| FUTURE | Local Coverage Determination (LCD) |
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# LCD - Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers (L39756)

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# Contractor Information

| CONTRACTOR NAME | CONTRACT TYPE | CONTRACT NUMBER | JURISDICTION | STATES |
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| CGS Administrators, LLC | MAC - Part A | 15101 - MAC A | J - 15 | Kentucky |
| CGS Administrators, LLC | MAC - Part B | 15102 - MAC B | J - 15 | Kentucky |
| CGS Administrators, LLC | MAC - Part A | 15201 - MAC A | J - 15 | Ohio |
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# LCD Information

## Document Information

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Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

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## Issue

### Issue Description

This Local Coverage Determination (LCD) has been developed to create a policy consistent with current evidence. The focus of this LCD is skin substitute grafts/cellular and tissue-based products (CTP) for the treatment of diabetic foot ulcers (DFU) and venous leg ulcers (VLU) in the Medicare population. Diabetic foot ulcers and VLU have multifactor etiologies requiring targeted therapy. Both are associated with significant morbidity, including amputations, and diminished quality of life. Numerous remedies including systemic and local treatments have been proposed. Skin substitute grafts/CTP are marketed as treatments for these ulcers. Their effectiveness is currently an active area of investigation. Despite lack of definitive improved health outcomes in the Medicare population, coverage will be provided for skin substitute grafts/CTP having peer-reviewed, published evidence supporting their use as advanced treatment for chronic ulcers shown to have failed established methods to affect healing.

### Issue - Explanation of Change Between Proposed LCD and Final LCD

Based on comments and literature submitted during the open comment period the following changes have been made from the proposed to final policy:

- The term ‘Failure to respond’ has been replaced with the phrase ‘50% ulcer area reduction.’ Clarification of documentation requirements, additional definitions and other clarifying language added as recommended by commenters.
- Ankle-Brachial Index (AB) was replaced with vascular assessment, uncontrolled diabetes removed examples of contraindications and Class III compression requirement removed.
- Language added to clarify that standard of care is expected to be continued throughout the course of treatment.
- Application limit expanded from 4 to 8 and duration increased from 12 to 16 weeks based on submitted literature, comments received, and recommendations from SMEs.
- Use of the KX-modifier is added as an attestation of medical necessity for use over 4 applications.
- Further description of wastage documentation requirements added to the B & C article.
- Clarified use of product over exposed muscle, tendon, or bone when consistent with the labeled indication. The relevant ICD-10-CM codes were added to B & C article.
- Additional references were added to section on product classification and further clarification of porcine dressings were detailed in the LCD.
- Four systematic reviews and a new section entitled “Real World Evidence”(RWE) with summary of previous and newly submitted RWE were added to evidence review section.
- Additional literature was added for to product section for Apis, Derma-Gide, DermaPure, Grafix, Kerecis, NuShield, Phoenix wound Matrix, PuraPly AM, Restrata, Supra SDRM, and Theragenesis (Pelnac). Derma-Gide, Kerecis and NuShield were added to the DFU covered list.
- The product Oasis Tri-Layer Wound was found to have insufficient evidence for coverage in DFUs and VLUs, therefore, it was removed from tables 1 & 2 and placed in table 3 in the LCD.

- The evidence for DFU and VLU was placed in separate tables and corresponding sections of the B&C article to ensure clarity that coverage is based on evidence for the indication in which has been studied.
- Additional literature added to the Societal Guidance section.
- Analysis of Evidence section expanded and provides further discussion on the limitations of the current body of literature, clarity on the methodology utilized to assess the literature, and explanation for the above changes. Multiple published sources to aid investigators in development of high-quality future studies have been added as requested by Stakeholders.
- Additional ICD-10-CM codes with clarifications were added to Billing and Coding Article.

## CMS National Coverage Policy

This LCD supplements but does not replace, modify, or supersede existing Medicare applicable National Coverage Determinations (NCDs) or payment policy rules and regulations for skin substitute grafts/CTP for the treatment of diabetic foot ulcers and venous leg ulcers. Federal Statute and subsequent Medicare regulations regarding provision and payment for medical services are lengthy. They are not repeated in this LCD. Neither Medicare payment policy rules nor this LCD replace, modify, or supersede applicable state statutes regarding medical practice or other health practice professions acts, definitions, and scopes of practice. All providers who report services for Medicare payment must fully understand and follow all existing laws, regulations, and rules for Medicare payment for skin substitute grafts/CTP for the treatment of DFU and VLU and must properly submit only valid claims for service and products utilized. Please review, understand and apply the necessity provisions in the policy according to the Manual guidelines. Relevant CMS manual instructions and policies may be found in the following Internet-Only Manuals (IOMs) published on the CMS Web site:

**IOM Citations:**

- CMS IOM Publication 100-02, *Medicare Benefit Policy Manual*
    - Chapter 15, Section 50.4.1 Approved Use of Drug

- CMS IOM Publication 100-03, *Medicare National Coverage Determinations (NCD) Manual*,
    - Chapter 1, Part 4 Section 270.3 Blood-Derived Products for Chronic Non-Healing Wounds, Section 270.4 Treatment of Decubitus Ulcers and Section 270.5 Porcine Skin and Gradient Pressure Dressings

- CMS IOM Publication 100-04, *Medicare Claims Processing Manual*,
    - Chapter 17, Section 40 Discarded Drugs and Biologicals

- CMS IOM Publication 100-08, *Medicare Program Integrity Manual*,
    - Chapter 13, Section 13.5.4 Reasonable and Necessary Provision in an LCD
- CMS IOM Publication 100-04, Medicare Program Integrity Manual,
    - Chapter 17, Section 10 Payment Rules for Drugs and Biologicals

**Social Security Act (Title XVIII) Standard References:**

- Title XVIII of the Social Security Act, Section 1862(a)(1)(A) states that no Medicare payment may be made for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury.
- Title XVIII of the Social Security Act, Section 1862(a)(7). This section excludes routine physical examinations.

