORECYTE, FOR TOPICAL USE ONLY, PER 0.5 CC
Q4241	POLYCYTE, FOR TOPICAL USE ONLY, PER 0.5 CC
Q4242	AMNIOCYTE PLUS, PER 0.5 CC
Q4245	AMNIOTEXT, PER CC
Q4246	CORETEXT OR PROTEXT, PER CC
Q4247	AMNIOTEXT PATCH, PER SQUARE CENTIMETER
Q4248	DERMACYTE AMNIOTIC MEMBRANE ALLOGRAFT, PER SQUARE CENTIMETER
Q4249	AMNIPLY, FOR TOPICAL USE ONLY, PER SQUARE CENTIMETER
Q4250	AMNIOAMP-MP, PER SQUARE CENTIMETER
Q4251	VIM, PER SQUARE CENTIMETER
Q4252	VENDAJE, PER SQUARE CENTIMETER
Q4253	ZENITH AMNIOTIC MEMBRANE, PER SQUARE CENTIMETER
Q4254	NOVAFIX DL, PER SQUARE CENTIMETER
Q4255	REGUARD, FOR TOPICAL USE ONLY, PER SQUARE CENTIMETER
Q4256	MLG-COMPLETE, PER SQUARE CENTIMETER
Q4257	RELESE, PER SQUARE CENTIMETER
Q4258	ENVERSE, PER SQUARE CENTIMETER
Q4259	CELERA DUAL LAYER OR CELERA DUAL MEMBRANE, PER SQUARE CENTIMETER
Q4260	SIGNATURE APATCH, PER SQUARE CENTIMETER
Q4261	TAG, PER SQUARE CENTIMETER
Q4262	DUAL LAYER IMPAX MEMBRANE, PER SQUARE CENTIMETER
Q4263	SURGRAFT TL, PER SQUARE CENTIMETER
Q4264	COCOON MEMBRANE, PER SQUARE CENTIMETER
Q4265	NEOSTIM TL, PER SQUARE CENTIMETER
Q4266	NEOSTIM MEMBRANE, PER SQUARE CENTIMETER
Q4267	NEOSTIM DL, PER SQUARE CENTIMETER
Q4268	SURGRAFT FT, PER SQUARE CENTIMETER
Q4269	SURGRAFT XT, PER SQUARE CENTIMETER
Q4270	COMPLETE SL, PER SQUARE CENTIMETER
Q4271	COMPLETE FT, PER SQUARE CENTIMETER
Q4272	ESANO A, PER SQUARE CENTIMETER
Q4273	ESANO AAA, PER SQUARE CENTIMETER
Q4274	ESANO AC, PER SQUARE CENTIMETER
Q4275	ESANO ACA, PER SQUARE CENTIMETER

Group 3 Codes: Diabetic Foot Ulcer and Venous Leg Ulcers The following HCPCS codes are **NON-COVERED** for Diabetic Foot Ulcers and Venous Leg Ulcers:	
Q4276	ORION, PER SQUARE CENTIMETER
Q4277	WOUNDPLUS MEMBRANE OR E-GRAFT, PER SQUARE CENTIMETER
Q4278	EPIEFFECT, PER SQUARE CENTIMETER
Q4279	VENDAJE AC, PER SQUARE CENTIMETER
Q4280	XCELL AMNIO MATRIX, PER SQUARE CENTIMETER
Q4281	BARRERA SL OR BARRERA DL, PER SQUARE CENTIMETER
Q4282	CYGNUS DUAL, PER SQUARE CENTIMETER
Q4283	BIOVANCE TRI-LAYER OR BIOVANCE 3L, PER SQUARE CENTIMETER
Q4284	DERMABIND SL, PER SQUARE CENTIMETER
Q4285	NUDYN DL OR NUDYN DL MESH, PER SQUARE CENTIMETER
Q4286	NUDYN SL OR NUDYN SLW, PER SQUARE CENTIMETER
Q4287	DERMABIND DL, PER SQUARE CENTIMETER
Q4288	DERMABIND CH, PER SQUARE CENTIMETER
Q4289	REVOSHIELD + AMNIOTIC BARRIER, PER SQUARE CENTIMETER
Q4290	MEMBRANE WRAP-HYDRO, PER SQUARE CENTIMETER
Q4291	LAMELLAS XT, PER SQUARE CENTIMETER
Q4292	LAMELLAS, PER SQUARE CENTIMETER
Q4293	ACESSO DL, PER SQUARE CENTIMETER
Q4294	AMNIO QUAD-CORE, PER SQUARE CENTIMETER
Q4295	AMNIO TRI-CORE AMNIOTIC, PER SQUARE CENTIMETER
Q4296	REBOUND MATRIX, PER SQUARE CENTIMETER
Q4297	EMERGE MATRIX, PER SQUARE CENTIMETER
Q4298	AMNICORE PRO, PER SQUARE CENTIMETER
Q4299	AMNICORE PRO+, PER SQUARE CENTIMETER
Q4300	ACESSO TL, PER SQUARE CENTIMETER
Q4301	ACTIVATE MATRIX, PER SQUARE CENTIMETER
Q4302	COMPLETE ACA, PER SQUARE CENTIMETER
Q4303	COMPLETE AA, PER SQUARE CENTIMETER
Q4304	GRAFIX PLUS, PER SQUARE CENTIMETER
Q4305	AMERICAN AMNION AC TRI-LAYER, PER SQUARE CENTIMETER
Q4306	AMERICAN AMNION AC, PER SQUARE CENTIMETER
Q4307	AMERICAN AMNION, PER SQUARE CENTIMETER
Q4308	SANOPELLIS, PER SQUARE CENTIMETER
Q4309	VIA MATRIX, PER SQUARE CENTIMETER
Q4310	PROCENTA, PER 100 MG

DYSTROPHIC EPIDERMOLYSIS BULLOSA

Group 1 Codes: Dystrophic Epidermolysis Bullosa

The following code may be medically necessary when criteria met and reported with an ICD-10-CM Diagnostic Code from group 2 Code in the following table for Dystrophic Epidermolysis Bullosa.

Code	Description
Q4100	ORCEL™
Group 2 Codes: Dystrophic Epidermolysis Bullosa A CPT/HCPCS code from the Group 1 Codes above must be reported with an ICD-10-CM Diagnosis code from the Group 2 Codes in the table below for Dystrophic Epidermolysis Bullosa.	
ICD-10 Code	**Description**
Q81.2	Dystrophic Epidermolysis Bullosa

SECOND- AND THIRD-DEGREE BURNS

Group 1 Codes: Second- And Third-Degree Burns The following codes may be medically necessary when criteria met and reported with an ICD-10-CM Diagnostic Code from group 2 Codes in the following table for 2nd and 3rd Burns.	
Codes	**Description**
Q4100	EPICEL - Dermal or full thickness burns that cover 30% or more of the body surface area (BSA)
Q4104	INTEGRA - Partial Thickness (second degree) burns
Q4182	TRANSCYTE - Full thickness (third degree) and deep partial thickness (second degree) burns prior to autograft
Group 2 Codes: 2ND AND 3RD DEGREE BURNS A CPT/HCPCS code from the Group 1 Codes above must be reported with an ICD-10-CM Diagnosis code from the Group 2 Codes in the table below for 2nd and 3rd Degree Burns	
ICD-10 Codes:	**Description**
T20	Burn and corrosion of head, face, and neck
T21	Burn and corrosion of trunk
T22	Burn and corrosion of shoulder and upper limb, except wrist and hand
T23	Burn and corrosion of wrist and hand
T24	Burn and corrosion of lower limb, except ankle and foot
T25	Burn and corrosion of ankle and foot

CLINICAL EVIDENCE

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

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

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 [16]. 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 [16]. 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 [17]. Very few studies explore long term safety of skin substitute grafts/CTP so true risk associated with these products remains unclear.

Health Care Disparities

There is a paucity of literature addressing health care disparities in the use of skin substitutes specifically for DFU and VLU. Diabetic management is known to be impacted by social determinants of health with worse outcomes noted in minority and socioeconomically disadvantaged populations. Comprehensive care models with multidisciplinary teams have proven effective in treatment of DFU by improving access to care, access to specialist and effective and timely treatment [18]. Teams include a combination of primary care, endocrinology, vascular surgeons, orthopedic surgeons, podiatrists, and wound care specialists. The literature reviewed for DFU included patients with diabetes. The majority of reviewed literature did not represent racial diversity with subjects outside the Medicare population. Future research should aim to

include a diverse population representative of those impacted by the condition and include representation of the Medicare population in age

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Review of Evidence: Breast Reconstruction

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

A 2013 study used data from the American College of Surgeon's National Surgical Quality Improvement Program to compare ADM-assisted tissue expander breast reconstruction (n=1717) to submuscular tissue expander breast reconstruction (n=7442) after mastectomy [19]. Complication rates did not differ significantly between the ADM-assisted (5.5%) and the submuscular tissue expander groups (5.3%; p=0.68). Rates of reconstruction-related complications, major complications, and 30-day reoperation did not differ significantly between cohorts.

Systematic Reviews

A meta-analysis by Lee and Mun (2016) included 23 studies (total N=6199 cases) on implant-based breast reconstruction that were published between February 2011 and December 2014 [20]. The analysis included an RCT and three prospective comparative cohort studies; the remainder was retrospective comparative cohort studies. Use of ADM did not affect the total complication rate (see Table 1). ADM significantly increased the risk of major infection, seroma, and flap necrosis, but reduced risks of capsular contracture and implant malposition. Use of ADM allowed for significantly greater intraoperative expansion (mean difference [MD], 79.63; 95% confidence interval [CI], 41.99 to 117.26; p<0.001) and percentage of intraoperative filling (MD=13.30; 95% CI, 9.95 to 16.65; p<0.001), and reduced the frequency of injections to complete expansion (MD = -1.56; 95% CI, -2.77 to -0.35; p=0.01).

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

Outcome Measures	Relative Risk	95% Confidence Interval	p-value
Infection	1.42	1.02 to 1.99	0.04
Seroma	1.41	1.12 to 1.78	0.004
Mastectomy flap necrosis	1.44	1.11 to 1.87	0.006
Unplanned return to the operating room	1.09	0.63 to 1.90	*NS*
Implant loss	1.00	0.68 to 1.48	*NS*
Total complications	1.08	0.87 to 1.34	*NS*
Capsular contracture	0.26	0.15 to 0.47	<0.001
Implant malposition	0.21	0.07 to 0.59	0.003

Adapted from Lee and Mun (2016) [20]
ADM: acellular dermal matrix; NS: Not significant

AlloDerm

Randomized Controlled Trials

McCarthy et al. reported on a multicenter, blinded RCT of AlloDerm in two-stage expander/implant reconstruction [21]. Seventy patients were randomized to AlloDerm ADM-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. The trial was adequately powered to detect clinically significant differences in immediate postoperative pain but underpowered to detect the secondary end point of pain during tissue expansion. There were no significant differences between the groups in the primary outcomes of immediate postoperative pain (54.6 AlloDerm vs 42.8 controls on a 100-point visual analog scale) or pain during the expansion phase (17.0 AlloDerm vs 4.6 controls), or in the secondary outcome of rate of tissue expansion (91 days AlloDerm vs 108 days controls) and patient-reported physical well-being. There was no significant difference in adverse events, although the total number of adverse events was small.

Comparisons Between Products

AlloDerm vs AlloMax

Hinchcliff et al. conducted an RCT that compared AlloDerm with AlloMax (n=15 each) for implant-based breast reconstruction [22]. Complications were assessed 7, 14, and 30 days postoperatively and biopsies of the ADMs were taken during implant exchange. Vessel density in the AlloMax biopsies was higher than in the AlloDerm biopsies. Complications were reported in 26.1% of AlloMax cases and 8.0% of AlloDerm cases; these complication rates did not differ statistically with the 30 patients in this trial.

AlloDerm vs DermaMatrix

Mendenhall et al. conducted an RCT that compared AlloDerm with DermaMatrix in 111 patients (173 breasts). There were no significant differences in overall rates of complications (AlloDerm, 15.4%; DermaMatrix, 18.3%; p=0.8) or implant loss (AlloDerm, 2.2%; DermaMatrix, 3.7%; p=0.5) between the two ADMs [23].

AlloDerm vs FlexHD

A retrospective review by Liu et al. compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts) [24]. Eighty-one percent of the sample was immediate reconstruction: 165 used AlloDerm and 97 used FlexHD. Mean follow-up was 6.4 months. Compared with breast reconstruction without the use of AlloDerm or FlexHD, ADM had a higher rate of delayed healing (20.2% vs 10.3%), although this finding might have been related to differences in fill volumes. In univariate analysis, there were no significant differences in complications (return to operating room, surgical site infection, seroma, hematoma, delayed healing, implant loss) between AlloDerm and FlexHD. In multivariate analysis, there were no significant differences between AlloDerm and FlexHD for the return to the operating room, surgical site infection, seroma, or delayed healing. Independent risk factors for implant loss included the use of FlexHD, single-stage reconstruction, and smoking.

AlloDerm vs FlexHD Pliable and DermACELL

Chang and Liu reported on a prospective comparison of FlexHD Pliable (32 breasts), AlloDerm (22 breasts), and DermACELL (20 breasts) in breast reconstruction [25]. The choice of ADM was based on different years when each ADM was available for use at the investigators' institution; patient demographics were comparable between groups.

The pieces of ADM used were all the same size (8 × 16 cm) to eliminate an effect of size on outcomes. The time to drain removal was longer with AlloDerm (26 days) than with FlexHD (20 days) or DermACELL (15 days; p=0.001). Complications were low (4 in the Flex Pliable group, two in the AlloDerm group, one in the DermACELL group), with no significant differences between groups. At the time of exchange for a permanent implant or free flap reconstruction, all grafts had completely incorporated into the mastectomy skin flaps. No patients developed complications requiring removal of the ADM.

Pittman et al. reported a retrospective pilot study of the use of AlloDerm (50 breasts) and DermACELL (50 breasts) [26]. The choice of ADM was based on products available during different years and patient demographics were similar between the 2 groups. Patients in the DermACELL group had a significantly lower incidence of “red breast syndrome” (0% vs 26%, 19 p=0.001) and fewer days until drain removal (15.8 days vs 20.6 days, p=0.017). There were no significant differences in the rates of other complications.

Strattice

Dikmans et al. reported on early safety outcomes from an open-label multicenter RCT that compared porcine ADM-assisted one-stage expansion with two-stage implant-based breast reconstruction (see Table 2) [27]. One-stage breast reconstruction with porcine ADM was associated with a higher risk of surgical complications, reoperation, and with removal of implant, ADM, or both (see Table 3). The trial was stopped early due to safety concerns, but it cannot be determined from this study design whether the increase in complications was due to the use of the xenogeneic ADM or to the comparison between one-stage and two-stage reconstruction.

Table 2. Summary of Key RCT Characteristics

Author	Countries	Sites	Dates	Participants	Interventions	
Dikmans et al (2017) [27]	EU	8	2013-2015	Women intending to undergo skin-sparing mastectomy and immediate IBBR	*ACTIVE* 59 patients (91 breasts) undergoing 1-stage IBBR with ADM	*COMPARATOR* 62 women (92 breasts) undergoing 2-stage IBBR

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

Table 3. Summary of Key RCT Outcomes

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

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

Breast Reconstruction Evidence Summary

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

Review of Evidence: Diabetic Foot Ulcer and Venous Leg Ulcer

Agency for Healthcare Research and Quality (AHRQ) Technical Brief

The AHRQ provided an evidenced-based technical brief for skin substitute grafts for treating chronic ulcers [3]. This technical brief was developed to describe assorted products that may be considered skin substitute grafts in the U.S., which are utilized for the treatment of chronic ulcers. In addition, systems utilized to classify skin substitute grafts were assessed, randomized controlled trials (RCTs) involving skin substitute grafts were reviewed, and recommendations were made regarding best practices for future studies. Search of the published literature since 2012 was conducted for systematic reviews/meta-analyses, RCTs, and prospective non-randomized comparative analysis studying commercially available skin substitute grafts for individuals with DFU, VLU, pressure ulcers, and arterial leg ulcers.

Seventy-six skin substitute grafts were identified and categorized using the Davison-Kotler classification system, a method structured according to cellularity, layering, replaced region, material used, and permanence. Of these, 68 (89%) were categorized as acellular dermal substitutes, largely replacements from human placental membranes and animal tissue sources. Acellular dermal substitutes prepared from natural biological materials are the most common commercially available skin substitute graft products for treating or managing chronic ulcers. Cellularity is a significant difference among skin substitute grafts as the presence of cells raises the rejection risk and production complexity. This category includes decellularized donated human dermis (14 products recognized), human placental membranes (28 products recognized), and animal tissue (21 products recognized). Fewer products are prepared from synthetic materials (two products recognized) or a blend of natural and synthetic materials (two products recognized). A limited number of skin substitute products are acellular replacements for

both the epidermis and dermis (one product recognized). Only 8 products were recognized that contained cells and would be classified in the cellular grouping.

Three systematic reviews and 22 RCTs studied the utilization of 16 distinct skin substitutes, comprising acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in DFU, pressure ulcers, and VLU. Twenty-one ongoing studies (all RCTs) assessed an additional nine skin substitute grafts with comparable classifications. It was noted that studies seldom reported clinical outcomes, such as amputation, ulcer recurrence at least two weeks after treatment ended, or patient-related outcomes, such as return to function, pain, exudate, and odor. This review found that more studies are needed to assess the effectiveness of most skin substitutes, and this future research needs to be better designed and include clinically relevant outcomes.

Of the 22 included RCTs, 16 studies contrasted a skin substitute with SOC. The SOC for each ulcer type involved sharp debridement, glucose control, compression bandages for VLU, pressure redistribution support surfaces for pressure ulcers, infection control, offloading, and daily dressing changes with a moisture-retentive dressing, such as an alginate or hydrocolloid type dressing. Though 85% of the studies examining acellular dermal substitutes portrayed the experimental intervention as favorable over SOC for ulcer healing and quicker time to heal, the data is not adequate to determine whether ulcer recurrence or other sequela are less frequent with acellular dermal substitutes. Only 3 studies contrasted cellular dermal substitutes with SOC. Clinical evidence for cellular dermal substitutes may be limited by the lack of robust, well-controlled clinical trials.

Of the 6 head-to-head comparative studies, results from 5 studies did not show substantial differences between skin substitute grafts in outcomes measured at the latest follow-up (>12 weeks). One study concluding at 12 weeks described a substantial difference in ulcer healing favoring an acellular dermal skin substitute over a cellular epidermal and dermal skin substitute. Another study compared two acellular dermal substitutes and seemed to have deliberately underpowered 1 arm of the study as the statistical significance was not elucidated or expected for this study arm. Of the 2 studies reporting on recurrence, one study described comparable recurrence, while the other study reported no recurrence at 26 weeks. The current evidence base, as portrayed by the authors for the literature reviewed, may be inadequate to determine superiority of one skin substitute graft product over another.

The report acknowledges the potential risk of bias due to 20 of the 22 RCTs reviewed being industry sponsored. This AHRQ Technical Brief also noted that a skin substitute's commercial availability is not a reflection of its legal status. Manufacturers self-determine whether their human cell, tissue, or cellular or tissue-based product (HCT/P) may be marketed without FDA preapproval and frequently misunderstand or mischaracterize the conditions necessary for the product to be regulated solely for communicable disease risk. The Code of Federal Regulations 21 CFR 1271.10(a) is referenced; FDA Announces Comprehensive Regenerative Medicine Policy Framework was cited [8].

Systemic Reviews

Santema et al. provided a systematic review and meta-analysis to assess the efficiency of skin substitute grafts utilized for the treatment of DFU regarding ulcer healing and limb salvage. Using the Cochrane Collaboration methodology, 17 clinical trials were identified, which included a total of 1,655 randomized study participants with DFU. The number of study participants per clinical trial ranged from 23 to 314. Fourteen studies included chronic or difficult to heal ulcers that were present for a minimum of 2, 4, or 6 weeks [28].

Skin substitute grafts were contrasted with SOC in 13 trials. The results collectively demonstrated that SOC treatment, combined with a skin substitute product enhanced the chances of attaining complete ulcer closure in contrast to SOC alone after 6 to 16 weeks (risk ratio [RR] 1.55, 95% confidence interval [CI] 1.30 to 1.85, low quality of evidence). Apligraf/GraftSkin, EpiFix, and Hyalograft 3D were the only individual products that demonstrated a statistically substantial beneficial effect on complete ulcer closure (i.e., full epithelialization without any evidence of drainage or bleeding). Four clinical trials contrasted 2 different types of skin substitutes, although no product demonstrated a greater effect over another. Sixteen of the trials evaluated the efficacy of a bioengineered skin substitute. Only 1 trial evaluated the efficacy of a non-bioengineered skin graft.

The total occurrence of lower limb amputations was only reported for 2 trials and the results for these 2 trials collectively produced a substantially lower amputation rate for individuals treated with skin substitute grafts (RR 0.42 95% CI 0.23 to 0.81), though the absolute risk difference (RD) was small (-0.06, 95% CI -0.10 to -0.01, very low quality of evidence). Of the included studies, 16 reported on adverse events (AEs) in diverse ways, although there were no reports of a substantial difference in the incidence of AEs between the intervention and the control group. Additionally, support of long-term effectiveness is lacking, and cost-effectiveness is unclear. Noted limitations included a variable risk of bias among the studies, the lack of blinding (i.e., study participants and investigators knew which patients were receiving the experimental therapy and which patients were receiving the standard therapy), and 15 of the studies conveyed industry involvement; the majority did not indicate if the industry applied any limitations regarding data analysis or publication [3].

Jones et al. systematic literature review sought to evaluate the effect of skin substitute grafts for the treatment of VLU. Using the Cochrane Collaboration methodology, one new trial was identified, generating a total of 17 RCTs, which included a total of 1,034 study participants. The studies were comprised of participants of any age, in any care setting with VLU. Given that the process for diagnosis of venous ulceration differed between studies, a standard definition was not applied. The trials also involved study participants with arterial, mixed, neuropathic, and diabetic ulcers provided that the outcomes for patients with venous ulcers were conveyed separately. To be included in the review, trials also had to report at least one of the primary outcomes objective measures of healing, e.g., relative or absolute rate of change in ulcer area, time for complete healing, or proportion of ulcers healed within the trial period [29].

Eleven studies contrasted a graft with SOC. Two of these studies (102 patients) contrasted an autograft with a dressing, 3 studies (80 patients) contrasted a frozen

allograft with a dressing, and 2 studies (45 patients) contrasted a fresh allograft with a dressing. Two studies (345 patients) contrasted a tissue- engineered skin (bilayer artificial skin) with a dressing. In 2 studies (97 patients) a single-layer dermal replacement was compared with SOC.

Six studies compare alternative skin grafting techniques. The first study (92 patients) differentiated an autograft with a frozen allograft; a second study (51 patients) contrasted a pinch graft (autograft) with a porcine dermis (xenograft); the third study (110 patients) compared growth-arrested human keratinocytes and fibroblasts with a placebo; the fourth study (10 patients) analyzed an autograft delivered on porcine pads with an autograft delivered on porcine gelatin microbeads; the fifth study (92 patients) contrasted a meshed graft with a cultured keratinocyte autograft; and the sixth study (50 patients) contrasted a frozen keratinocyte allograft with a lyophilized (freeze-dried) keratinocyte allograft.

Overall, the results show that substantially more ulcers healed when treated with bilayer artificial skin than with dressings. There was inadequate evidence from the other trials to establish whether other types of skin grafting improved the healing of venous ulcers. The authors concluded that bilayer artificial skin, used together with compression bandaging, improves venous ulcer healing as compared to a simple dressing plus compression.

It was noted that the overall quality of the studies reviewed was poor, thus affecting the risk of inherent bias. Many studies did not have inclusion criteria or insufficient information regarding randomization techniques. In addition, withdrawals and AEs were inadequately reported. Deficient data regarding withdrawals and the inclination to perform per-protocol analyses rather than intention-to-treat (ITT) analyses signify that the outcomes in the original study documentation may be biased [29].

A 2017 meta-analysis of RCT comparing amniotic tissue products to SOC in nonhealing DFU was conducted. PubMed, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews search identified 596 potentially relevant articles of which 5 met the selection criteria. The pooled set included 259 patients and the pooled relative risk of healing with amniotic products compared with control was 2.7496 (2.05725–3.66524, p< 0.001). The products included in this analysis were Amnioexcel, EpiFix, and Grafix. Four trials changed the amniotic product weekly; 1 paper reported an average of 2.5 applications of EpiFix, and in 1 study where reapplication was at the discretion of the clinician, no decrease in healing was found compared to the per protocol application changes. The author concludes that there is benefit in healing rates of amniotic products for DFU and if this impacts other outcomes and subsequent complications such as amputation and death, further investigation will be required [30].

A 2020 systematic review/meta-analysis reported on complete healing rates for DFU with acellular matrix [31]. Nine RCT with 897 patients were included. They report those treated with an acellular matrix had higher healing rates at 12 weeks (risk ratio [RR] =1:73, 95% confidence interval [CI[: 1.31 to 2.30) and 16 weeks (RR = 1:56, 95% CI: 1.28 to 1.91), a shorter time to complete healing (mean difference [MD] = −2:41; 95%

CI: -3.49 to -1.32), and fewer AEs (RR = 0:64, 95% CI: 0.44 to 0.93) compared to SOC. RCTs include Graftjacket, Oasis ultra matrix, DermACELL, Integra and AlloPatch. The heterogenicity reported varies depending on the outcome measures but the analysis is limited by high variety in wound types, differing products and number of applications, variations in SOC in control arms, different durations of treatment and risk of bias in the included studies [31].

A 2017 systematic review and meta-analysis identified 6 RCT comparing acellular dermal matrix (ADM) to SOC for DFU. Different commercial products of ADM were included in this meta-analysis, including DermACELL, Graftjacket, Integra Dermal Regeneration Template (IDRT), and human reticular acellular dermis matrix (HR-ADM). The pooled group included a total of 632 DFU patients and sample size of the studies ranged from 14-154 for a duration of 4-16 weeks. Studies were pooled and analyzed (with and without the study that only extended to four weeks) and concluded that complete healing rate in the ADM group was higher than SOC [risk ratio (RR) 2.31, 95% confidence interval (CI) 1.42 to 3.76 I2=74% which is 2.31 times more likely for complete wound healing than SOC at 12 weeks. The authors rated the strength of evidence as moderate and acknowledge the limitation related to lack of blinding. This meta-analysis is limited by risk of publication bias, lack of uniform ADM the products, variation in dressing products and potential variation within SOC, different application number amongst the different studies, small samples of individual studies, short term follow up, and fairly high heterogeneity within some outcome measures leading to the authors call for more robust studies [32].

A 2012 systematic review of RCTs evaluating wound closure rates for patients treated with advanced wound matrix compared to SOC for VLU was conducted [33]. One RCT was found for three products Apligraf [n = 130 treatment, n = 110 control]; Oasis Wound Matrix [n = 62 treatment, n = 58 control]; and Talymed [n = 22 treatment, n = 20 control]. In the Talymed study 62 patients in the treatment arm with varying applications frequency reported statistically significant closure rate compared to SOC, but this was only found in 1 of the 3 arms (biweekly application group). Risk of bias assessment was not conducted, but they reference the AHRQ report [3] which reported higher degree of bias for the Apligraf and Oasis studies that were included due to lack of blinding. Limitations of this report include variations in assessment period across the studies, baseline wound characteristics were not compared, and only one arm of the Talymed study was included with a sample size too small to determine effect.

Systematic reviews for skin substitute graft/CTP are challenged by multiple factors. These reviews pool different products with different features, types of wounds, baseline health factors, duration of treatment, number of applications and variations in SOC creating significant factor variance. Even within the same study variability in SOC and managements are not clearly defined. Most included studies have notable risk of bias, small sample sizes, and short-term follow-up resulting in overall low-quality literature. The systematic reviews are limited by the quality of the included studies and

heterogeneity between studies so even with positive outcomes, there is a lack certainty that the effect is due to the skin substitute/CPT itself.

Clinical Trials for Skin Substitute Grafts or CTP for Diabetic Foot Ulcers

Affinity

A multi centered, RCT was conducted across 14 centers to assess the clinical outcomes of hypothermically stored amniotic membrane (HSAM) versus SOC for DFU. After a 2-week screening phase, 76 participants were randomized with random allocation sequence to either Affinity or SOC and followed for 16 weeks. Wound measurements were validated with an Aranz laser-assisted wound measurement device. Product was changed weekly or until the ulcer healed. Wound closure for Affinity-treated ulcers (n=38) was significantly greater than SOC (n=38) by 12 weeks (55 vs 29%; p = 0.02) and 16 weeks (58 vs 29%; p = 0.01) respectively [34]. Strengths of the study include the randomization, screening and follow-up phase, comparison to SOC, adequately powered, the use of multi-centered sites and an overall low risk of bias. Limitations include lack of blinding, and short-term follow-up. This study also addresses a population with complex wounds extending into the muscle or tendon which is a particularly difficult population to treat. Additional studies include a basic science report exploring the mechanism of how the product may work [35], and a case report and series.

AlloPatch/Flex HD/Allopath HD/Matrix HD

Zelen et al. performed a RCT to evaluate the healing rates, safety, and cost using an open-structure human reticular acellular dermal matrix (HR-ADM) (i.e., AlloPatch® PliableTM) plus SOC to SOC alone for DFU. A total of 40 subjects were randomized to HR-ADM plus SOC (n = 20) (AlloPatch applications weekly) or SOC alone (n = 20). The primary outcome of this study focused on a comparison of ulcer healing at 6 weeks between these 2 groups. Wounds were considered as healed if there was complete (100%) re-epithelization with no drainage and no need for dressing. At 12 weeks, 80% (16/20) of the AlloPatch-treated ulcers had healed contrasted with 20% (4/20) of the ulcers treated with SOC alone (p=0.00036). The mean time to heal within 12 weeks was 40 days (95% CI: 27–52 days) for the AlloPatch versus 77 days (95% CI: 70–84 days) for the SOC group (p=0.00014). The average number of AlloPatch grafts used to achieve closure per ulcer was 4.7 (SD=3.3) at 12 weeks. There was no occurrence of increased AEs or SAEs between groups, or any AEs related to the graft. This study concluded that the use of AlloPatch plus SOC is more effective in the treatment of DFU than with SOC alone. However, this study had high risk of bias due to missing outcome data and was also limited by short-term follow-up, and small sample size. The authors also followed the patients that failed SOC arm and were eligible for cross-over treatment in a retrospective format. Twelve patients received the allograft and 83% achieved complete wound healing with mean time of 21 days to closure [37]. Due to the retrospective study design, it is not clear if the wounds would have closed with continued SOC during this timeframe.

AmnioBand

Glat et al. conducted a RCT to contrast a dehydrated human amnion and chorion allograft (dHACA) (i.e., AmnioBand) with SOC and a tissue-engineered skin substitute (TESS) (i.e., Apligraf) with SOC in the treatment of DFU. At the 12-week assessment, it was found the mean time to healing was 32 days. (95% CI, 22.3–41.0) for the AmnioBand group versus 63 days (95% CI, 54.1–72.6) for the Apligraf group. The healing rate at 12 weeks was 90% (27/30) for the AmnioBand group versus 40% (12/30) for the Apligraf group. Limitations noted for this study include lack of blinding, short-term follow-up, and high risk of bias [38].

DiDomenico et al. conducted a prospective, RCT to compare a dehydrated human amnion and chorion allograft (dHACA) (i.e., AmnioBand) used with SOC to SOC alone in the treatment of DFU for up to 12 weeks. At 6 weeks, 70% (14/20) of the DFU in the AmnioBand group achieved healing compared to 15% (3/20) of the DFU in the SOC group. At 12 weeks, 85% (17/20) of the DFU in the AmnioBand group healed compared with 25% (5/20) in the SOC group (mean time to heal of 36 and 70 days, respectively). At 12 weeks, the average number of grafts used per healed wound for the AmnioBand group was 3.8 ± SD 2.2 (median 3.0). All analyses used the ITT approach, and the risk of bias was low. Limitations were short-term follow-up and lack of blinding [39].