**Code of Federal Regulations (CFR) References:**

- CFR, Title 21, Volume 8, Chapter 1, Subchapter L, Part 1271.10 Human cells, tissues, and cellular and tissue-based products

## Coverage Guidance

### Coverage Indications, Limitations, and/or Medical Necessity

### Coverage Guidance

Compliance with the provisions in this LCD may be monitored and addressed through post payment data analysis and subsequent medical review audits.

### History/Background and General Information

Application of skin substitute graft/CTP for ulcer care indications other than DFU or VLU are not addressed by this LCD. Use of skin substitute graft/CTP must meet the reasonable and necessary threshold for coverage and these products must be used in accordance with their intended use as approved/regulated by the United States (U.S.) Food and Drug Administration (FDA).

Depending on the purpose of the product and its proposed functions, skin substitute graft/CTP are regulated by the FDA premarket approval (PMA) process, FDA 510(k) premarket notification process, or the FDA regulations for human cells, tissues, and cellular and tissue-based products (HCT/Ps). A product with proposed benefit to chronic ulcer healing does not assume the designation of a skin substitute graft/CTP. FDA classification and indication are not the sole determinants of designation as a skin substitute graft/CTP or provide the reasonable and necessary threshold for coverage.

Chronic DFU and VLU may be unresponsive to initial therapy or persist despite appropriate standardized care. A DFU or VLU that has failed to respond to standard of care treatment after 4 weeks (28 days) may be considered chronic and the addition of a skin substitute graft/CTP may be considered reasonable and necessary for certain patients.[1-6]

Patients receiving skin replacement surgery with a skin substitute graft/CTP should be under the care of a physician/non-physician practitioner for the treatment of their systemic disease process (e.g., diabetes mellitus, chronic venous insufficiency, or peripheral vascular disease). It is imperative that systemic disease be monitored and treated to ensure adequate healing of the ulcer.[2,6,8]

The medical record documentation must support the medical necessity for skin replacement therapy and the product’s use as an ulcer treatment, other than as a wound dressing or covering.

### Covered Indications

If the patient meets all criteria as outlined in this LCD, application of a skin substitute graft/CTP in the treatment of DFU and VLU is considered reasonable and necessary:

1. The presence of a chronic, non-infected DFU having failed to achieve at least 50% ulcer area reduction with documented standard of care (SOC) treatment (outlined below) for a minimum of 4 weeks with documented compliance.[6,8,9]
2. The presence of a chronic, non-infected VLU having failed to respond to documented SOC treatment (outlined below) for a minimum of 4 weeks with documented compliance.

4,6,10,11

For purposes of this LCD, SOC treatment includes[4,5,8,10,12,13]

- Comprehensive patient assessment (history, exam, vascular assessment) and diagnostic tests indicated as part of the implemented treatment plan.
- For patients with a DFU: assessment of Type 1 or Type 2 diabetes and management history with attention to certain comorbidities (e.g., vascular disease, neuropathy, osteomyelitis), review of current blood glucose levels/hemoglobin A1c (HbA1c), diet and nutritional status, activity level, physical exam that includes assessment of skin, ulcer, and vascular perfusion), and assessment of off-loading device or use of appropriate footwear.
- For patients with a VLU: assessment of clinical history (that includes prior ulcers, higher body mass index, history of pulmonary embolism or superficial/deep venous thrombosis, higher number of pregnancies, and physical inactivity), physical exam (edema, skin changes and vascular competence), evaluation of superficial or deep venous reflux, perforator incompetence, and chronic (or acute) venous thrombosis. The use of a firm strength compression garment (>20 mmHg) or multi-layered compressive dressings is an essential component of SOC for venous stasis ulcers.[2,4,5]

3. An implemented treatment plan to be continued throughout the course of treatment demonstrating all the following:[5,6,11,14]

- Debridement as appropriate to a clean granular base.[15,16]
- Documented evidence of offloading for DFU and some form of sustained compression dressings for VLU
- Infection control with removal of foreign body or nidus of infection.
- Management of exudate with maintenance of a moist environment (moist saline gauze, other classic dressings, bioactive dressing, etc.).
- Documentation of smoking history, and counselling on the effect of smoking on wound healing. Treatment for smoking cessation and outcome of counselling, if applicable.

4. The skin substitute graft/CTP is applied to an ulcer that has failed to heal or stalled in response to documented SOC treatment. Documentation of response requires measurements of the initial ulcer, pre-SOC ulcer measurements, weekly SOC ulcer measurements, post-completion SOC ulcer measurements following (at least) 4 weeks of SOC, ulcer measurements at initial placement of the skin substitute graft/CTP, and before each subsequent placement of the skin substitute graft/CTP. Failure to heal or stalled response despite SOC measures must have preceded the application for a minimum of 4 weeks and established SOC treatment must continue for the course of therapy. Continuous compression therapy for VLU must be documented for the episode of care.[8,10,17]
5. The medical record documentation must include the interventions having failed during prior ulcer evaluation and management. The record must include an updated medication history, review of pertinent medical problems diagnosed since the previous ulcer evaluation, and explanation of the planned skin replacement with choice of skin substitute graft/CTP product. The procedure risks and complications must also be reviewed and documented.[11-13,18,19]
6. The patient is under the care of a qualified provider for the treatment of the systemic disease process(es) etiologic for the condition (e.g., venous insufficiency, diabetes, neuropathy) and documented in the medical record.[5,6,11,19]

**Coverage requirements for skin substitute grafts/CTP**

To qualify as skin substitute graft/CTP the product must be:

1. A non-autologous human cellular or tissue product (e.g., dermal or epidermal, cellular and acellular, homograft, **OR** allograft), **OR** non-human cellular and tissue product (i.e., xenograft), **OR** biological product (synthetic or xenogeneic) applied as a sheet, allowing scaffold for skin growth, intended to remain on the recipient and grow in place or allow recipient's cells to grow into the implanted graft material[20] **AND**
2. Supported by high certainty supporting evidence to demonstrate the product's safety, effectiveness, and positive clinical outcomes in the function as a graft for DFU and/or VLU.[4,11] Substantial equivalence to predicate products does not allow sufficient evidence to support similar cleared products.

Note: Liquid or gel preparations are not considered grafts. Their fluidity does not allow graft placement and stabilization of the product on the wound.[18]

The following are considered reasonable and necessary[2,4-6,9,20]:

1. The maximum number of applications of skin substitute graft/CTP within the episode of skin replacement therapy (defined as 12 to 16 weeks from the first application of a skin substitute graft/CTP) is 8 applications.[21] The mean number of applications associated with complete wound healing is 4; however with documentation of progression of wound closure under the current treatment plan and medical necessity for additional applications, up to 8 applications may be allowed. Use of greater than 4 applications require an attestation from the provider showing that the requirements specified in the LCD have been met and the additional applications are medically necessary. In absence of this attestation, denial of the additional applications will occur. Please refer to the Billing and Coding article for instruction on reporting applications 5 to 8.
2. The usual episode of care for skin substitute graft/CTP is 12 weeks; however, some wounds may take longer to heal. An additional 4 weeks will be allowed, totaling 16 weeks from initial application, with documentation that includes progression of wound closure under current treatment plan.
3. The skin substitute graft/CTP must be used in an efficient manner utilizing the most appropriate size product available at the time of treatment. Excessive wastage (discarded amount) should be avoided by utilization of size appropriate packaging of the product consistent with wound size. The graft must be applied in a single layer without overlay of product or adjacent skin in compliance with the correct label application techniques for the skin substitute graft/CTP.
4. Only skin substitute grafts/CTP with labeled indications for use over exposed muscle, tendon or bone can be used in these cases and only in the absence of contraindications (e.g., infected, ischemic, or necrotic wound bed).

**Limitations**

The following are considered not reasonable and necessary[2,4-6,10,22]:

1. Greater than 8 applications of a skin substitute graft/CTP within an episode of care (up to 16 weeks).
2. Repeat applications of skin substitute graft/CTP when a previous application was Unsuccessful treatment is defined as increase in size or depth of an ulcer, no measurable change from baseline, and no sign of significant improvement or indication that significant improvement is likely (such as granulation, epithelialization, or progress towards closure).
3. Application of skin substitute graft/CTP in patients with inadequate control of underlying conditions or exacerbating factors, or other contraindications (e.g., active infection, progressive necrosis, active Charcot arthropathy of the ulcer extremity, active vasculitis, ischemia).[6]
4. Use of surgical preparation services (e.g., debridement), in conjunction with routine, simple or repeat skin replacement therapy with a skin substitute graft/CTP.
5. All liquid or gel skin substitute products or CTPs for ulcer care.[18]
6. Placement of skin substitute graft/CTP on infected, ischemic, or necrotic wound bed.[10,11]

**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; and when all procedures are 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 LCD, the general requirements for medical necessity as stated in CMS payment policy manuals, all existing CMS national coverage determinations, and all Medicare payment rules.

**Definitions**

**Autografts/tissue cultured autografts:** Include the harvest or application of an autologous skin graft. These products are designed to circumvent the challenges with autologous skin grafts in the treatment of chronic wounds, ulcers or burns.

**Chronic Wound:** A chronic wound may be defined as a wound physiologically impaired due to a disruption of the wound's healing cycle resulting from impaired angiogenesis, innervation, cellular migration, or other deficits for 4 weeks or longer.[3-5,23]

**Cellular and Tissue-Based Products (CTP) grafts (also called skin substitute graft):** Includes homologous human cellular and tissue products (e.g., dermal or epidermal, cellular and acellular, homograft or allograft), non-human cellular and tissue products (i.e., xenograft), and biological products (synthetic or xenogeneic) that form a sheet scaffolding for skin growth when applied in a sheet over an open wound or ulcer to augment closure or skin growth.[2,20]

There is a lack of clarity in the definition of skin substitute. For the purpose of this policy, skin substitute grafts will align with the AMA CPT codebook[20] description "non-human skin substitute grafts and biological products that form a sheet scaffolding for skin growth". This surface is not intended to be removed but grows into place or serves as base for new skin to grow.

**Cellular, acellular, and matrix-like products (CAMPs):** Cellular, acellular, and matrix-like products, also referred to as a cellular/tissue product (CTP).[24]

**Failed response:** Increased size or depth, no change in baseline size or depth, or no sign of improvement or indication that improvement is likely (such as granulation, epithelialization, or progress towards closing.