DiDomenico et al. performed a RCT to compare a dehydrated human amnion and chorion allograft (dHACA) (i.e., AmnioBand) used with SOC to SOC alone in the treatment of DFU for up to 12 weeks. Eighty patients participated in the study: 40 patients in the AmnioBand group and 40 patients in the SOC group. The AmnioBand was applied weekly during the study period until healing occurred (complete epithelialization without drainage), the patient was withdrawn, or the study was completed. At six weeks, 68% (27/40) of the DFU in the AmnioBand group achieved healing contrasted to 20% (8/40) of the DFU in the SOC group ($p=1.9 \times 10-5$). At 12 weeks, 85% (34/40) of the DFU in the AmnioBand group achieved healing compared with 33% (13/40) of the DFU in the SOC group. The average time to heal within 12 weeks was substantially quicker for the AmnioBand group contrasted with the SOC group, 37 days versus 67 days in the SOC group (p=0.000006). The average number of grafts used per healed wound during the same time was 4.0 (SD: 2.56) at 12 weeks. All analyses used the ITT approach, and the risk of bias was low. Limitations include lack of blinding, and short-term follow up [40].

AmnioBand is also reviewed in the VLU section.

Amnioexcel

Snyder et al. performed a multi-center RCT for assessment of a dehydrated amniotic membrane allograft (DAMA) (i.e., Amnioexcel) with SOC (n=15) in comparison to SOC alone (n=14) for chronic DFU for 6 weeks. The Amnioexcel with SOC group wounds were debrided, Amnioexcel applied, covered with non-adherent dressings, lightly secured, and wrapped with a compression dressing. Patients in the Amnioexcel with SOC group had a total of 4.3 + 1.7 allografts applied; Frequency of the application was left to individual provider. Results showed that 33% of patients in the Amnioexcel with SOC group achieved complete wound closure at or before week 6, compared with 0% of the SOC alone group (ITT population, p=0.017). The per protocol population showed 45.5% of patients in the Amnioexcel with SOC group achieved complete wound closure,

while 0% of SOC-alone patients achieved complete closure (p=0.0083). Limitations of this study included 4 early withdrawals leaving only 25 patients in the final cohort, small sample size, lack of blinding, and high risk of bias due to stratification of wound type prior to randomization, per-protocol reporting only without intention to treat analysis, and lack of validation of outcome measurements. The authors call for the need for additional studies which are necessary to confirm if the findings were related to the allograft and longer-term follow-up [41].

Apligraf (formerly GraftSkin)

A prospective RCT was comprised of patients with DFU. A total of 208 patients from 24 sites were randomly assigned into either the Apligraf® (formerly GraftSkin®) (n=112 patients) or SOC (n=96 patients) group and followed for twelve weeks. Complete wound healing was reported in 56% of GraftSkin patients compared to 38% of the control group. Authors report GraftSkin time to complete closure was significantly lower than the SOC group (p=0.0026). Forty-four patients withdrew from the study before study completion. Average applications of GraftSkin per patient were 3.9 (range 1-5) for the duration of the study. The average number of applications of 3.9 (range 1-5) with one application [n=10]), two applications [n=11], three applications [n=15], four applications [n=17] and five applications [n=59]) used per patient over twelve weeks. Ulcer recurrence was 5.9% in the GraftSkin group and 12.9% in the control group at six month follow up. Limitations include high risk of bias, moderate number of patients lost to follow up, and additional dressing changes allowed in both groups if ulcer was not healed by week five [42].

A prospective, multicenter, open-label RCT compared Apligraf plus SOC to SOC alone in DFU patients in the European Union (EU) and Australia to a similar study in the U.S. The EU and Australian studies were comparable and data from both studies were pooled. The EU and Australian studies were comprised of 72 patients, 33 in the Apligraf group and 29 in SOC group and the U.S. study was compromised of 208 patients: 112 in Apligraf group and 96 in the control group. The mean ulcer duration was significantly longer in the EU and Australian study (21 months) compared to 10 months in the U.S. Adverse events were reported for 12 weeks in both studies and were comparable and not related to the graft. At 12 weeks, combining the data from both studies, 55.2% of the Apligraf group achieved wound closure as compared to 34.3% in SOC arm (P = 0.0005; Fishers exact test), and Apligraf subjects had a significantly shorter time to complete wound closure (P = 0.0004; log-rank test). Limitations include premature study closure (non-safety related) for the EU and Australian studies which were underpowered due to halting study enrollment. Due to pooling of two different studies, it was difficult to assess risk of bias of the individual studies [43].

An international multi-center, RCT was conducted in patients with DFU. This study was halted due to “registration process difficulties”. A total of 82 patients were randomized into the Apligraf group + SOC (n=33) and SOC alone (n=39). At 12 weeks, wound closure in the Apligraf group (n=33) was 51.5% as compared to 26.3% in the SOC group (n=38). The Apligraf group achieved complete wound healing over a shorter duration as compared to the SOC group (p=0.059, Log-rank test). The Apligraf group took a median of 84 days to heal compared to no median reported in the SOC group due to less than 50% achieving wound closure. An average of 1.8 Apligraf applications

over 12 weeks were utilized. Limitations include no median time to heal in the SOC group, halting of the study, and lack of blinding [44].

Additional evidence of Apligraf is reviewed in the following sections AmnioBand [38], EpiFix [45], TheraSkin, and retrospective study(n=226) [43] and in the VLU section. In the Kirsner et al. study the average number of applications over 4 weeks was 3.5 for EpiFix and 2.5 for Apligraf [46].

Artacent

Sledge et al. [47] performed an observational study which included 26 patients with DFU (4.65±4.89cm2) with failure to heal by >50% after two to four weeks of SOC treatment and randomized to a larger clinical trial that had been discontinued for logistical reasons. Patients were randomized to weekly or biweekly applications of dual layer amniotic membrane plus SOC for twelve weeks. A total of 17/26 (65%) achieved complete closure. The small sample size precluded meaningful comparison between the weekly and biweekly applications. Limitations of the study include risk of bias, observational design, lack of control group, variability in length of SOC treatment, small sample size, and inability to determine if healing was impacted by the product, as well as frequency of product applications or other factors. The evidence was not sufficient to determine if the product was effective for treatment of DFU.

Biovance

An observational study included 179 chronic wounds of which 47 were DFU. Twenty-eight ulcers studied had failed 32 previous treatments with 1 or more advanced biologic treatments and 48.4% of these showed improvement after treatment with Biovance within an average of eight weeks. For all wound types (n=166) the closure rate was 41.6% within eight weeks with mean application of 2.12 products [48]. The study was limited by not reporting wound reduction size, outcomes for wound types were not reported separately and small sample size, lack of randomization, blinding, or controls. Without a control group, the percentage of wounds that would have healed with SOC is unknown. Additional evidence includes a case series with 14 subjects [49]. Evidence was not sufficient to determine the efficacy of this product for wound healing.

DermACELL

A multi-centered, RCT compared healing rates with a human acellular dermal matrix (DermACELL) (n=53), SOC (n=56) and a second acellular dermal matrix (Graftjacket) (n=23) for full thickness DFU. One to 2 applications of the graft were applied at the discretion of the Investigator for 16 weeks. The DermACELL arm had a significantly higher proportion of completely healed ulcers than the SOC arm (67.9% vs 48.1%; *p*=0.0385) and a nonsignificant higher proportion than the Graftjacket arm (67.9% vs 47.8%; *p*= 0.1149). There were no serious AEs related to the graft reported [50]. This same study population was reported by Cazzell et al. after subjects were followed for 24 weeks [51]. These two studies were published in two different journals but share authors and data sets are identical, so it appears to be the same study population. The DermACELL group had a significantly higher healing rate over SOC at 16 and 24 weeks which was not found in the Graftjacket group. Closed ulcers in the single application DermACELL arm remained healed at a significantly greater rate than the conventional care arm at four weeks post termination (100% vs. 86.7%; p =0.0435). Strength of the

studies include randomization, consistent diagnostic criteria with the same type of ulcers and 24-week follow-up [51]. Limitations of the study include variation in SOC, lack of blinding, short-term follow-up, randomization methodology was not reported, and some concerns of risk of bias.

A prospective single arm, multicentered trial included 61 participants with large and complex DFU, with the average size 29.0 sq cm and, 59/61 had exposed bone. Participants received treatment with acellular dermal matrix allograft (DermACELL). Up to one additional application was allowed if the wound required further coverage for exposed deep tissue, was less than 75% granulated at four weeks or less than 50% granulated after eight weeks. Wound measurements were validated with a laser measurement device. Fourteen participants did not complete the 16 weeks of which eight required surgical intervention for their targeted wound, but there were no AEs related to the allograft. The authors report 100% granulation and 31.9% closure by 16 weeks in the per protocol group with nine receiving a second application with an average of 1.2 applications. In the intention to treat group 90.2% achieved granulation and 24.6% closure by 16 weeks with an average of 1.2 applications. The study did not extend past 16 weeks, but it was postulated that many of the wounds not healed would continue healing if allowed additional time. This underscores the challenges in this difficult population of large ulcers extending to bone [52]. This study is limited by lack of control arm or randomization, short term follow-up, and small sample size.

Dermagraft

A RCT study at 35 centers enrolled 314 patients and reported on 245 with chronic DFU. Patients meeting the inclusion criteria were matched and randomized to Dermagraft or SOC. Subjects received up to 7 additional applications at weekly intervals over the course of the study. The authors reported complete wound closure in 30% (39/130) in the Dermagraft group as compared to 18.3% (21/115) in the SOC group at week 12. They reported similar AEs in both groups with fewer ulcer related AEs in the Dermagraft group [53]. The study is limited by concerns for risk of bias, and short-term follow-up. In 1996 a multi-centered RCT with 50 subjects was conducted comparing Dermagraft at 3 different doses to SOC for DFUs over a 12-week period. Treatment groups included weekly application of one piece of Dermagraft for a total of 8 applications (Group A [n=12]), application of 2 pieces of Dermagraft every 2 weeks for a total of 8 (Group B [n=14]), application of 1 piece of graft every 2 weeks for a total of 4 (Group C [n=11]), and SOC alone (Group D [n=13]). The authors noted that Group A demonstrated statistically significant wound healing (p=0.017) by 12 weeks with a 50% closure rate compared to 50%, 18.2% and 23.1% closure rates for groups B, C, and D respectively [54]. This study is limited by small sample size, short-term follow-up, lack of blinding, and risk of bias.

Dermagraft was reported in a RCT comparing Dermagraft to TheraSkin for DFU [55]. (see TheraSkin section). Dermagraft is also reviewed in the VLU section.

EpiCord

Tettelbach et al. [56] performed a multi-center, RCT, to compare dehydrated human umbilical cord (i.e., EpiCord) with SOC to treat chronic DFU. A total of 155 patients were treated and included in the ITT analysis: 101 in the EpiCord group and 54 in the SOC

group. T healing rate at twelve weeks was 70% (71/101) for the EpiCord group and 48% (26/54) in the SOC group (p=0.0089). The median number of EpiCord allografts applied was seven (range 2-12). Strengths of this study include a control group (alginate), larger sample size and low risk of bias. Limitations of the study include lack of blinding, and short-term follow-up.

EpiCord was also included in a systematic review in which the authors conclude biological skin substitutes were 1.67 times more likely to heal by 12 weeks than SOC dressings (p<0.00001). They also state that further studies are needed to determine the benefits of the different products and the long-term implications of these products [57].

EpiFix

A RCT aimed to investigate wound healing for DFU with EpiFix compared to SOC. Twenty-five subjects were randomized to EpiFix with replacement of the product every 2 weeks or SOC and followed for 6 weeks. The authors report wound healing in 92% of the EpiFix group and 8% of the SOC group. “The EpiFix material, placed on every other week regimen, aggressively closed the wounds under consideration in a far shorter time than standard wound treatment” [58]. Sample size was too small to draw conclusions based upon these results and the study was challenged by lack of blinding and high risk of bias. The outcomes in the SOC arm were concerning because the results were well below those reported by other studies for SOC treatment. In addition, the protocol SOC was not defined in the paper.

A 2016 multi-center RCT with 100 participants compared dehydrated human/amnion/chorion membrane (dHACM) (i.e. EpiFix®) to SOC and bioengineered skin substitute (Apligraf®), concluding that dHACM was superior in achieving complete wound closure within 4–6 weeks. The proportion of wounds achieving complete closure within the 12-week study period were 73% (24/33), 97% (31/32), and 51% (18/35) for Apligraf, EpiFix and SOC, respectively (adjusted p=0.00019). Mean time-to-heal was 47.9 days (95% CI: 38.2–57.7) with Apligraf, 23.6 days (95% CI: 17.0–30.2) with EpiFix group and 57.4 days (95%CI: 48.2–66.6) with the SOC only group (adjusted p=3.2x 10.7). Median number of grafts used per healed wound were six (range 1–13) and 2-5 (range 1–12) for the Apligraf and EpiFix groups. The study was limited by small sample size, lack of blinding and high risk of bias [45].

A multi-centered RCT which included 110 patients with DFU was undertaken to determine whether EpiFix led to improved wound healing compared to SOC. Both ITT and per-protocol participants receiving weekly EpiFix (n=47) were significantly more likely to completely heal than those not receiving EpiFix (n=51), ITT was 70% versus 50%, p=0.0338, per-protocol was 81% versus 55%, p = 0.0093) [59]. The study had a low risk of bias. Limitations included the short term follow up, and lack of blinding.

EpiFix was included in multiple systematic reviews and meta-analysis. The AHRQ report [3], Cochrane Systematic Review [30] and Paggiaro systematic review [60]. There is also a NICE innovation briefing on EpiFix [61]. Additional literature includes case series, lab studies and additional studies in the VLU population reviewed in that section below.

A prospective RCT was performed to compare weekly applications of Apligraf (n=20), EpiFix (n=20), or SOC (n=20) effectiveness in DFU. Three sites and 65 subjects entered the 2-week run-in period while 60 were randomized to treatment group. Wound closure was as follows for 4 and 6 week follow up: EpiFix (85% and 95%), Apligraf (35% and 45%), and SOC (30% and 35%). The mean number of applications used in the Apligraf group was 6.2 per patient and 2.15 for EpiFix in 6 weeks. All EpiFix patients exited the study by the 6 week follow up while 20% of the Apligraf patients remained unhealed at 12 weeks. Limitations include that the study was inadequately powered to reach statistical significance between Apligraf and SOC group at 6 weeks, short duration of follow up after patient healing period, and the lack of comparison of 12-week healing rates due to missing outcome data which created a high risk of bias [62].

Grafix

Lavery et al. [63] performed an RCT to contrast the effectiveness of a human viable wound matrix (hVWM) (i.e., Grafix®) to SOC for ulcer closure in chronic DFU. Patients in the active treatment group received SOC plus an application of Grafix once a week (± 3 days) for up to 84 days (blinded treatment phase) and the control group received SOC ulcer therapy once a week (± 3 days) for up to 84 days. The percentage of patients who attained complete ulcer closure was substantially higher in the active treatment group (62%) compared with the control group (21%, p=0.0001). The median time for healing was 42 days in the active treatment arm contrasted with 69.5 days in the control arm (p=0.019). There were less AEs in the active arm (44% versus 66%, *p*=0.031) and less ulcer-related infections (18% versus 36.2%, p=0.044). The authors concluded that treatment with Grafix substantially improved DFU healing in comparison to SOC therapy. Limitations of the study included lack of blinding, short-term follow-up, and high risk of bias.

Additional literature includes a retrospective report of 441 wounds from a healthcare database to evaluate the proportion of DFU that achieved complete closure with viable cryopreserved placental membranes (vCPM) (Grafix PRIME and Grafix CORE) as compared to standard wound care by 12 weeks and the number of wound related infections and amputations [64]. They reported closure in 59.4% of 350 wounds with the median treatment duration of 42 days and a median of 4 applications (95% CI 4-5) of vCPM with a 3% rate of amputation and an incidence of 2% for infections. Smaller wounds were quicker to heal. There was no comparison to wounds that did not have vCPM applied. Limitations of the study include its retrospective nature, lack of standardized treatment practices, no comparator group, lack of a control cohort, risk of incomplete records, and variabilities in evaluations.

Grafix CORE

Frykberg et al. (2017) [65] conducted a prospective, multicentered, open labeled single arm RCT using vCPM (Grafix CORE®, Osiris Therapeutics, Inc) in 31 complex DFU with exposed deep structures. The wounds were cleaned and debrided weekly with weekly application of vCPM and protective foam dressings. Fifty-nine percent achieved complete wound closure by 16 weeks. These data show that vCPM is a safe and effective option for the successful management of complex wounds with exposed

tendon and bone. As vCPM was not combined with other advanced modalities (i.e. NPWT) during treatment in this study, it would be of interest in the future to investigate the cumulative benefits of vCPM as part of a multimodal approach to complex wounds with exposure of deep structures or bone. This study was limited by a lack of comparison to standard wound care, no disclosure of funding sources suggesting higher potential risk of bias and high dropout rate given the small number of patients enrolled. Evidence was not sufficient to determine the efficacy of this product for wound healing.