**Healed ulcer (completed healing):** 100 percent re-epithelialization without drainage or dressing noted on 2 occasions at least 2 weeks apart.[4]

**Scaffolding**: a support, delivery vehicle, or matrix for facilitating the migration, binding, or transport of cells or bioactive molecules used to replace, repair, or regenerate tissues.[25]

**Stalled Wound:** An ulcer that has entered a nonhealing or intransigent phase.[26]

**Standard of Care (SOC):** This policy refers to a Best Practice recommendation and it is not to be interpreted as the legal definition of SOC for either diabetic foot ulcers or venous leg ulcers.

**Wound dressing or coverings:** Applications applied to wounds as a selective barrier to maintain a clean wound environment, cover and protect wounds from the surrounding environment to promote optimal environment for wound healing.

**Summary of Evidence**

A literature search was conducted using the following key words: non-healing; ulcer; chronic; diabetic foot; foot ulcer; venous leg ulcer; guidelines; ulcer healing; skin substitutes; dermal skin substitute; human skin allograft; randomized trial; standard of care; venous leg ulcer; skin grafts; ulcer dressing; human derived products; animal derived products; FDA regulations. The literature search was filtered to locate articles within 5-10 years, full-text articles, clinical trials, and systematic reviews/meta-analyses (SR/MA). In general, improved health outcomes of interest include patient quality of life and function.

Evidence was analyzed to address the certainty of evidence that the change in outcome is due to the product being investigated and improves patients' outcomes. Case reports, case series and retrospective reports were not reviewed for product coverage due to low certainty evidence but used as an adjunctive measure for other aspects pertinent to this subject. Review papers, editorials and unpublished reports were not included in the analysis. Literature for use of products outside of DFU and VLU was not included in the evidence review. The literature for DFU frequently overlapped with diabetic lower extremity ulcers so both are included in the review.

**Evidence-Based Guidelines for Standard of Care**

Diabetic foot ulcers may affect up to 6% of Medicare beneficiaries with either Type I or Type II diabetes. Chronic wounds such as DFU and VLU impact patient quality of life due to impaired mobility, pain, and progressive morbidity.[2,4,6,7] Evidence-based guidelines indicate that SOC treatment of lower extremity ulcers (e.g., DFU and VLU) may include mechanical offloading, infection control, mechanical compression, limb elevation, debridement of necrotic tissue, management of systemic disease and medications, nutrition assessment, tissue perfusion and oxygenation, education regarding care of the foot, callus, and nail and fitting of shoes, as well as counseling on the risk of continued tobacco use. In addition, maintenance of a moist ulcer environment through appropriate dressings facilitates development of healthy granulation tissue and epithelialization and potentiates complete healing at an ulcer site. Dressings are an integral part of ulcer management by not only maintaining a moist environment but by stopping contamination and absorbing exudate.[5,6,8,10,12,13,19]

A comprehensive assessment of patients and their ulcers will also facilitate appropriate care by identifying and optimizing systemic causes of impaired healing. The presence of a severe illness or systemic disease and drug treatments with immunosuppressive agents and systemic steroids may inhibit ulcer healing by changes in immune response, metabolism, inflammation, nutrition, and tissue perfusion. Therefore, this information in conjunction with a detailed history of the ulcer itself is essential.[6,8,10]

Vascular evaluation is also vital for all patients with DFU or VLU to demonstrate adequate perfusion for wound healing. Palpation of pulses may be problematic in cases of medial arterial calcification and is not a reliable indicator of sufficient perfusion in diabetes. An objective, non-invasive measure of perfusion/oxygenation to determine if there is adequate flow for wound healing is helpful in predicting ulcer healing and/or the need for vascular intervention.

Venous ulcers require a series of diagnostic testing to verify superficial or deep venous reflux, perforator incompetence, and chronic (or acute) venous thrombosis. In this regard, venous duplex ultrasound is recommended and if the venous duplex ultrasound does not provide definitive diagnostic information, a venous plethysmography is recommended. Patients with mixed arterial and venous disease require a combination of arterial and venous noninvasive testing. The use of the most supportive high-compression method is strongly recommended in the treatment of venous ulcers. High strength compression may be applied using techniques such as multilayered elastic compression, inelastic compression, Unna boots, compression stockings, and others. The extent of compression should be modified for patients with mixed venous/arterial disease.[5,9,10]

The clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum recommend that patients with VLU have the ulcer classified using the Clinical class, Etiology, Anatomy, and Pathophysiology (CEAP) classification (confirmed by duplex scan). The Venous Clinical Severity Score (VCSS) is recommended to assess changes in response to therapy. Specific classification of venous disease is essential for standardization of venous disease severity and evaluation of treatment efficiency.[10]

The Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine has recommended a SOC treatment schedule for DFU that includes weekly to monthly ulcer evaluations of ulcer size and healing progress, infection control, debridement of all devitalized tissue and surrounding callus material, dressings that maintain a moist ulcer environment, control of exudate, and avoiding maceration of adjacent intact skin. Adequate glycemic control is also recommended to reduce the incidence of DFU and infections with periodic assessments of appropriate footwear or off-loading devices.[8,10,17]