Graftjacket

A pilot study was conducted to evaluate the potential role of Graftjacket in ulcer management with 40 subjects comparing Graftjacket to gauze dressings with a suggested potential role in ulcer management. Rates of healing were reported as decrease in wound area by 67.4% in the Graftjacket group compared to 34% in the SOC group at 4 weeks [66]. A second RCT study was conducted to evaluate the effectiveness of Graftjacket for chronic non-healing lower extremity wounds. Subjects received a single application of Graftjacket (n=14) compared to controls treated with gauze dressings (n=14) and followed for 16 weeks. A total of 85.71% of the treatment group ulcers were healed compared to 28.57% of the control group at the conclusion of the study (p=0.006) [67]. Limitations of both studies included a small sample size and high risk of bias.

A multi centered RCT compared subjects with DFU receiving acellular matrix (Graftjacket Regenerative Tissue Matrix) (n=47) to SOC (n=39). The authors reported a complete healing time of 69.6% at 5.7 weeks for the treatment group compared to 46.2% at 6.8 weeks for the control group. The proportion of healed ulcers between the groups was statistically significant (p= 0.0289) with odds of healing 2.7 times higher in the study group than the SOC group. Subjects received a single application and were followed to 12 weeks. Six adverse events were reported but not related to the graft except in one case where the graft was no longer on the wound [68]. Strengths of the study include randomization and defined control group with certain limitations noted such as a short term follow up and high risk of bias.

These 3 studies were pooled in a meta-analysis (n=154) comparing Graftjacket to SOC and reported a statistically significant reduction in ulcer size in 1.7 weeks and a fourfold improvement in the chance of healing in the Graftjacket group. The authors conclude that a single application of this product after sharp debridement and offloading may improve healing for DFU and the model used predicted an average of 1.7 weeks reduction in healing time with this approach. The median number of applications per patient, after initial application, was 1 (range 1-15). There were differences in outcome measures in the 3 studies challenging the pooled results. Limitations include high risk of bias including publication and reporting biases, study selection biases, incomplete data selection, and a high risk of bias, due to small sample sizes and differences in endpoints [69].

Additional studies include two RCT in which Graftjacket was compared to DermACELL and SOC, but with only 23 subjects in Graftjacket arm, the study was not sufficiently powered to draw conclusions [51]. Other investigations (see section on DermACELL),

include a Cochrane review analysis [28] and multiple studies investigating the role of the product in tendon repair and breast reconstruction.

Integra

Driver et al. [70] conducted The Foot Ulcer New Dermal Replacement Study (FOUNDER), a RCT with 153 patients in the control arm who received SOC treatment and 154 patients in the active treatment arm received Integra Dermal Regeneration Matrix for DFU. Both groups underwent 14-day run-in periods where they received SOC treatment and eligible patients were randomized with software algorithm and ulcers were measured at onset. Complete closure of the ulcer at 16 weeks was significantly greater in the active group (51%; 79/154) in comparison to the control group (32%; 49/153, p=0.001). There were no significant adverse events in either group. Strength of the study included the randomized design, large sample size, control group, multi-centered, run-in period, set wound type and inclusions/exclusion criteria. Limitations of the study include lack of double blinding, the short- term follow-up and high risk of bias.

A prospective pilot study evaluated 10 patients treated with Integra bilayer wound matrix for DFU [71]. The authors report 70% (7/10) achieved complete wound healing by 12 weeks. This study is limited by study design, very small sample size and short-term follow-up. Additional literature includes case reports, series, and retrospective reviews.

Kerecis Omega3

A double blinded RCT compared fish skin allograft (Kerecis Omega3 Wound) to dehydrated human amnion/chorion membrane allograft (EpiFix) for induced wounds. Subjects (n=170) received punch biopsies, and the graft was placed over the induced wound. The subject and assessor were blinded to the treatment group. Wounds treated with fish skin healed significantly faster (hazard ratio 2.37; 95% confidence interval: (1.75–3.21; p = 0.0014) compared with wounds treated with EpiFix over a 28-day period. The average was 1.6 applications per subject for the Kerecis Omega3 wound and 1.4 applications for EpiFix [72]. This was a high-quality study, but the results were not applicable to chronic non-healing wounds.

A multi-centered RCT compared fish skin allograft (Kerecis Omega Wound) + SOC to SOC alone in 49 patients with chronic DFU after a 2-week screening period. At 12 weeks, 16 of 24 patients' DFU (67%) in the fish skin arm were completely closed, compared with 8 of 25 patients' DFU (32%) in the SOC arm (p =0.0152 [N = 49]; significant at p<0 .047). The median number of applications to achieve closure was 5 (in arm 1) [73]. Limitations include high risk of bias due to missing outcome date, small sample size and short-term follow-up period.

Additional literature includes review papers. Seth et al. summarizes case reports, case series and retrospective studies, and noted that additional RCTs are ongoing [74, 75]. This evidence is insufficient to validate net positive outcomes for DFU or VLU.

MatriStem

A multi centered observational study was conducted at 13 US centers and included 56 subjects comparing MatriStem MicroMatrix (MSMM) and MatriStem Wound Matrix (MSWM) (porcine-derived) (n=27) to ulcers treated with Dermagraft (n=29) for DFU. The matrix was applied weekly until wound closure or 1 application per week without

wound closure whichever came first to a maximum of 8 applications. Subjects were followed for 6 months for ulcer recurrence with one recurrence in both groups. There were no statistically significant differences between the 2 groups in the following: complete wound closure at day 56 (p=0.244), change in wound size over eight-week treatment period (p=0.762); complete wound closure at day 70 (p=0.768); or mean time to closure (p=0.523) [76]. This study's strength includes the multicentered sites and following subjects for 6 months for recurrence, but only 10 subjects were followed for this duration. The small sample size is not sufficient to determine efficacy of this product for wound healing.

Microlyte Matrix

Manning et al. [77] performed an open-label, prospective pilot study to evaluate a bioresorbable polymeric matrix infused with ionic and metallic silver (i.e., Microlyte matrix) as a primary wound contact dressing in the treatment of 32 patients (median age of 62 years) with a total of 35 hard-to-heal wounds along with SOC. The wounds encompassed venous stasis ulcers, DFU, postoperative surgical wounds, burn wounds, and chronic, non-pressure lower extremity ulcers unresponsive to standard protocols of care. Of the 35 chronic wounds, the majority consisted of venous stasis ulcers (54%) (19/35), followed by DFU (23%; 8/35). The mean wound surface area at the start of the study was 6.7 sq cm (range 0.1 sq cm – 33 sq cm); the median wound surface area was 2.1 sq cm. These wounds were considered as nonhealing for a median of 39 weeks (range, 3-137 weeks) and suspected to have persistent microbial colonization that had not responded to standard antimicrobial products and antibiotics.

The micrometer-thick bioresorbable matrix conforms closely to the underlying wound bed to exert localized and sustained antimicrobial action of noncytotoxic levels of silver. The matrix was applied to the wounds once every 3 days to provide a scaffold for uniform loading of silver nanoparticles and a template for cells migration and then covered with a secondary dressing. Any residual matrix still in the wound was not removed due to the bioresorbable nature of the matrix. Three patients were lost to follow-up after initial application. At three weeks, 72% of wounds (22/32) had an average wound area reduction of 66%. Of the 16 venous stasis ulcers, 11 improved by an average healing rate of 60%, and 6 of 8 DFU improved by an average wound area reduction of 79%. At the 3-week assessment, the burn wound, and postoperative wounds had an average wound area reduction of 38% and 58%, respectively. By 12 weeks, 91% of wounds (29/32) either healed completely (i.e., fully re-epithelialized) or improved substantially with an average wound area reduction of 73%. The venous stasis ulcers and DFU had an average wound area reduction greater than 75%, with visual signs of healthy granulation tissue formation and re-epithelialization. The study had certain limitations which included a small sample size, and use of the same clinical investigator who performed all assessments during the study [77]. There was not sufficient evidence to determine the efficacy of this product for wound healing.

Mirragen

There has been interest in bioactive glass as a pathway to wound healing due to postulated ability to release ions that can stimulate processes, such as hemostasis, antibacterial efficacy, epithelial cell migration, angiogenesis, and fibroblastic cell proliferation [78]. A literature review of bioactive glass applications introduced the

potential of this product and called for further research to understand the clinical role [79-80]. A randomized trial was conducted to evaluate a unique resorbable glass microfiber matrix (Mirragen; Advanced Wound Matrix) compared to SOC for 12 weeks. All patients received standard diabetic wound care and 20 were treated with the matrix while the others received SOC only. The primary endpoint was non-infected wound healing at 12 weeks. The authors report that in the intent-to-treat analysis results at 12 weeks showed that 70% (14/20) of the Mirragen-treated DFU healed compared with 25% (5/20) treated with SOC alone (adjusted p = 0.006) [81]. Strengths of the study include robust design, randomization, ITT analysis, and multiple sites. While the study was adequately powered per sample sized calculation the large drop-out in the SOC group (12/20) resulted in high-risk bias due to missing outcome data. Combined with the small sample size, lack of blinding and short-term follow-up ranging from 6-12 weeks there was not sufficient evidence to understand safety, effectiveness, and long-term outcomes of this product.

NEOX CORD/TTAX01

A multi-centered prospective trial of cryopreserved human umbilical cord (TTAX01; NEOX) enrolled 32 subjects with complex wounds which extended to muscle, fascia or bone with underlying osteomyelitis with a mean duration of 6.1 ± 9.0 (range: 0.2–47.1) months and wound area at screening of 3.8 ± 2.9 (range: 1.0–9.6) sq cm which was increased to 7.4 ± 5.8 (range: 1.1–28.6) sq cm after aggressive debridement. Initial closure occurred in 18 of 32 (56%) wounds, with 16 (50%) of these having confirmed closure in 16 weeks with a median of one-product application. Ulcers with biopsy confirmed osteomyelitis (n=20) showed initial closure in 12 (60%) and confirmed closure in 10 (50%). Mean healing time was 12.8 ± 4.3 weeks. The average number of applications was 1.5 + 0.8 applications (median of 1, range 1–3) over 16 weeks [82]. These same patients were reported on in a follow-up report that included 30 subjects with evaluation for safety, while subjects with a remaining open or closed index wound (n=29) were evaluated for efficacy. One subject had his unhealed wound removed in a minor amputation in the previous study. They were followed for 1 year and the adverse events reported were all typical for the population under study, and none were attributable to NEOX. One previously healed wound re-opened, 1 previously unconfirmed closed wound remained healed, and 9 new wound closures occurred, with 25 of 29 (86.2%) healed in the ITT population. This included use of additional products, minor amputation (n=2) and one major amputation [83]. Limitations include small sample size, lack of controls, and no randomization. However, this investigation did assess complex wounds that are rarely included in clinical studies. Additional literature includes a basic science report, case series and small retrospective reports.

These studies have inherent limitations due to the small sample size and observational design and there is no way to be certain that the treated wounds would have similar healing as compared to other skin substitutes or SOC. The potential benefit in a complex population (exposed tendon, muscle, and bone) warrants further investigation.

NeoPatch

A multi-centered prospective study [84] was conducted with 63 patients with chronic DFU. Wounds were classified by size into ‘small’ (≤2.0 cm2), ‘medium’ (>2.0–4.0 cm2), and ‘large’ (>4.0–25.0 cm2). After a 2-week run in period patients were treated with

chorioamniotic allograft (NeoPatch) on a weekly basis until the study period ended or wound closure to a maximum of 11 applications. At week 12, 13/23 small ulcers, 5/15 medium, and 1/10 large ulcers achieved closure, with a mean number of applications of 6.2, 6.6, and 8.0, respectively. The mean for the entire group was 40% closure (19/48) with 6.4 applications in 12 weeks. Of the adverse events reported most were related to the ulcer with no reported adverse events attributable to the allograft. Limitations of the study include the lack of randomization, control group, short term follow-up, small sample size, and potential risk of bias.

Oasis Ultra Tri-Layer Matrix

A RCT comprised of 11 centers and 82 subjects with DFU was completed to compare clinical outcomes of patients treated with tri-layer Oasis vs. SOC [85]. Patients were randomized into Oasis group (n=41) or SOC (n=41) group and evaluated for 12 weeks or until complete wound closure was achieved. The Oasis group achieved a significantly greater number of complete closures compared to the SOC group (54% vs. 32%, P=0.021) at 12 weeks. Limitations include unblinded design, short duration of follow up, and high risk of bias. Strengths of the study were comprised of the randomization process and use of a digital wound measurement device.

PriMatrix

Lantis et al. [86] conducted a multicenter RCT to evaluate the safety and efficacy of a fetal bovine acellular dermal matrix (PriMatrix) plus SOC versus SOC alone for treating hard-to-heal DFU. Participants (n=226) and 161 completed the protocol with 59.5% (47/79) with wound closure in the PriMatrix group and 35.4% (29/82) in the SOC group (p=0.002) in the per protocol analysis. Of wounds that healed, median time to close was 43 days for PriMatrix group and 57 days for SOC group. The median number of applications of PriMatrix to achieve closure was 1. Adverse events were similar between groups and no product-related serious adverse events occurred. The author noted study limitations such as short term follow up, inability to blind investigators or subjects to treatment type, patient selection bias towards healthier patients, and an overall high risk of bias.

A prospective trial reported on 55 subjects from 9 centers with DFU treated with PriMatrix and followed for 12 weeks [87]. 76% healed by 12 weeks with a mean time to healing of 53.1 ± 21.9 days. The mean number of applications for these healed wounds over 12 weeks was 2.0 ± 1.4, with 59.1% healing with a single application of PriMatrix and 22.9% healing with 2 applications. For subjects not healed by 12 weeks, the average wound area reduction was 71.4%. Study is limited by observational design without control group.

Additional literature includes a basic science report [88] and a retrospective review [88, 90].

PuraPly

A prospective, noninterventional, multicentered study was conducted to evaluate the effectiveness of purified native type I collagen matrix plus polyhexamethylene biguanide antimicrobial (PHMB) on cutaneous wounds (PuraPly AM®). A cohort of 307 patients with VLU (n=67), DFU (n=62), pressure ulcers (n=45), post-surgical wounds (n=54), and other wounds (n=79) were treated with PuraPly and followed for 12 weeks. The number

of applications ranged from 1-2 (21.8%) to 10 (<2%). They report that 73.2% of wounds were reduced from baseline and 63.4% had reached ≥70% reduction in area at 12 weeks with 37% of wounds achieving complete wound closure at 12 weeks. The average number of applications was 5.2 with 21.8% receiving 1 or 2 applications (21.8%) and <2% receiving 10 or more applications. No adverse events were reported related to the product [91]. The study is limited by lack of a control group, blinding or randomization, short term follow-up, and high-risk of bias. While this study shows promising results, it is difficult to determine whether the treated wounds would have similar healing as compared to other skin substitutes or SOC. Additional literature includes a case series and retrospective review.

Restrata

In a 2017 report Restrata is introduced as a fully synthetic, resorbable electrospun material (Restrata Wound Matrix) that exhibits structural similarities to the native extracellular matrix. The product was tested in a swine model [92]. A retrospective review of the product reported on 82 ulcers in patients with DFU (n=34) or VLU (n=34) and other wounds (n=14). They report 85% of these wounds achieved compete closure at 12 weeks [92]. Limitations include study design without controls not sufficient to conclude if the outcome were directly related to the novel product and insufficient follow-up time to establish safety.

TheraSkin

A RCT trial investigated 50 subjects with DFU were treated with cryopreserved bioactive split thickness skin allograft (TheraSkin) and 50 were treated with SOC (collagen alginate dressing). The authors reported at 12 weeks 76% (38/50) of the TheraSkin group versus 36% (18/50) for the SOC group achieved healing. The number of allografts to achieve healing was not reported [81]. Strengths of the study include randomization, ITT analysis, and low risk of bias. Despite the high dropout rate in SOC arm (n=19) the investigator used the last observation carried forward method to account for missing outcome data in the SOC group. Limitations in the study include small sample size, lack of blinding, and short-term follow-up.

A prospective study reported on 17 patients with DFU treated with the bioengineered skin substitute (Apligraf) and 12 were treated with a cryopreserved split thickness skin allograft (TheraSkin). Most received a single application with the decision to reapply left to the treating provider. The authors report 41.3% of the ulcers treated with Apligraf and 66.7% of the ulcers treated with TheraSkin were closed at 12 weeks, 47.1% treated with Apligraf closed at 20 weeks. The number of closed TheraSkin treated ulcers remained 66.7% at 20 weeks. The average number of applications of Apligraf was 1.53(SD=1.65). The number of applications of TheraSkin was 1.38 (SD= 0.29). There were no significant adverse events reported [94]. Limitations of the study include small sample size, lack of control, short term follow-up, and high risk of bias.

Sanders et al. [55] performed a multi-centered RCT to contrast an in vitro- engineered, human fibroblast-derived dermal skin substitute (HFDS) (i.e., Dermagraft to a biologically active cryopreserved human skin allograft (HSA) (i.e., TheraSkin®) in the treatment of DFU. The primary objectives were to establish the relative number of DFU healed (100% epithelization without drainage) and the number of grafts needed by week

12. Twenty-three eligible patients were randomly assigned to the Dermagraft treatment group (12 patients) (mean age 57) or the TheraSkin treatment group (11 patients) (mean age 60). Patients in the TheraSkin group received a product application every other week and patients in the HFDS group were treated every week with SOC. After the week 12 visit, no additional biologically active products were used in either treatment group. Patients with incomplete ulcer closure continued to be evaluated through week 20; subsequent treatment was then provided outside the scope of the study. At week 12, seven (63.6%) ulcers in the TheraSkin treatment group versus four (33.3%) in the Dermagraft treatment group were healed (P=0.0498). At the end of week 20, 90.91% of ulcers in the TheraSkin group versus 66.67% of ulcers in the Dermagraft group were healed (P=0.4282). The average of 8.92 applications (range 6-12 applications) in up to 20 weeks for Dermagraft and mean applications of 4.36 (range 2-7) in up to 20 weeks for TheraSkin [55].

Time to healing in the TheraSkin group was substantially less (8.9 weeks) than in the HFDS group (12.5 weeks) (log-rank test, P=0.0323). The results of this study showed that, after 12 weeks of care, DFU treated with HSA were probably twice as likely to heal as DFU managed with Dermagraft with about half the number of grafts required. Limitations noted for this study include small sample size, short-term follow-up and high risk of bias [55].

Additional literature includes two large retrospective matched cohort studies [96, 97] several cost-analysis, and an animal model study.

Clinical Trials for Skin substitute graft/CPTs for Venous Leg Ulcers

Amnioband

Serena et al. [98] performed an open-label, multicenter RCT comparing 2 application treatments of dehydrated human amniotic and chorion allograft (dHACA) (i.e., AmnioBand) with SOC versus SOC alone for the treatment of 60 patients with VLU. Patients were randomized into 1 of 3 study groups: SOC alone (control), weekly AmnioBand with SOC or biweekly AmnioBand with SOC (20 patients per group). At 12 weeks, healing rates were 30/40 (75%) in the two AmnioBand groups and 6/20 (30%) in the SOC group; p= 0.001. Treatment with AmnioBand continued to be significant after adjustment for wound area (p= 0.002), with an odds ratio of 8.7 (95% CI: 2.2-33.6). Only six VLU (30%) were healed in the SOC group contrasted to 15 (75%) in the weekly AmnioBand group (p= 0.02) and 15 (75%) in the biweekly AmnioBand group (p= 0.02). There were no significant differences in the proportion of wounds with percent area reduction (PAR) ≥40% at 4 weeks among all groups. All analyses used the ITT approach, and the risk of bias was low. Limitations include lack of blinding and short-term follow [98].

Apligraf (formerly GraftSkin)

Falanga et al. (1998) performed a multicenter RCT to evaluate allogeneic human skin equivalent (HSE) Apligraf group (n=146) versus SOC (n=129) in 275 patients with VLU. At 6 months, 63% Apligraf vs. 49% SOC patients were healed. Median time to complete wound closure was 61 days in the Apligraf group vs. 181 days in the SOC group. An average of 3.34 applications of Apligraf per patient were utilized [99]. There were some

concerns for risk of bias due to per protocol analysis only as well as short-term follow-up.

A prospective RCT included 120 patients with hard to heal VLU for a duration of greater than 1 year. Patients were randomized into an Apligraf plus compression therapy (n=74) or standard compression therapy (n=48) groups. Wound closure at 6 months was reported as 47% for the Apligraf group versus 19% for the control group. The authors conclude at 6 months, that patients treated with Apligraf were twice as likely to achieve complete wound closure as compared to standard compression therapy. They report Apligraf was over 60% more effective than the control in achieving wound closure. Limitations include high risk of bias, and lack of blinding [100].

A prospective randomized pilot study was conducted to estimate the relative difference in the effectiveness of Apligraf and TheraSkin and compression therapy for the treatment of VLU. A total of 31 participants were randomized and they reported a higher healing rate in the TheraSkin cohort (93.3%) as compared to the Apligraf cohort (75.0%) at 12 weeks, but it was not statistically significant. At 20 weeks follow up, the TheraSkin cohort remained at a 93.3% versus Apligraft cohort at an 83.3% healing rate. The mean number of applications was 3.33 in the Apligraf group and 2.27 in the TheraSkin group for 12 weeks. Limitations of this study include low sample size, and high risk of bias. There were no adverse events reported [101].

DermACELL

Cazzell [102] conducted a multicenter, RCT designed to evaluate the safety and efficacy of human decellularized acellular dermal matrices (DermACELL AWM®) (n=18) contrasted with SOC (n=10) in patients with chronic VLU. The study participants were randomly assigned to the D-ADM (i.e., DermACELL AWM®) treatment arm or a SOC treatment arm in a 2:1 ratio. A blinded, independent adjudicator also assessed the healing condition of all ulcers. Patients could have a maximum of two DermACELL applications, which included the first application at baseline and 9 (50%) received a second application during the study. At 24 weeks, patients in the DermACELL arm demonstrated a strong trend of reduction in the ulcer area, with a mean reduction of 59.6%, in comparison to the SOC arm, with a mean reduction of 8.1%. Also, the ulcer areas in the SOC arm increased more than 100% in size for one-third (3/9) of the patients. Furthermore, healed ulcers in the DermACELL arm stayed closed at a significantly greater rate after initial confirmation of complete ulcer closure than healed ulcers in the control arm. Limitations noted for this study included a small patient population with an unbalanced proportion between the 2 groups (2:1) that ensured a low probability of achieving statistical significance, insufficient criteria for investigators to follow when deciding if a second application would be appropriate, and a short-term follow-up. The overall risk of bias was low.

Dermagraft

Harding et al. [103] conducted a multicenter RCT that assessed the human fibroblast-derived dermal substitute (HFDS) (i.e., Dermagraft®) plus compression therapy contrasted with compression therapy alone in the treatment of VLU. The primary outcome variable was the proportion of patients with completely healed study ulcers by 12 weeks. Sixty-four (34%) of 186 patients in the Dermagraft group demonstrated

healing by week 12 compared with 56 (31%) of 180 patients in the control group (P=0.235). For ulcers ≤ 12 months duration, 49 (52%) of 94 patients in the Dermagraft group contrasted with 36 (37%) of 97 patients in the control group healed at 12 weeks (P=0.029). For ulcers ≤ 10 cm2, complete healing at week 12 was shown in 55 (47%) of 117 patients in the HFDS group contrasted with 47 (39%) of 120 patients in the control group (p=0.223). The most common AEs were ulcer infection, cellulitis, and skin ulcer. The occurrence of AEs was not significantly different between the treatment and control groups. Statistical significance was not achieved for the primary outcome of complete closure in patients with VLU completely healed by 12 weeks. The study had some concerns for risk of bias due to high dropout rate and lack of validation of outcome measurements [103].

EpiFix

A multi-centered, RCT was conducted to evaluate a dehydrated human amnion/chorion membrane allograft (EpiFix) (n=53) with SOC to SOC alone (n=31) for VLU. Subjects randomized to allograft received 1 (n=26) or 2 applications (n=27). At 4 weeks, 62% in the allograft group and 32% in the control group showed a greater than 40% wound closure (*p*=0.005), and wound size reduction of 48.1% and 19%, respectively. The authors reported the group with 2 applications (baseline and 2 weeks later) had the fastest healing time [104]. Limitations include lack of blinding, small sample size, and short-term follow up.

Another multi-centered RCT comparing EpiFix + SOC to SOC alone (multilayer compression therapy) for 109 subjects with VLU and followed for 16 weeks. Participants receiving weekly application of EpiFix (n=52) and compression were significantly more likely to experience complete wound healing than those receiving standard wound care and compression (n=57) (60% versus 35% at 12 weeks, P=0.0128, and 71% versus 44% at 16 weeks, p=0.0065) [105]. Limitations of the study include lack of blinding, short term follow up, and high risk for bias.

Oasis Products

Oasis Wound Matrix:

Landsman et al. conducted an RCT of 26 subjects with DFU. Subjects were randomized and treated with either Dermagraft (n=13), or Oasis Wound Matrix (n=13) in conjunction with SOC. Wound dressing was applied for 12 weeks and subjects were followed for 20 weeks. Closure rate for Oasis was 76.9% and Dermagraft is 84.6% with average closure time of 40.90 ± 32.32 days. No statistically significant difference was reported in closure time between the two groups. The average number of applications was 2.54 (±0.78) of Dermagraft and 6.46 ± 1.39 of Oasis in 12 weeks [106]. Limitations include small sample size, short term follow-up and some concerns for bias.

Niezgoda et al. [107] conducted a multicenter RCT to compare the rate of healing in DFU patients. Patients were randomized to either the OASIS Wound Matrix (n=37) group or Regranex Gel (n=36) plus a secondary dressing group. At 12-week follow-up, the Oasis group achieved 49% wound healing as compared to 28% in the Regranex group. Limitations included small sample size, lack of standardization between centers

in debridement techniques, frequency of wound dressing changes, lack of blinding, and some concerns for bias [107].

A 2010 RCT [108] was conducted to compare the Oasis Wound Matrix (n=25) to SOC (n=25) in VLU. Investigators assessed the wounds weekly and utilized digital planimetry for wound measurement. At 8 weeks complete wound closure was achieved in 80% (20/25) of Oasis Wound Matrix patients as compared to 65% (15/23) in the SOC group ($p<0.05$). A statistically significant difference was reported for mean ulcer duration. Complete healing was achieved in the treatment group, 5.4 weeks, vs. 8.3 weeks in the SOC group, ($p=0.02$). Granulation tissue was considered in cases where complete wound closure was not achieved by 8 weeks. The granulation of tissue increased from baseline to 8 weeks in the Oasis group and was reported as 50% and 65%, respectively, while the control group reported a loss of granulation from a baseline of 50% to a decrease of 38% at 8 weeks. Two subjects withdrew from the control group due to relocation. No adverse effects were reported. Limitations include small sample size, lack of blinding, and some concerns for bias [108].

Mostow and colleagues [109] conducted a multicenter RCT comprised of 120 patients with VLU to compare the Oasis Wound Matrix plus SOC (n=62) to SOC alone (n=58). Following a 2-week screening period, patients were randomized into 1 of the 2 groups and followed for 12 weeks. A total of 19 patients assigned to the SOC alone group crossed over into the treatment group due to a lack of healing at 6 months. Healing was achieved in 26% (5/19) of these patients after receiving an average of 4 applications of the Oasis product. The primary outcome was proportion of healed ulcers at 12 weeks. Although the data was still analyzed, 20% of patients were lost to follow up (12 in each group). At 12 weeks, the treatment group achieved 55% healing as compared to 34% in the SOC group. Ulcer recurrence did not occur in any of the healed patients in the treatment group over a 6-month period. The average number of applications for VLU was 4 (applied to 5/19 crossover patients). A total of 23 adverse events were reported and evenly distributed between the two groups. Limitations include lack of blinding, small sample size, short duration of follow up, limited number of wounds evaluated at 6 months, and high risk of bias [109].

Additional literature is reviewed in Dermagraft section. Literature reviewed but not summarized in this policy includes a retrospective comparative study in the treatment of VLU [110].

Unspecified Oasis Products

O'Donnell and associates conducted a systematic review of RCTs to determine if complex wound coverings impacted wound healing as compared to simple wound dressings. A total of 20 RCTs were included and stratified into 3 classes semi occlusive/occlusive group (n = 8), growth factor group (n = 7), and human skin equivalent group (n = 5). Five of the RCTs (25%) yielded statistical significance for improved proportion of ulcer healing in the treatment group over the control: zinc oxide pastes bandage (79% vs 56%) and Tegasorb (59% vs 15%) in the semi occlusive/occlusive group and perilesional injection of granulocyte-macrophage colony-stimulating factor (57% vs 19%) and porcine collagen derived from small-intestine submucosa (Oasis; 55% vs 34%) in the growth factor group. In the sole significant RCT

from the human skin equivalent group, Apligraf (63%) was superior to Tegapore (49%)" [12].

See Apligraf section.

A 2019 single blinded RCT comprised of patients with DFU compared 8 weeks of treatment using either Dermagraft (n=29) or Oasis devices (n=31) (active treatment phase) followed by 4 weeks of SOC (maintenance phase), and SOC (n=29) alone. Each treatment group achieved a statistically significant reduction in wound area from weeks 1 to 28. No differences were reported between groups in complete wound closure by 12 or 28 weeks of treatment. Complete wound closure at 12 weeks was Dermagraft (8/17) 47.1%, Oasis (14/19) 73.7%, and SOC 57.9% (11/19). Complete wound closure by study conclusion was Dermagraft (11/17) 64.7%, Oasis (15/19) 78.9%, and SOC 73.7% (14/19). The study was an interim report and did not have enough enrolled to meet the sample size needed, and there was a high risk of bias due to per-protocol analysis only for this interim data. The authors were surprised at the higher healing rates for SOC than what was reported in the U.S. literature and postulated that unintentional bias may have resulted in lower efficacy in the SOC group or favoring SOC in their study [111]. The results were not identified as being published therefore there is a potential risk for publication bias. See the Dermagraft section.

Romanelli et al. conducted a RCT to compare Oasis (n=27) and Hyaloskin (n=27) products in the healing VLU at 16 weeks of treatment. Patients were assessed by complete wound healing, time until dressing change, pain and comfort. A total of 82.6% of Oasis ulcers achieved complete wound closure as compared to 46.2% of Hyaloskin ulcers. Treatment favored Oasis treated ulcers which were statistically significant for time to dressing change ($p< 0.05$), pain ($p< 0.05$) and patient comfort ($p< 0.01$). Four patients were lost to follow up. No adverse events were reported. Limitations include self-reporting bias, small sample size, lack of blinding, and some concerns for bias related to randomization. [112].

Demling and associates reported an interim analysis of a prospective RCT to examine the effectiveness of Oasis products compared to SOC in treating VLU. The primary outcome was wound closure at 12 weeks. At 12 weeks, 84 patients were evaluated in which 71% (32/45) of Oasis vs. 46% (18/39) SOC patients achieved complete wound healing. Significant improvements in the incidence of healing were reported in the Oasis patients vs. SOC ($p=0.018$). Interim results were reported on per-protocol analysis rather than the intention to treat population introducing a high risk of bias [113]. The results were not identified in the literature and do not appear to have been published, which potentiates the risk for publication bias.

Talymed

A RCT enrolled 82 patients comparing a poly-N-acetyl glucosamine, nanofiber-derived, technology (Talymed) to SOC for VLU. Subjects were randomized to treatment with Talymed applied once, every other week, every 3 weeks, or SOC alone and followed for wound healing at 20 weeks. At 20 weeks, the proportion of patients with completely healed VLU was 45.0% (n = 9 of 20), 86.4% (n = 19 of 22), and 65.0% (n = 13 of 20) for groups receiving standard care plus Talymed only once, every other week, or every 3

weeks, respectively, versus 45.0% (n = 9 of 20) for those receiving standard care alone [114]. The biweekly application group showed improvement over the standard of care arm ($p<0.01$). Strengths include randomization, blinded investigator, and presence of a control arm. The investigation had limitations which consisted of a small sample size and high risk of bias due to missing outcome data. While these results were promising the sample size was too small to determine if the outcomes were related to the product. The authors acknowledge that this was a pilot study and there was a need for a larger study to confirm the findings. Further, 2 of the 3 study arms did not show significant differences from the SOC group.

Additional literature consists of case report [115] and was included in a systematic review [33] (see above).