**Evidence-Based Guidelines for Skin Substitute Grafts/CTP**

Skin substitute grafts/CTP are a heterogeneous group of biological and synthetic elements that allow the temporary or permanent exclusions of ulcers. Dermal substitutes may vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, but all have a mutual goal to attain resemblance with an individual's skin to the greatest extent possible.[17] Skin substitute grafts/CTP are considered an advanced therapy in addition to the established SOC treatment protocols for ulcer care to increase the chances of healing. In this regard, evidence-based guidelines recommend ulcer bed preparation prior to the application of any biologically active dressing which includes complete removal of slough, debris, and necrotic tissue.[19] Skin substitute grafts may be considered in conjunction with SOC treatment for DFU that have failed to demonstrate more than 50% ulcer area reduction after a minimum of 4 weeks of standard therapy.[8] For VLU, if substantial (≥50% ulcer area reduction) in ulcer improvement is not demonstrated after a minimum of 4 weeks of standard therapy, skin substitute grafts or CTP may be considered in addition to ongoing compression therapy.[4,6,10]

**Product Classifications**

Several classification systems have been proposed to categorize products; however, there is no universally accepted classification system. The products vary widely ranging from synthetic or natural, a variety of origins, additives and processing that impacts the final product.[27] Even products derived from the same origin are variable since these

products undergo proprietary processing. Skin substitute grafts/CTP may share similarities, but they are individually unique in their proprietary processing, thickness, cell count, presence of living cells and other features. In 2001 a classification system was proposed that put skin substitutes into 3 groups: Class I cultured epidermal equivalents alone, Class II dermal components which are from processed skin or have been manufactured with extracellular matrix proteins, and Class III both dermal and epidermal.[28] Kumar created a classification system in 2008 which divides products into 3 classes based on temporary, single and bilayer materials and included dermal or epidural and natural or synthetic into the classification.[29] The Davison-Kotler classification system was developed to classify the differences between the products based on functionality according to cellularity (acellular or cellular), layering (single or bilayer), replaced region (epidermis, dermis, or both), material used (natural, synthetic, or both), and permanence (temporary or permanent).[28] The result is products within the same class vary significantly and the impact on the product's function indeterminant in many cases.[30]

There are few studies comparing products which may allow functional assessment of products within the same class despite these differences. The AHRQ technical assessment of 76 products classified using the Davison-Kotler classification system found cellularity to be a significant differentiating factor among skin substitute grafts. The 2020 AHRQ reports[4] conclude due to processing variations each product must be studied in a "properly conducted clinical trial". A 2024 SR/MA[31] concludes "enough evidence is still lacking to determine a statistical difference between broad categories of CAMPs; and hence decision makers should consider published head-head comparative studies, real-world evidence and cost-effectiveness evidence between individual CAMPs to decide on which to use in practice." The International Consensus Document in Journal of Wound Care[24] explains "differences in product composition and the proprietary processing methods used by manufacturers make each CAMP unique, creating a need for more comparative studies."

There are several porcine derived products that function as surgical dressings. The role of these or other products utilized as a dressing disqualifies it for consideration as a skin substitute graft/CTP. Evidence to support a CTP role is necessary for all products including porcine derived.

**Potential Harm**

The potential harm of skin substitutes is challenged by lack of studies with high level of certainty 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 product delivered to and sustained within the wound site, and effect on the wound basement membrane is not fully understood.[32] 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.[32] Allergies and hypersensitivity to products may occur and limit the use of the product. Concerns have been raised regarding specific constituent molecules within the matrix, which have 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. There is concern that the microenvironment created may promote tumorigenesis or metastasis and the risk associated with various grafts has not been established.[33] 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 skin substitutes/CTP for DFU and VLU specifically. 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.[34] 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. Most of the reviewed literature did not represent racial diversity, and subjects were younger than 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 distribution.

**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.[4] This technical brief was developed to describe assorted products that may be considered skin substitute grafts in the U.S., 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. A systematic search of the published literature since 2012 was conducted for systematic reviews/meta-analyses, RCTs, and prospective non-randomized comparative studies of 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 derived 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 (2 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 containing intact cells to 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 9 skin substitute grafts with comparable classifications. It was noted that studies seldom reported clinical outcomes, such as amputation, ulcer recurrence at least 2 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 decreased 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 2 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, 1 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 whether 1 skin substitute graft product is superior to another.

The report acknowledges the potential risk of bias due to 20 of the 22 RCTs of the studies 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 cells, tissues, or cellular or tissue-based product (HCT/P) may be marketed without FDA preapproval and frequently misunderstand or mischaracterize the conditions they must meet for the product to be regulated solely for communicable disease risk. The Code of Federal Regulations (CFR) was referenced; 21 CFR 1271.10(a). Also, the 'FDA Announces Comprehensive Regenerative Medicine Policy Framework' was cited.[18]

**Systemic Review and Meta-Analysis**

Santema et al.[35] 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.

Products 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 compared 2 different types of skin substitutes, showing no product demonstrating a greater effect than 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.[35]

Jones et al.[36] systematic literature review sought to evaluate the effect of skin substitute grafts for the treatment of VLU. Using the Cochrane Collaboration methodology, 1 new trial was identified, generating a total of 17 RCTs,

including 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 1 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.

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 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 certainty of the studies reviewed was poor, thus affecting the risk of inherent bias. Many studies did not have inclusion criteria or sufficient 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.[36]

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.[37]

A 2020 systematic review/meta-analysis reported on complete healing rates for DFU with acellular matrix.[38] Nine RCTs 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 included GraftJacket, Oasis ultra matrix, DermACELL, Integra and AlloPatch. The heterogenicity reported varied with the outcome measures but the analysis was limited by high variety in wound types, differing products, number of applications, variations in SOC in control arms, different durations of treatment and risk of bias in the included studies.