Risk of Bias Assessment

A risk of bias assessment was conducted for all RCTs to evaluate them using the same tool and identify areas of potential concern in study designs. Risk of Bias 2 tool [116] (RoB2) was used and is described in the Cochrane handbook [117] and utilized in GRADE. This tool is different than the tool used in the AHRQ report [3] and the other systematic reviews published prior to 2019 (see the section addressing Systematic Reviews) when the updated tool was published. The revised version requires a judgement about the risk of bias arising from each domain- based on answers to the signaling questions. Judgements are 'Low', 'High', or can express 'Some concerns' and included in the evidence review and Table 1 for each product assessed. The overall result must reflect the highest value assigned to any domain. While almost all included studies were funded by industry, this is not an underlying reason to determine that bias exists using RoB2. This tool requires evaluation of multiple aspects of the trial design and assesses if risk of bias was introduced regardless of funding source.

Table 4: Evidence for Covered Products

SKIN SUBSTITUTES/CTP (per sq cm unless otherwise stated)	Ulcer Type	Literature	Risk-of-bias Assessment
AFFINITY	DFU	1. RCT (n=76) reported wound closure at 16 weeks of 63% for Affinity arm and 38% in SOC (n=38) [34].	1. Low risk [34]
AMNIOBAND, GUARDIAN	DFU	1. RCT (n=60) reported healing rate at 12 weeks was 90% for the Amnioband group versus 40% for the Apligraft group [38]. 2. RCT (n=40) reported at 12 weeks 85% of the DFU in the Amnioband group healed compared with 25% in the SOC group. [39] 3. RCT (n=80) reported at 12 weeks, 85% of the DFU in the Amnioband group achieved healing compared with 33% of the DFU in the SOC group. [40]	1. High risk due to missing outcome data [38] 2. Low risk [39] 3. Low risk [40]
AMNIOBAND, GUARDIAN	VLU	1. RCT (n=60) healing rates at 12 weeks were 75% in the two Amnioband groups and 30% in the SOC group. [98]	1. Low risk [98]

APLIGRAF	DFU	1.RCT (n=208) reported wound closure at 12 weeks of 56% for Apligraf and 38% for SOC [42] 2.RCT (n=72) reported on wound closure at 12 weeks of 55.2% for Apligraf and 34.3% for SOC [43] 3.RCT (n=82) reported on wound healing at 12 weeks of 51.5% for Apligraf and 26.3% for SOC [44] 4.RCT (n=60) reported on wound closure at 6 weeks of 95% for EpiFix, 45% for Apligraft and 35% for SOC [62]	1. High risk due to lack of validation of outcome measurements [42] 2. Unable to complete due to pooling data from 2 different studies into one paper [43] 3. High risk due to lack of validation of outcome measures [44] 4. High risk due to missing outcome data [62]
APLIGRAF	VLU	1.RCT (n=275) reported on wound closure at 6 months of 63% for Apligraf and 49% for SOC. [118] 2. RCT (n=120) reported on wound closure at 24 weeks of 47% for Apligraf and 19% SOC. [100] 3. RCT (n=31) reported on wound healing at 12 weeks of 93.3% for Theraskin and 75% for Apligraf [101]	1. Some concerns due to potential deviations from intended intervention (no ITT) [118] 2. 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 of outcome measures in unblinded study [100] 3. 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 [101]
DERMACELL, AWM, POROUS	DFU	1. 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 [50 -51] 2. Prospective study (n=61) of large complex wounds treated with DermACELL with 24.6% closure at 16 weeks [52]	1. 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 [50-51] 2. NA
DERMACELL, AWM, POROUS	VLU	1. RCT (n=28) reported on wound closure of 59.6% for DermACELL and 8.1% for SOC at 24 weeks [102]	1. Low risk [102]
DERMAGRAFT	DFU	1. RCT (n=314) reported wound closure at 12 weeks of 30% of Dermagraft group and 18.3% in SOC group [53] 2. RCT (n=23) reported wound closure at 20 weeks with 90.91% in Theraskin group and 66.67% in Dermagraft group [55] 3. RCT (n=50) on wound closure at 12 weeks with 50% for Dermagraft and 8% SOC group [54]	1. Some concerns due to missing outcome data [53] 2.High risk due to unclear randomization, potential deviations from intended intervention (no ITT) and lack of validation of outcome measurements [55] 3. High risk due to missing outcome data, lack of validation of outcome and unclear randomization. [54]

DERMAGRAFT	VFU	1. RCT (n=366) reported on wound closure at 12 weeks of 34% for Dermagraft and 31% for SOC [103]	1. Some concerns due to high dropout rate (missing outcomes), and lack of validation of outcome measurements [103]
EPICORD		1. RCT (n=155) reported wound closure at 12 weeks of 70% for EpiCord and 48% for SOC [56]	1. Low risk [56]
EPIFIX	DFU	1. RCT (n=25) reported wound healing at 6 weeks in EpiFix group of 92% and 8% in SOC group [58] 2. RCT (n=104) reported wound closure 12 weeks of 73% for Apligraf, 97% for EpiFix and 51% for SOC [45] 3. RCT (n=110) reported on wound closure at 12 weeks of 70% EpiFix and 50% SOC in the ITT analysis [59] 4. RCT (n=60) reported on wound closure at 6 weeks of 95% for EpiFix, 45% for Apligraft and 35% for SOC [62]	1. High risk due to lack of validation of outcome measurements [58] 2. High risk due to unbalanced and missing outcome data [45] 3. Low risk [59] 4. High risk of bias due to missing outcome data [62]
EPIFIX	VLU	1. RCT (n=53) reported wound reduction in 4 weeks was 62% for EpiFix and 32% for SOC [104] 2. RCT (n=109) reported wound closure at 16 weeks for VLU was 71% for EpiFix and 44% for SOC.107 The follow-up report included ITT analysis reported similar results with 50% in EpiFix group and 31% in SOC [119]	1. Low risk [104] 2. The 2018 paper was high risk due to potential deviations from intended intervention (no ITT) and missing outcome data [105] while the 2019 [119] was high only due to missing outcome data.
FLEXHD/ALLOPATH HD/ ALLOPATCH PLIABLE/ MATRIX HD	DFU	1. RCT (n=40) reported wound healing at 12 weeks of 80% for AlloPatch and 20% for SOC 36, additional 40 patients enrolled and reported similar results [120]	1. High risk due to missing data outcomes [120]
GRAFIX STRAVIX PRIME PL		1. RCT (n=97) reported wound closure at 12 weeks was 62% in Grafix group and 21% in SOC group. [63] 2. Retrospective report (n=441) [64]	1. High risk as randomization was not described, and missing outcome data [63] 2. NA
GRAFTJACKET	DFU	1. RCT (n=40) reported on wound healing at 12 weeks with a 67.4% reduction with Graftjacket and 34% with SOC [66] 2. RCT (n=28) reported on wound closure at 16 weeks of 85.71% in Graftjacket arm and 28.57% in SOC [67] 3. RCT (n=86) reported on mean wound healing time of 12 weeks was 30.4% with Graftjacket and 53.9% with SOC [68] 4. RCT (n=168) reported on wound closure at 16 weeks of 67.9% for DermACELL, 47.8% for Graftjacket, and 48.1% for SOC [50-51] 5. These studies were included in a meta-analysis [69] and Graftjacket in another [121]	1 & 2. High risk due to unclear randomization, potential deviations from intended intervention (no ITT), lack of validation of outcome measurements, and statistical plan not described [66-67] 3. High risk due to unclear randomization, lack of validation of outcome measurements [68] 4. Low risk [50-51] 5. NA
INTEGRA OR OMNIOGRAFT DERMAL REGENERATION TEMPLATE	DFU	1. RCT (n=307) reported wound closure at 16 weeks of 51% in Integra group and 32% in SOC group [70]	1. High risk due to missing outcome data [70]

OASIS TRI-LAYER WOUND	DFU	1. RCT (n=82) reported on wound closure at 12 weeks with 54% for Oasis Tri-layer and 32% for SOC [85]	1. High risk due to missing outcome data [85]
OASIS WOUND MATRIX	DFU	1. RCT (n=26) reported no difference in closure time for Dermagraft (84.6% or Oasis Wound Matrix (76.9%) [106] 2. RCT (n=73) reported on wound healing at 12 weeks of 49% for Oasis wound matrix and 28% for Regranex gel [107] Additional literature on pressure ulcers.	1. Some concerns due to no validation of wound measurements [106] 2. Some concerns due lack of validation of outcome measurements [107]
OASIS WOUND MATRIX	VLU	1. RCT (n=48) reported wound closure at 8 weeks of 80% for Oasis wound matrix and 65% for SOC. [108] 2. RCT (n=120) reported on wound healing at 12 weeks of 55% in Oasis group and 34% in SOC [109] 3. RCT (n=89 reported on wound closure at 12 weeks with 47.1% for Dermagraft, 73.7% for Oasis and 57.9% for SOC [111] 4. RCT (n=84) reported on wound closure at 12 weeks of 71% Oasis and 46% SOC [112]	1. Some concerns due to randomization process [108] 2. High risk due to missing outcome data, lack of validation of outcome measurements [109] 3. High risk of bias due to per-protocol analysis only [111] 4. High risk due to per-protocol analysis, missing outcome data and uncertain method for outcome measurements or blinding protocol [112]
PRIMATRIX	DFU	1. RCT (n=161) reported wound closure at 12 weeks of 59.5% for PrimMatrix arm and 35.4% for SOC arm [86] 2. Prospective trial(n=55) [87], retrospective [88-90] and lab [88]	1. High risk due to lack of blinding and analysis of outcome measures [86] 2. NA
THERASKIN	DFU	1. RCT (n=50) reported on wound healing at 12 weeks was 76% for TheraSkin and 36% for SOC [94] 2. RCT (n=23) reported wound closure at 20 weeks with 90.91% in TheraSkin group and 66.67% in Dermagraft group [55] 3. A small prospective study (n=29) [95] retrospective cohort studies, [96, 97] and lab study [122]	1. Low risk [94] 2. High risk [55] 3. NA

Table 5: Evidence for Non-Covered Products

SKIN SUBSTITUTES (Per sq cm unless otherwise stated)	**EVIDENCE** (Published, peer reviewed literature to support use in chronic DFU/VFU	**COMMENTS**
AC5 ADVANCED WOUND SYSTEM (AC5)	No literature identified	
ACESSO DL, ACESSO TL	No literature identified	
ACTIVATE MATRIX	No literature identified	
ALLODERM	Evidence in breast surgery and hernia repair	Insufficient evidence for DFU/VLU
ALLOGEN, PER CC	No literature identified	
ALLOSKIN, ALLOSKIN AC	Literature in burn and orthopedics	Insufficient evidence

ALLOWRAP DS OR DRY	Literature in tarsal tunnel, thoracic outlet syndrome, proctectomy, and burns	Insufficient evidence
AMERICAN AMNION, AMERICAN AMNION AC, AMERICAN AMNION, TRI-LAYER	No literature identified	
AMNIO BIO OR AXOBIOMEMBRANE	No literature identified	
AMNIO QUAD-CORE	No literature identified	
AMNIO WOUND	No literature identified	
AMNIOAMP-MP	No literature identified	
AMNIOARMOR	No literature identified	
AMNIOBAND PARTICULATE, 1 MG	No literature identified	
AMNIOCORE, AMNIOCORE PRO, AMNIOCORE PRO+	No literature identified	
AMNIOCYTE PLUS, PER 0.5CC	No literature identified	
AMNIOEXCEL, AMNIOEXCEL PLUS OR BIODEXCEL	Small RCT [41]	Insufficient evidence (see LCD section Amnioexcel)
AMNIOMATRIX OR BIOMATRIX, INJECTABLE, 1 CC	No literature identified	
AMNIO-MAXX OR AMNIO-MAXX LITE	No literature identified	
AMNIOREPAIR OR ALTIPLY	No literature identified	
AMNIOTEXT PATCH	Case report [123]	Insufficient evidence
AMNIOTEXT, PER CC	No literature identified	
AMNIO-TRI-CORE AMNIOTIC	No literature identified	
AMNIOWRAP2	No literature identified	
APIS	Retrospective comparative study of 47 wounds [124], case series [125]	Insufficient evidence
ARCHITECT ECM PX FX	No literature identified	
ARTACENT AC, 1 MG	No literature identified	
ARTACENT AM	Observational study (n=26) [126]	Insufficient evidence
ARTACENT CORD	No literature identified	
ARTACENT WOUND	Observational study (n=26) [126]	Insufficient evidence
ARTHROFLEX	Evidence for rotator cuff repair	Insufficient evidence for DFU/VLU
ASCENT, 0.5 MG	No literature identified	
AXOLOTL AMBIENT OR AXOLOTL CRYO, 0.1MG	No literature identified	
AXOLOTL GRAFT OR AXOLOTL DUALGRAFT	No literature identified	
BARRERA SL OR BARRERA DL	No literature identified	
BELLACELL HD OR SUREDERM	Literature for breast surgery	Insufficient evidence for DFU/VLU
BIO-CONNEKT WOUND MATRIX	No literature identified	
BIODFENCE DRYFLEX	No literature identified	
BIONEXTPATCH	No literature identified	

BIOVANCE, BIOVANCE TRI-LAYER OR BIOVANCE 3L	Observational study [48], case series [49]	Insufficient evidence (see LCD section Biovance)
CAREPATCH	No literature identified	
CELERA DUAL LAYER OR CELERA DUAL MEMBRANE	No literature identified	
CELLESTA CORD, CELLESTA OR CELLESTA DUO	No literature identified	
CELLESTA FLOWABLE AMNION PER 0.5CC	No literature identified	
COCOON MEMBRANE	No literature identified	
COGENEX AMNIOTIC MEMBRANE	No literature identified	
COGENEX FLOWABLE AMNION, PER 0.5CC	No literature identified	
COLL-E-DERM	No literature identified	
COMPLETE AA, COMPLETE ACA, COMPLETE SL, COMPLETE FT	No literature identified	
CORECYTE, FOR TOPICAL USE ONLY, PER 0.5CC	No literature identified	
CORETEXT OR PROTEXT, PER CC	No literature identified	
CORPLEX P	No literature identified	
CORPLEX P, PER CC	No literature identified	
CRYO-CORD	No literature identified	
CYGNUS	No literature identified	
CYGNUS DUAL	No literature identified	
CYGNUS, MATRIX	Lab study131	Insufficient evidence
CYMETRA, INJECTABLE, 1 CC	No literature identified	
CYTAL (FORMERLY MATRISTEM)	One RCT8 and 2 case series [128, 129]	Insufficient evidence (see LCD section MatriStem)
DERMABIND DL, DERMABIND CH, DERMABIND SL	No literature identified	
DERMABIND TL OR AMNIOBIND	No literature identified	
DERMACYTE AMNIOTIC MEMBRANE ALLOGRAFT	Case report [130]	Insufficient evidence
DERMA-GIDE	No literature identified	
DERMAPURE	Retrospective review (n=37) [131]	Insufficient evidence
DERMAVEST, PLURIVEST	Case series [132], Lab study [133]	Insufficient evidence
DERM-MAXX	No literature identified	
DUAL LAYER IMPAX MEMBRANE	No literature identified	
EMERGE MATRIX	No literature identified	
ENVERSE	No literature identified	
EPIEFFECT	No literature identified	
EPIFIX INJECTABLE, 1 MG	No literature identified	
ESANO A, ESANO AAA, ESANO AC, ESANO ACA	No literature identified	
EXCELLAGEN, 0.1 CC	Lab paper [134]	Insufficient evidence
EZ-DERM	Literature in burn	Insufficient evidence