A 2017 systematic review and meta-analysis identified 6 RCTs 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 4 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 $I^2$=74% which was 2.31 times more likely for complete wound healing than SOC at 12 weeks. The authors rated the strength of evidence as moderate and acknowledged the limitation related to lack of blinding. This meta-analysis is limited by risk of publication bias, lack of uniform ADM in the products, variation in dressing products with potential variation within SOC, different application numbers among 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.[39]

A 2012 systematic review of RCTs evaluating wound closure rates for patients treated with advanced wound matrix compared to SOC for VLU was conducted.[40] One RCT was found for 3 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[4] 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.

A 2017 systematic review and meta-analysis was conducted to evaluate literature on the efficacy and time sensitivity of human amnion/chorion membrane treatment in patients with chronic DFUs. A total of 7 RCTs were included in the analysis. The overall test effect in the group assessed at 4, 6, and 12 weeks was Z = 4.14 [P<0.0001; odds ratio (OR) 0.05; 95% confidence interval (CI) 0.01–0.21, Z = 4.28 (P<0.0001; OR 0.07; 95% CI 0.02–0.23), and Z = 4.96 (P<0.00001; OR 0.10; 95% CI 0.04–0.24, respectively. Authors conclude a significantly faster healing rate of DFUs resulted with utilization of human amnion/chorion membrane plus SOC as compared to SOC alone with optimal time to assess of 4 and 12 weeks. Limitations include studies which assessed the treatment of clinically infected wounds, use of various products among studies and small sample sizes in included studies.[41]

A 2022 systematic review and meta-analysis included RCT comparing dehydrated human amnion and chorion allograft (DHACA) to SOC. The pooled effect from 11 RCTs (n=655) suggest that DHACA was superior to SOC regarding the complete wound healing in both 6th and 12th week (RR = 3.78; 95% CI: [2.51, 5.70]; $P < 0.00001$) and (RR = 2.00; 95% CI: [1.67, 2.39], $P < 0.00001$ respectively). High of bias was reported in 10/12 studies due to lack of blinding, randomization, and others. They concluded overall quality of evidence as moderate. They report no conflict of interest with any of the suppliers of the products. Included studies included Amnioband[42,43], Grafix[44], EpiFix[45-48], AmnioExcel[49], Affinity[50, 46,48] and one unpublished report. The report is limited by the risk of bias associated with the individual studies, and heterogenicity between the studies.

A 2024 systematic review and meta-analysis evaluate the effectiveness of cellular, acellular, and matrix-like products (CAMPs) in management of DFU based on RCTs. The authors acknowledge that the different treatment approaches, surgical technique patient demographic and compliance with SOC are so variable between different RCT it is not possible to compare products against each other. To mitigate variables between the RCTs, wound closure outcomes were calculated as risk ratios and concluded CAMPs are superior to SOC for wound closure for DFU with a Risk Ratio (RR) of 1.72 [1.56, 1.90], $p< 0.00001$. "Enough evidence is still lacking to determine a statistical difference between broad categories of CAMPs; and hence decision makers should consider published head-head comparative studies, real-world evidence and cost-effectiveness evidence between individual CAMPs to decide on which to use in practice."[31]

A 2024 systematic review commissioned by International Working Group of the Diabetic Foot (IWGDF)[51] reviewed 262 studies across 9 interventions of wound care using Grades of Recommendation Assessment, Development, and Evaluation (GRADE) methodology. The interventions reviewed include debridement, dressings, oxygen and other gases, physical alteration of wound bed, skin substitutes, autologous products, growth factors and cellular therapies, pharmacological interventions, negative pressure wound therapy, and educational interventions. They reported the overall certainty for evidence for most wound healing interventions is low or very low. Twenty-six RCTs addressing skin substitutes were reviewed. The authors summarized "this body of research has greatly expanded over the last decade and now contains a significant number of enrolled people with diabetes related foot ulcers but presents a very complex review challenge given the non-uniformity of products, significant drop out rates, inconsistent blinding, and analysis that was often per protocol and not intention to treat." The report is divided into cellular, acellular, and autologous skin products of which all were high risk of bias except 1 pilot study with acceptable risk and overall low certainty of evidence. The authors warned positive results should be interpreted with caution, given the methodological challenges and bias in these studies. The summary notes an overall lack of evidence for wound healing interventions and calls for further high-quality investigations.

In summary, systematic reviews for skin substitute graft/CTP are challenged by multiple factors. These reviews pool various 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-certainty literature. The systematic reviews are limited by the quality of the included studies and heterogeneity between studies; even with positive outcomes, there is a lack certainty that the effect is due to the skin substitute/CPT interventions.

**Real World Evidence**

A large retrospective cohort study of US Medicare claims data pools 333,363 DFU and 122,012 VLU and concluded viable lyopreserved placental membrane (Grafix PL Prime) and viable cryopreserved placental membrane (Grafix Prime) was associated with "significantly decreased wound recurrence and performed as well or better for 1-year mortality and adverse outcome (AO) prevention compared with SOC and other CTPs." Other CTPs were also found to improve AO prevention and 1-year mortality compared to SOC alone. However, the authors acknowledge limitations such as having to assume correct diagnosis based on coding of the claims, no medical review to determine how CTPs were applied, use and compliance of SOC measures, and impact of other treatments or co-morbidities. The study was not sufficiently powered to evaluate associations with amputations. The other CTPs are not identified so it does not allow for comparison between products and if in related to specific products or the class in general. It does not assess for complications which may not have been reported in the claims data. The researchers feel this supports benefit of these products despite these limitations and acknowledge future research is needed stating studies comparing products, "such as head-to-head clinical trials or comparative effectiveness research with real-world evidence for branded products that includes adequate sampling for a longer window for recurrence, small area variation by geography, and mortality and amputation rates would improve our understanding of their clinical benefits."[52]