FLOWERAMNIOFLO, 0.1 CC	No literature identified	
FLOWERAMNIOPATCH	No literature identified	
FLOWERDERM	No literature identified	
FLUID FLOW OR FLUID GF, 1 CC	No literature identified	
GAMMAGRAFT	Bench139/ case report	Insufficient evidence
GENESIS AMNIOTIC MEMBRANE	No literature identified	
GRAFIX CORE, GRAFIXPL CORE	Prospective study in 31 complex wounds achieving 59% closure. [65] Retrospective report (n=441) [64]	Insufficient evidence (see LCD section GrafixCORE)
GRAFIX PLUS	No literature identified	
GRAFTJACKET XPRESS, INJECTABLE, 1 CC	No literature identified	
HELICOLL	Literature for split-thickness graft donor sites.	Insufficient evidence for DFU/VLU
HMATRIX	Literature in breast surgery, head and neck, and hand/arm reconstruction, and abdominal wall closure.	Insufficient evidence for DFU/VLU
HYALOMATRIX	Literature in burns, trauma, skin cancer. Evidence in ulcer management includes case series [136, 137, 138, 139] and a review article [140]	Insufficient evidence
INNOVABURN OR INNOVAMATRIX XL	Review paper [141]	Insufficient evidence
INNOVAMATRIX AC, INNOVAMATRIX FS	No literature identified	
INNOVAMATRIX PD 1MG	No literature identified	
INTEGRA BILAYER DERMAL MATRIX WOUND DRESSING	No literature identified	
INTEGRA FLOWABLE WOUND MATRIX, INJECTABLE, 1 CC	No literature identified	
INTEGRA MESHED BILAYER WOUND MATRIX	No literature identified	
INTERFYL, 1 MG	Literature on soft tissue reconstruction	Insufficient evidence for DFU/VLU
KERAMATRIX OR KERASORB	No literature identified	
KERECIS OMEGA3/ KERECIS OMEGA3, MARIGEN SHIELD	RCT (n=170) for healing in punch biopsy site [72], RCT (n=49) reported wound closure at 12 weeks of 67% for Kerecis and 32% for SOC with high risk of bias due to missing outcome data. [73]	Insufficient evidence (see LCD section Kerecis)
KEROXX (2.5G/CC), 1 CC	No literature identified	
LAMELLAS XT, LAMELLAS	No literature identified	
MATRION	Lab study [66]	Insufficient evidence
MATRISTEM MICROMATRIX, 1 MG, MATRISTEM WOUND MATRIX, MATRISTEM BURN MATRIX	One RCT8 and 2 case series [128, 129]	Insufficient evidence for DFU/VLU (see LCD section Matristem)
MEDISKIN	Literature for split-thickness graft donor sites.	Insufficient evidence

MEMBRANE GRAFT OR MEMBRANE WRAP	No literature identified	
MEMBRANE WRAP-HYDRO	No literature identified	
MEMODERM, DERMASPAN, TRANZGRAFT, OR INTEGUPLY	Case report [142]	Insufficient evidence
MLG-COMPLETE	No literature identified	
MICROLYTE, MATRIX	Prospective observational study in 35 chronic wounds with 91% healing or improved at 12 weeks. [77]	Insufficient evidence (see LCD section Microlyte Matrix)
MIRO3D	No literature identified	
MIRODERM	Prospective pilot study in 7 wounds, [143] and prospective observational study of 38 ulcers [144]	Insufficient evidence
MIRRAGEN ADV WOUND MATRIX	Bench papers [78, 79]/ case series [145], small RCT [81]/ review paper [80]	Insufficient evidence (see LCD section Mirragen)
MYOWNSKIN	No literature identified	
NEOMATRIX	No literature identified	
NEOPATCH OR THERION	No literature identified	
NEOSTIM TL, NEOSTIM MEMBRANE, NEOSTIM DL	No literature identified	
NEOX 100 OR CLARIX 100	Prospective trail (n=32) [82, 83]	Insufficient evidence (see LCD section Neox)
NEOX CORD 1K, NEOX CORD RT, OR CLARIX CORD 1K	No literature identified	
NEOX FLO OR CLARIX FLO, 1 MG	Case series [146]	Insufficient evidence
NOVACHOR	No literature identified	
NOVAFIX, NOVAFIX DL	No literature identified	
NOVOSORB SYNPATH DERMAL MATRIX	Book chapter (bench studies) [147] (review article) [148]	Insufficient evidence
NUDYN DL OR NUDYN DL MESH, NUDYN SL OR NUDYN SLW	No literature identified	
NUSHIELD	Case report [149], Retrospective report with 50 wounds. [150] Literature in talar dome lesions.	Insufficient evidence for DFU/VLU
OASIS BURN MATRIX	No literature identified	
OMEZA COLLAGEN MATRIX, PER 100 MG	Bench papers [151, 152]	Insufficient evidence lacks clinical studies
ORION	No literature identified	
PALINGEN OR PROMARX, 0.36 MG PER 0.25CC	Literature in plantar fasciitis	Insufficient evidence for DFU/VLU
PALINGEN, PALINGEN XPLUS, OR PROMARX	Literature in plantar fasciitis	Insufficient evidence for DFU/VLU
PERMEADERM B, PERMEADERM C	No literature identified	
PHOENIX WOUND MATRIX	No literature identified	
POLYCYTE, FOR TOPICAL USE ONLY, PER 0.5CC	No literature identified	
PORCINE IMPLANT, PERMACOL	Literature in hernia repair	Insufficient evidence
PROCENTA, PER 200 MG	No literature identified	
PROGENAMATRIX	No literature identified	

PURAPLY, PURAPLY XT	Prospective, noninterventional study (n=307) [91]	Insufficient evidence (see LCD section PuraPly)
PURAPLY, AM	Prospective, noninterventional study (n=307) [91], case series [153-155]	Insufficient evidence (see LCD section PuraPly)
REBOUND MATRIX	No literature identified	
REGUARD, FOR TOPICAL USE	No literature identified	
RELESE	No literature identified	
RIPRIZA	Literature in plastic surgery	Insufficient evidence for DFU/VLU
RESOLVE MATRIX	No literature identified	
RESTORIGIN	No literature identified	
RESTORIGIN, 1 CC	No literature identified	
RESTRATA	Retrospective review [80] wounds [92]	Insufficient evidence due to low quality
REVITA	No literature identified	
REVITALON	No literature identified	
REVOSHIELD AMNIOTIC BARRIER, PER SQ CM	No literature identified	
SANOPELLIS	No literature identified	
SIGNATURE APATCH	No literature identified	
SKIN SUB, NOS		
SKIN SUBSTITUTE, FDA CLEARED AS A DEVICE, NOT OTHERWISE SPECIFIED		
SKIN TE	Skin TE	
STRATTICE TM	literature in abdominal wall closure/hernia repair	Insufficient evidence
SUPRA SDRM	No literature identified	
SUPRATHEL	No literature identified	
SURFACTOR OR NUDYN, PER 0.5CC	No literature identified	
SURGICORD	No literature identified	
SURGIGRAFT, SURGRAFT TL, SURGRAFT FT, SURGRAFT XT, SURGIGRAFT-DUAL	No literature identified	
SURGIMEND COLLAGEN MATRIX, PER 0.5 SQ CM	literature in breast surgery	Insufficient evidence
SURGRAFT	No literature identified	
SYMPHONY	No literature identified	
TAG	No literature identified	
TALYMED	One RCT116, one case report [115], literature on use in bone wound healing [156] and lab research [157]	Insufficient evidence (see LCD section Talymed)
TENSIX	Case reports [142]	Insufficient evidence
THERAGENESIS	No literature identified	
TRANSCYTE	Literature in burns	Insufficient evidence
TRUSKIN	No literature identified	
UNITE BIOMATRIX	Abstract and case report [158]	Insufficient evidence
VIA MATRIX	No literature identified	
VENDAJE, VENDAJE AC	No literature identified	

VIM	No literature identified	
WOUNDEX FLOW, BIOSKIN FLOW, 0.5 CC	No literature identified	
WOUNDEX, BIOSKIN	Retrospective study (n=20) [159]	Insufficient evidence
WOUNDFIX, BIOWOUND, WOUNDFIX PLUS, BIOWOUND PLUS, WOUNDFIX XPLUS OR BIOWOUND XPLUS	No literature identified	
WOUNDPLUS MEMBRANE OR E-GRAFT	No literature identified	
XCELL AMNIO MATRIX	No literature identified	
XCELLERATE	No literature identified	
XCELLISTEM, 1 MG	No literature identified	
XCM BIOLOGIC TISSUE MATRIX	Literature for chest wall defects	Insufficient evidence for DFU/VLU
XWRAP AMNIOTIC MEMBRANE	No literature identified	
ZENITH AMNIOTIC MEMBRANE	No literature identified	

Number of Applications

A 2021 industry-sponsored study presented a retrospective analysis from the Medicare Limited Data set (2015-2018) comparing lower extremity diabetic ulcers (LEDUs) treatment with advanced treatments (AT) defined as cellular and acellular dermal substitutes, compared to no advanced treatments (NAT). Out of 9,738,760 patients identified with a diagnosis of diabetes, 909, 813 had a lower extremity diabetic ulcer (LEDU). Patients treated exclusively with AT or NAT were included in the analysis (i.e., patient treated with another type of advanced treatment were excluded). A set of covariates that included patient demographics, LEDU characteristics, year of episode start, prior treatments, prior visits, and comorbidities was identified. Based on this set, propensity scores were used to create two comparable groups with similar distributions of observed covariates. In propensity-matched Group 1, AT patients had fewer minor amputations ($p = 0.0367$), major amputations ($p < 0.0001$), ED visits ($p<0.0001$), and readmissions ($p<0.0001$) contrasted with NAT patients (12,676 episodes per cohort). The authors then took a second step in the analysis to attempt to determine the effectiveness of AT following parameter for use contrasted to patients with AT not following parameter for use. They reported patients had fewer minor amputations ($p = 0.002$) in those following parameters for use (1,131 episodes per cohort). They conclude advanced treatments with skin substitutes were associated with significant reduction in major and minor amputations, emergency room visits, and hospital readmissions compared to those without advanced treatments. They also conclude that following the parameters improved outcomes [13]. The study is limited by lack of blinding and randomization which restricts the ability to determine if these outcomes were directly related to the treatment with skin substitute. It is unclear whether the study considered a number of factors that would be expected to influence outcomes, including visit frequency, compliance with care, infection treatment, and the use of additional products/treatments. It is difficult to draw the conclusion that the improvement was due

solely to the advanced treatment with skin substitutes and not related to other factors from a retrospective study.

The study does report on frequency of application. Patients who received AT with skin substitute grafts (propensity-matched Group 1) had 3.7(3.6) applications on average (n=12,313). In Group 2 the average number of applications in the parameter for use group was 4.9(3.8) (n=1131) and in the not following parameter for use group the average was 3.5 (3.3) [13].

The number of applications in the reported literature is variable and differs among products. Factors to consider include whether the application was made per protocol, whether those protocols require a product change or is at the discretion of the provider, and any applications made on an as needed basis. In a meta-analysis of amniotic products, 4/5 trial protocols were designed to change the product weekly. In the fifth trial where changes were left to provider discretion, there was no decease in wound healing [30].

National Institute for Health and Care Excellence (NICE) Diabetic foot problems: prevention and management

The clinical guideline on diabetic foot problems considers dermal or skin substitute grafts as an appropriate addition to standard care in treating diabetic foot ulcers only when healing has not progressed with SOC on the advice of the multidisciplinary foot care service [160].

International Working Group on the Diabetic Foot (IWGDF) [161]

IWGDF recommends the consideration of placental-derived products as an adjunctive treatment to the best standard of care when standard care alone has failed to reduce the size of the ulcer. (GRADE Strength of recommendation:

Weak; Quality of evidence: Low). This was based on several studies, including those of moderate bias, suggesting that placenta-derived products may have a beneficial effect on ulcer healing. The authors also state these findings need to be confirmed in large, randomized trials and there is insufficient evidence to support superiority of any product(s).

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

For both recommendations, 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).

Wound Healing Society (WHS) [11][162]

The WHS has published updated evidence-based guidelines on the treatment of diabetic ulcers. 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 [11].

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 [162].

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, amniotic membrane 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. 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 standard of care (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 (CTP). 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 [15].

Analysis of Evidence (Rationale for Determination)

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 substitute/CTP 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).

Despite these limitations, a promising trend within the literature towards outcome improvement is identified. Therefore, to be considered reasonable and necessary for coverage, each skin substitute/CTP must demonstrate net positive health outcome(s) in a well-defined patient population. Specifically, wound closure attributable to the individual product(s) proven in clinical trials with meaningful degree of certainty is required. Therefore, a limited coverage position for specific products in specific patient populations has been taken to facilitate access to skin substitute graft/CTP products with clinically meaningful net-positive clinical outcome(s) validated by evidentiary review.

The intent of a skin substitute graft/CTP is to augment wound healing by promotion of skin growth and wound closure. Inherent to this process is stability and adherence of the product which allows it to remain in place to promote skin growth and wound closure with incorporation of the graft. A product requiring removal or replacement without the benefit of incorporation more clearly is characterized as a dressing. There is a trend within the published literature suggesting that products with fewer applications result in shorter closure time. However, direct comparisons of products have not been conducted. Most products resorb into the wound, therefore additional product may be beneficial to facilitate continued wound closure in the event the wound is improving with the use of the skin substitute graft. While there are no studies that directly assess the

number of applications required for wound closure, reports throughout the literature suggest the mean closure time is approximately 4 applications within 12 weeks. In the largest reported cohort of 12,313 ulcers treated with skin substitute grafts the mean number of applications was 3.7 with a standard deviation of 3.6 [13]. Moreover, products evaluated in the evidence review also reported a similar number of applications and time duration. Based on this evidence most ulcers would be expected to close within a maximum of 4 applications and 12 weeks. Ulcer size and immune compromise has been cited by expert opinion as grounds for additional applications secondary to extended time to heal. Therefore, an exception has been added to the policy to ensure that patients who have documented benefit of wound healing with the skin substitute graft use may receive additional applications or duration of care with documented clinical indications. The additional application or extension would be identified with a modifier and documentation in the medical record will be required to explain the clinical rationale for the exception and may be subject to medical review.

There is a clear need for further investigation and understanding of skin substitute grafts and their role in management of chronic wounds such as DFU and VLU. Future investigations will clarify the role of these products, compare products, establish standardized practice for utilization and allow a better understanding of products (and alternative treatments) most beneficial to healing diverse wounds, with the expectation of improved outcomes for patients suffering from these complex conditions.

Review of Evidence: Dystrophic Epidermolysis Bullosa

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

Fivenson et al. [164] reported the off-label use of Apligraf in 5 patients with recessive dystrophic epidermolysis bullosa who underwent syndactyly releasee.

Dystrophic Epidermolysis Bullosa Evidence Summary
Dystrophic Epidermolysis Bullosa Dystrophic epidermolysis bullosa is a rare disorder. Because this is a rare disorder, it is unlikely that RCTs will be conducted to evaluate whether OrCel improves health outcomes for this condition.

Review of Evidence: Second- Or Third-Degree Dermal Burns

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is bioengineered skin substitutes.

Comparators

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

Outcomes

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

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

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

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

Study Selection Criteria

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

Epicel

One case series from 2000 has described the treatment of 30 severely burned patients with Epicel [165]. The cultured epithelial autografts were applied to a mean of 37% of total body surface area (TBSA). Epicel achieved permanent coverage of a mean of 26% of TBSA, an area like that covered by conventional autografts (mean, 25%). Survival was 90% in these severely burned patients.

Integra Dermal Regeneration Template

A 2013 study compared Integra with split-thickness skin graft and with viscose cellulose sponge (Cellonex), using 3, 10´5 cm test sites on each of 10 burn patients [166]. The

surrounding burn area was covered with meshed autograft. Biopsies were taken from each site on days 3, 7, 14, and 21, and at months 3 and 12. The tissue samples were stained and examined for markers of inflammation and proliferation. The Vancouver Scar Scale was used to assess scars. At 12-month follow-up, the 3 methods resulted in similar clinical appearance, along with similar histologic and immunohistochemical findings.

Branski et al. reported on a randomized trial that compared Integra with a standard autograft-allograft technique in 20 children with an average burn size of 73% TBSA (71% full-thickness burns) [167]. Once vascularized (about 14 to 21 days), the Silastic epidermis was stripped and replaced with thin (0.05 to 0.13 mm) epidermal autograft. There were no significant differences between the Integra group and controls in burn size (70% vs. 74% TBSA), mortality (40% vs. 30%), and hospital length of stay (41 vs. 39 days), all respectively. Long-term follow-up revealed a significant increase in bone mineral content and density (24 months) and improved scarring in terms of height, thickness, vascularity, and pigmentation (at 12 months and 18-24 months) in the Integra group. No differences were observed between groups in the time to first reconstructive procedure, cumulative reconstructive procedures required during 2 years, and cumulative operating room time required for these procedures. The authors concluded that Integra can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

Heimbach et al. reported on a multicenter (13 U.S. burn care facilities) post approval study involving 222 burn injury patients (36.5% TBSA; range, 1% to 95%) who were treated with Integra Dermal Regeneration Template [168]. Within 2 to 3 weeks, the dermal layer regenerated, and a thin epidermal autograft was placed over the wound. The incidence of infection was 16.3%. Mean take rate (absence of graft failure) of Integra was 76.2%; the median take rate was 98%. The mean take rate of epidermal autograft placed over Integra was 87.7%; the median take rate was 95%.