A retrospective propensity matched analysis to assess the comorbidities, treatment patterns and outcomes of Medicare patients with VLUs. Episode claims were used to document demographics, comorbidities, and treatments of Medicare patients who developed VLUs, as well as other outcomes, such as time to ulcer closure, complications rates, and hospitalizations.[13] Chronic venous insufficiency (CVI) patients (n=1225278) developed at least one VLU during the study time frame and 79% had their episode claim completed within a year. During the study period, 59% of patients developed another VLU with 38.4% of VLU episodes receiving documented VLU conservative care. In wounds that had not progressed at 30 days, advanced treatment yielded favorable outcomes (14.3-day reduction in

VLU length of treatment) when a matrix-like product was utilized on a weekly or biweekly basis as well as a >50% reduction in emergency department visits. The authors concluded Medicare enrollees have complex ailments that do not get addressed adequately resulting in high rates of complications. Patients at risk of VLU who receive early identification and advanced CAMP treatment demonstrated improved quality of life. This study is limited by the retrospective design, exclusion of 60% of claims for lack of wound description, poor quality data and risk of bias.[14]

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.[22] 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 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.

A multicentered private wound care practice conducted a retrospective review of Medicare patients receiving CTPs between January 2018 to December 2023.[21] The study utilized paired-sample t-test to compare wound area averages of 257 wounds before and after treatment with CTP over a 16-week period. There was a significant difference in the DFU area in $cm^2$ after the CTP series was complete ($M = 1.62$, $SD = 3.54$), compared to initial DFU areas ($M = 6.97$, $SD = 6.54$), $t(122) = 10.59$, $p <.001$, with similar findings for VLU. The investigators sought to determine the number of applications of CTPs needed to reduce wound size and promote closure. Mean age was 71 ± 14 with 64.6% male, 35.4% Black, 61.3 % white and 3.3% other. Eight wounds had exposed bone, muscle, tendon, or fascia (3.11%). Half received monotherapy and half combination therapy defined as several different CTP products throughout episode of treatment. The average DFU was 6.97±6.54 $cm^2$ at baseline and average VLU was 8.68±6.65 $cm^2$ at baseline. The study reports wound reduction after CTP applications up to 10 applications. Of note the reduction was exponentially greater during the first 5 applications (28.12->67.87% between applications 1-5 for DFU and 23.21->64.5% between applications 1-5 for VLU) with minimal change after 7 applications (77.88->80.21->80.01% after applications 8, 9, 10 respectively for DFU and 76.05->78.01->81.37% after applications 8, 9, 10 respectively for VLU). The mean number of applications to achieve closure was 5.77 ± 2.71 with 6.06 ± 2.74 for DFU and 5.57 ± 2.69 for VLU. They also reported Black had mean applications of 6.58 ± 2.23 as compared to White 5.36 ± 2.77. There were 9 products used in the study with 3 products use on 25 or more wounds. Affinity demonstrated 72.22% closure (n=36), NovaFix DL 40% closure (n=30) and Zenith 57.69% closure (n=26). PuraPly XT had 100% closure in 4 wounds. Strengths of this analysis include that all enrolled studies had been treated with SOC for four weeks prior to application of the CTP, and a diverse population inclusive of DFU and VLU offering generalizability to real world practices. This study provides valuable insight into the number of applications and impact of the applications over 16 weeks. Being retrospective, the study is not designed or adequately sized to determine if wound closure is affected by the CTP, compare individual products, or determine the efficacy of the products, for wound healing. Also see Grafix section.

**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 (63 vs. 38%; p = 0.01) respectively.[50] 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[53], and a case report and series.

**AlloPatch/Flex HD/AllopathHD/Matrix HD**

Zelen et al.[54] 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 Pliable[)] 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. Risk of bias from missing outcome data was reduced because the protocol requires that ulcers that were not healing exit the study at 6 weeks explaining the higher drop-out rate in the SOC arm and included these subjects in the ITT analysis. 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.[55] Due to the retrospective study design it is not clear if the wounds would have closed with continued SOC during this timeframe. A retrospective study[55] and bench study[56] provides additional support.

Literature was also found in breast reconstruction, rotator cuff repair, hernia repair, and lab research.[56-58]

**Amnioband**

Glat et al.[59] 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.[59]

DiDomenico et al.[42] 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.[42]

DiDomenico et al.[43] 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 6 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 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.

Additional literature includes a retrospective report.[60] Amnioband is also reviewed in the VLU section.

**Amnioexcel**

Snyder et al.[49] 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 $4.3 \pm 1.7$ 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.[49]

**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 12 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 1 application [n=10]), 2 applications [n=11], 3 applications [n=15], 4 applications [n=17] and 5 applications [n=59]) used per patient over 12 weeks. Ulcer recurrence was 5.9% in the Graftskin group and 12.9% in the control group at 6 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 5.[61]

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 2 different studies, it was difficult to assess risk of bias of the individual studies.[62]

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.[63]

Additional evidence of Apligraf is reviewed in the following sections Amnioband[59], Epifix[47], Theraskin, and retrospective study(n=226)[64] 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.[64]

**Apis**

A retrospective evaluation of 47 similar size chronic wounds treated with SOC (n=20) or the novel Manuka honey and hydroxyapatite sheet (BCMH) (n=27). They reported that wounds closed twice as fast in the BCMH group compared to the SOC group.[65] This is limited by lack of randomization, blinding, controls and risk of recall, attrition, and performance bias. This is insufficient evidence for coverage. Additional evidence is in the form of case series and lab research.[66-69]