Hicks et al. conducted a systematic review of Integra dermal regeneration template for the treatment of acute full thickness burns and burn reconstruction [169]. A total of 72 studies with 1084 patients (4 RCTs, 4 comparative studies, 5 cohort studies, 2 case control studies, 24 case series, and 33 case reports) were included in the review. Most patients (74%) were treated with Integra for acute burns, and the remainder (26%) for burn reconstruction. The take of the skin substitute was 86% (range 0 to 100%) for acute burn injuries and 95% (range 0 to 100%) for reconstruction. The take of the split-thickness skin graft over the template was 90% for acute burn injuries and 93% for reconstruction. There was high variability in reporting of outcomes, but studies generally supported satisfactory cosmetic results in patients who have insufficient autograft and improvement in range of motion in patients who were treated with Integra for burn reconstruction. There was an overall complication rate of 13%, primarily due to infection, graft loss, hematoma formation, and contracture. An infection rate of 18% was noted in a systematic review of complication rates in 10 studies that used Integra dermal regeneration template for burns [170].

Omega3 Wound

Luze et al. conducted a systematic review of the use of acellular fish skin grafts in burn wound management [171]. The reviewers identified 5 studies of Omega3 Wound but no RCTs. The identified studies were preclinical (animal), case series, retrospective observational, and 1 small (N = 21) cohort study. The review authors concluded that while the approach is promising, large-cohort studies are needed.

ReCell Autologous Cell Harvesting Device

Two RCTs have evaluated ReCell for deep dermal burns (Table 6) [172, 173]. In both studies, 2 similar areas with a burn injury in the same individual were randomized to the control or treatment intervention (i.e., all participants received both treatments). The studies differed in their populations, interventions, and outcome measures. In the earlier study, participants all had deep partial thickness burns, while in the 2019 study the population included individuals with mixed-depth, full thickness burns. Holmes et al. 2018 was a head-to-head comparison of ReCell alone versus skin grafting alone, and Holmes et al. 2019 compared ReCell in combination with skin grafting. In the earlier study, the primary effectiveness endpoints were the incidence of wound closure at 4 weeks and the incidence of complete donor site healing at 1 week. In the 2019 trial, the co-primary effectiveness endpoints were non-inferiority of the incidence of RECELL-treated site closure by week 8 when compared to the control, and the superiority of the 37% relative reduction in donor skin for the ReCell treatment when compared with the control.

Study results are detailed in Table 7 and limitations in Tables 8 and 9. Although the ReCell device was comparable to standard care on outcomes such as complete wound closure; confidence in the strength of the overall body of evidence is limited by individual study limitations and heterogeneity of populations, interventions, and outcome measures across studies. Additional RCT evidence in the intended use population is needed.

Table 6. Randomized Controlled Trials of ReCell for Thermal Burns- Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
Holmes et al NCT01138917 [36]	US	9	2010-2015	Individuals ages 18 to 65 years, with acute, deep partial-thickness thermal burns from 1% to 20% TBSA that required autografting for definitive closure.	*Active* ReCell device N = 101	*Comparator* Meshed STSG Treatment N = 101
Holmes et al NCT02380612 [37]	US	6	2015-2017	Individuals ages 5 years or older, with acute thermal burn involving 5% to 50% of TBSA that underwent autografting for definitive closure	*Active* ReCell device treatment applied over STSG N = 30	*Comparator* Meshed STSG Treatment Alone N = 30

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

Table 7. Randomized Controlled Trials of ReCell for Thermal Burns- Results

Study	Wound Closure (95% re-epithelialization) at 4 weeks	Wound Closure (95% re-epithelialization) at 8 weeks	Complete donor site healing at 1 week (100% re-epithelialization)	Relative Reduction in Donor Skin	Pain (VAS)	Participant Satisfaction and Scar Assessment	Adverse Events (Incidence)
Holmes et al, NCT011 38917 [36]							

ReCell	81/83 (97.6%)		21.8%		NSD at 16 weeks (data in figure)	NSD in subject satisfaction with appearance or in scarring at 16, 24, and 52 weeks (data in figures)	Treatment site: 35.6% Donor site: 4.0%
STSG	83/83 (100%)		10.0%				Treatment site: 21.8% Donor site: 6.9%
Between-group difference	−2.4% (95% CI: −8.4% to 2.3%)		p =.04				Treatment site: p=.0013 Donor site: 6.9% p =.25
Holmes et al, NCT023 80612 [37]							
ReCell plus STSG	50%	24/26 (92%)		368 (SD 150) cm2	NSD between groups in treatment area pain from week 1 to week 12 or week 52	NSD in subject satisfaction with appearance or in scar assessment at any time point	NSD between groups in pre-specified safety events 17 individuals (57%) experienced AEs at control and ReCell sites; 27% had mild AEs, 37% moderate AEs. 1 death, attributed to underlying condition.
STSG alone	48%	22/26 (85%)		264 (SD 119) cm2			
Between-group difference		-7.7% Upper limit of the 97.5% CI 6.4% (i.e. within the pre-defined non-inferiority margin 10%)		32%; p<.001			

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

Table 8. Randomized Controlled Trials of ReCell for Thermal Burns-Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Holmes et al (2018), NCT011 38917					
Holmes et al (2019), NCT023 80612	2. Participants had mixed depth full thickness burns			5. Unclear if 32% reduction in donor site skin is clinically meaningful	

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

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

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

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

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

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

Table 9. RCT of ReCell for Thermal Burns- Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Holmes et al (2018), NCT011 38917				83/101 participants evaluated in	noninferiority margin based on 90 subjects	

				modified per protocol analysis		
Holmes et al (2019), NCT023 80612				26/30 participants evaluated in per protocol analysis		3. confidence intervals not reported

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

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

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

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

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

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

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

Section Summary: Deep Dermal Burns

Epicel is FDA-approved under a humanitarian device exemption (HDE) for the treatment of deep dermal or full-thickness burns comprising a TBSA of 30% or more, with patient survival of 90%. Integra Dermal Regeneration Template has been compared with autograft in a within-subject study and with autograft-allograft in a small RCT with 10 patients per group. Outcomes are at least as good as with autograft or allograft, with a reduction in scarring and without risks associated with cadaver skin. This product has also been studied in a large series with over 222 burn patients, showing a take rate of 76% and with a take rate of epidermal autograft placed over Integra of 87.7%. The ReCell device has been evaluated in 2 RCTs. One RCT evaluated ReCell as an adjunct to meshed autologous skin grafting and the other compared ReCell head-to-head with skin grafting. Although the ReCell device was comparable to standard care on outcomes such as complete wound closure, confidence in the strength of the overall body of evidence is limited by individual study limitations and heterogeneity of populations, interventions, and outcome measures across studies. Additional RCT evidence in the intended use population is needed.

Review of Evidence: Tendon Repair

Graftjacket

Barber et al. reported an industry sponsored multicenter RCT of augmentation with Graftjacket human ADM for arthroscopic repair of large (>3 cm) rotator cuff tears involving two tendons [174]. Twenty-two patients were randomized to Graftjacket augmentation and 20 patients to no augmentation. At a mean follow-up of 24 months (range, 12-38 months), the American Shoulder and Elbow Surgeons score improved from 48.5 to 98.9 in the Graftjacket group and from 46.0 to 94.8 in the control group (p=0.035). The Constant score improved from 41 to 91.9 in the Graftjacket group and from 45.8 to 85.3 in the control group (p=0.008). The University of California, Los

Angeles score did not differ significantly between groups. Gadolinium-enhanced magnetic resonance imaging (MRI) scans showed intact cuffs in 85% of repairs in the Graftjacket group and 40% of repairs in the control group. However, no correlation was found between MRI findings and clinical outcomes. Rotator cuff re-tears occurred in 3 (14%) patients in the Graftjacket group and 9 (45%) patients in the control group.

Rashid et al. reported disruption of the native extracellular matrix with either Graftjacket or Permacol (porcine acellular dermis) as a patch overlay for rotator cuff repair in a small, controlled study with 13 patients [175]. The disruption was greater in the Permacol group and there was an immune response in 1 of 3 patients following use of the xenograft.

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

Review of Evidence: Surgical Repair of Hernias or Parastomal Reinforcement

Systemic Reviews

A 2013 systematic review evaluated the clinical effectiveness of acellular collagen-based scaffolds for the repair of incisional hernias [176]. The bioprosthetic materials could be harvested from bovine pericardium, human cadaveric dermis, porcine small intestine mucosa, porcine dermal collagen, or bovine dermal collagen. Products included in the search were Surgisis, Tutomesh, Veritas, AlloDerm, FlexHD, AlloMax, CollaMend, Permacol, Strattice, FortaGen, ACell, DermaMatrix, XenMatrix, and SurgiMend. Sixty publications with 1212 repairs were identified and included in the review, although meta-analysis could not be 21 performed. There were four level III studies (two AlloDerm, two Permacol); the remainder were level IV or V. The largest number of publications were on AlloDerm (n=27) and Permacol (n=18). No publications on incisional hernia repair were identified for AlloMax, FortaGen, DermaMatrix, or ACell. The overall incidence of a surgical site occurrence (e.g., postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, mechanical failure) was 82.6% for porcine small intestine mucosa, 50.7% for xenogeneic dermis, 48.3% for human dermis, and 6.3% for xenogeneic pericardium. No comparative data were identified that could establish superiority to permanent synthetic meshes.

AlloDerm as an Overlay
Espinosa-de-los-Monteros et al. retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases [177]. They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias.

However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

Comparisons Between Products

AlloDerm vs Surgisis Gold
Gupta et al. compared the efficacy and complications associated with use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair [178]. The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine submucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7 to 10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in 8 (24%) hernia recurrences. Fifteen (45%) of the AlloDerm patients developed a diastasis or bulging at the repair site. Seroma formation was only a problem in two patients.

AlloDerm vs FlexHD
A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery [179]. From 2005 to 2007, AlloDerm was used to repair large (>200 cm2) symptomatic complicated ventral hernias that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD was used to repair large, complicated ventral hernias in patients meeting the same criteria (n=40). The two groups were comparable at baseline. At one year follow-up, all AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, true recurrence) requiring a second repair. Eleven (31%) patients in the FlexHD group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

FlexHD vs Strattice
Roth et al. reported on a prospective study assessing clinical and quality of life outcomes following complex hernia repair with a human (FlexHD) or porcine (Strattice) ADM [180]. The study was funded by the Musculoskeletal Transplant Foundation, which prepares and supplies FlexHD. Patients were enrolled if they had a hernia at least six cm in the transverse dimension, active or prior infection of the abdominal wall, and/or enterocutaneous fistula requiring mesh removal. Eighteen (51%) of the 35 patients had undergone a previous hernia repair. After abdominal wall repair with the ADM, 20 (57%) patients had a surgical site occurrence, and nearly one-third had hospital readmission. The type of biologic material did not impact hernia outcomes. There was no comparison with synthetic mesh in this study, limiting interpretation.

Strattice vs Synthetic Mesh
Bellows et al. reported early results of an industry-sponsored multicenter RCT that compared Strattice (non-cross-linked porcine ADM, n=84) with a standard synthetic mesh (n=88) for the repair of inguinal hernias [181]. The trial was designed by the surgeons and was patient- and assessor-blinded to reduce risk of bias. Blinding continued through two years of follow-up. The primary outcome was resumption of activities of daily living at one year. Secondary outcomes included complications, recurrences, or chronic pain (i.e., pain that did not disappear by three months post-

surgery). At three-month follow-up, there were no significant differences in either the occurrence or type of wound events (relative risk, 0.98; 95% CI, 0.52 to 1.86). Pain was reduced from one to three days postoperative in the group treated with Strattice, but at three-month follow-up pain scores did not differ significantly between groups.

Strattice Versus No Reinforcement
Also, in 2014, the PRISM Study Group reported a multicenter, double-blinded, randomized trial of Strattice for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies [182]. Patients were randomized to standard stoma construction with no reinforcement (n=58) or stoma construction with Strattice as parastomal reinforcement (n=55). At 24-month follow-up (n=75), the incidence of parastomal hernias was similar for the two groups (13.2% of controls, 12.2% of study group).

Adverse Events

Permacol (porcine acellular dermal matrix) was reported in a case series of 13 patients to result in recurrent intestinal fistulation and intestinal failure when used for abdominal reconstructive surgery [183].

Section Summary: Surgical Repair of Hernias or Parastomal Reinforcement
Current evidence does not support a benefit of ADMs in hernia repair or prevention of parastomal hernia. Additional RCTs are needed to compare biologic mesh with synthetic mesh and to determine if there were a patient population that would benefit from these products.

SUMMARY OF CLINICAL EVIDENCE

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function ¾ including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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

effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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

Diabetic Lower-Extremity Ulcers
For individuals who have diabetic lower-extremity ulcers who receive AlloPatch, Apligraf, Dermagraft, Integra, or TheraSkin, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. RCTs reporting complete wound healing outcomes with at least 12 weeks of follow-up have demonstrated the efficacy of AlloPatch (reticular ADM), Apligraf and Dermagraft (living cell therapy), Integra (biosynthetic), and TheraSkin over the standard of care (SOC). The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.
For individuals who have diabetic lower-extremity ulcers who receive ADM products other than AlloPatch, Apligraf, Dermagraft, Integra, or TheraSkin, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients who only required a single application of the ADM. Studies are needed to further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of Graftjacket, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies. An RCT of Omega3 Wound (Kerecis) has been published and 2 larger RCTs are registered and reported as completed but have not been published. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Lower-Extremity Ulcers due to Venous Insufficiency
For individuals who have lower-extremity ulcers due to venous insufficiency who receive Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. RCTs have demonstrated the efficacy of Apligraf living cell therapy and xenogeneic Oasis Wound Matrix over the SOC. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

Dystrophic Epidermolysis Bullosa
For individuals who have dystrophic epidermolysis bullosa who receive OrCel, the evidence includes a case series. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. OrCel was approved under a humanitarian drug exemption for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. Outcomes have been reported in a small series (e.g., 5 patients). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

Surgical Repair of Hernias or Parastomal Reinforcement
For individuals who are undergoing surgical repair of hernias or parastomal reinforcement who receive acellular collagen-based scaffolds, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, QOL,

and treatment-related morbidity. Several comparative studies including RCTs have shown no difference in outcomes between tissue engineered skin substitutes and either standard synthetic mesh or no reinforcement. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

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

Practice Guidelines and Position Statements

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

National Institute for Health and Care Excellence

In 2023, NICE updated its guidance on the prevention and management of diabetic foot problems [184]. 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 [185]. The guidance recommended that additional research was needed to address the uncertainties regarding the potential benefits of ReCell [185]

U.S. Preventive Services Task Force Recommendations

Not applicable.

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BCBSM/BCNA Medical Policy History

Policy Effective Date	UM Committee Approval Date	Comments
07/17/2024	07/17/2024	Medicare Advantage policy established
09/18/2024	09/18/2024	Interim update: Under Inclusionary Guidelines: removed Q4116 from “may be medically necessary” list under second and third degree burns and moved to “may be medically necessary” list under breast reconstruction. Under Inclusionary Guidelines: removed Q4182 from “may be medically necessary” list under breast reconstruction and moved to “may be medically necessary” list under second and third-degree burns. Codes were listed correctly under coding information section.
02/12/2025	2/7/2025	Interim update – Policy updated to address Medicare Administrative Contractors (MAC) implementation of newly published Local Coverage Determination (LCD) *Skin Substitute Grafts, Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers (DFU) and Venous Leg Ulcers (VLU)*. Internal clinical coverage criteria for skin substitute services for DFU and VLU removed. Statement added to refer reader to appropriate service area LCD. No changes to the clinical criteria for other indications that are not related to DFU or VLU. Coding information related to DFU and VLU removed due to now in related Local Coverage Article (LCA). Clinical evidence section related to DFU and VLU removed due to now in LCD. Reference section updated with the removal of reference to DFU and VLU referenced in the clinical evidence section that was removed. Policy description on the first page updated to include broader indications for skin and tissue services. Foundational policy language updated to new version.
04/11/2025	04/11/2025	Interim update – Due to multiple delays in CMS Local Coverage Determination related to Skin Substitute Grafts, Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers (DFU) and Venous Leg Ulcers (VLU) (new anticipated date 1/1/2026) BCBSM will revert back to original policy that was approved 09/18/2024 with updated foundational language previously approved by UMC.