**Artacent**

Sledge et al.[70] performed an observational study which included 26 patients with DFU (4.65±4.89cm$^2$) with failure to heal by >50% after 2 to 4 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 12 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 with 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 8 weeks. For all wound types (n=166) the closure rate was 41.6%

within 8 weeks with mean application of 2.12 products.[71] 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,[72] a retrospective report in total ankle replacement[73], and a bench paper[74]. 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.[75] This same study population was reported by Cazzell et al. after subjects were followed for 24 weeks.[76] These 2 studies were published in 2 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 DermaACELL arm remained healed at a significantly greater rate than the conventional care arm at 4 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.[76] 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 $cm^2$ and, 59/61 had exposed bone. Participants received treatment with acellular dermal matrix allograft (DermACELL). Up to 1 additional application was allowed if the wound required further coverage for exposed deep tissue, was less than 75% granulated at 4 weeks or less than 50% granulated after 8 weeks. Wound measurements were validated with a laser measurement device. Fourteen participants did not complete the 16 weeks of which 8 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 9 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.[77] This study is limited by lack of control arm or randomization, short term follow-up, and small sample size.

Additional studies are in the form of lab research.[58,78] Breast reconstruction and burns were not reviewed in this analysis.

**Derma-Gide**

Armstong et al. conducted a multi-centered RCT comparing purified reconstituted bilayer matrix (PRBM) to SOC for treatment of chronic DFU. Forty subjects were enrolled and after a 2-week screening phase; 20 received PRBM + SOC and 20 received SOC alone. No patients were lost to follow up. At 12 weeks, The ITT arm had 85% (17/20) ulcers healed compared to 30% (6/20) in the SOC arm (p<0.001). In the per protocol analysis, 95% (16/17) in treatment arm compared to 30% in SOC arm (6/20) healed (p<0.001). Healing time was an average of 37 days (95% CI: 26-48, median 21 days) vs 67 days (95% CI: 55-78, median inestimable) in the SOC arm.[79] This study was continued increasing sample size to 105 with 54 receiving PRBM + SOC and 51 SOC alone. Of the 80 who completed the per protocol analysis 92% (43/47) vs. 67% (22/33) (p = 0.005) reported healing at 12 weeks. In the ITT group 83% (45/54) vs. 45% (23/51), (p = 0.00004) reported healing at 12 weeks. Mean healing time was 42 days in PRBM group compared to 62 days in SOC arm. Mean application was 5.7 (SD:3.55); for PRBM grafts applied.

The study protocol required ulcer with percentage area reduction <50% at week 6 to be withdrawn so alternative treatment options. This resulted in a higher drop-out rate in the SOC arm compared to treatment (17 vs. 5).[80] Strengths of the study includes blinding of assessors, standardization of measurements (digital imaging confirmation), 2-week wash-out period, and clear protocol for managing PAR <50% prior to removing patients from the study arm and inclusion in ITT analysis to account for missing data points. Limitations to this study include differences in mean wound size between the treatment and SOC arm (>15%) leading to some concerns with randomization, short-term follow-up (12 weeks), and relatively small sample size.

Additional studies are in the form of a retrospective case series and bench report.[81-83]

**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.[84] 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 application frequencies 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 in Group A as compared to 21.4, 18.2 and 7.7% closure rates for groups B, C, and D, respectively.[85] This study is limited by small sample size, short-term follow-up, and high risk of bias due to concerns lack of reporting of randomization method and blinding.

Dermagraft was reported in a RCT comparing Dermagraft to Theraskin for DFU[86] (see Theraskin section). Dermagraft is also reviewed in the VLU section.

**DermaPure**

A prospective observational pilot study of 20 patients with treatment-resistant ulcers received a single application of DermaPure and monitored for 6 months on at least 7 occasions. Surface area decreased from 23-100% for all wounds and 60% achieved complete closure.[87] A retrospective observational analysis of patients (n=37) from 29 wound clinics demonstrated effective wound healing in 28 patients after a single application of DermaPure. They report all wounds healed by 56 weeks with an average healing time of 10.58 weeks with DFU healing in 8.21 weeks, VLU in 11.29 weeks and surgical/traumatic wounds in 11.8 weeks.[88] While the current evidence is insufficient for coverage, the single application product is promising.

Additional literature includes bench reasearch.[89,90]

**Epicord**

Tettelbach et al.[91] 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. The healing rate at 12 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 7 (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.[92]

**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."[45] 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 6 (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.[47]

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).[48] 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[4], Cochrane Systematic Review[37] and Paggiaro systematic review.[93] There is also a NICE innovation briefing on EpiFix.[94] 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 each 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.[46]

**Grafix**

Lavery et al.[44] 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 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. While the potential bias was high due to lack of description of randomization the groups were equally matched suggesting adequate randomization protocol. Missing outcome data was present in both groups and ITT analysis was conducted to reduce the potential for bias.

Raspovic et al. conducted a retrospective analysis using electronic health records from 58 wound care centers included 441 cases of DFUs treated with viable cryopreserved placental membranes (vCPM) Grafix PRIME and Grafix CORE).[95] This population included older patients with more co-morbidities and larger ulcers than RTC evaluating vCPM representing "real world data". Primary endpoint was the proportion of DFUs that achieved complete closure while other endpoints included time and number of grafts to closure, probability of wound closure by week 12 and the number of wound related infections and amputations. 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.

Sub analysis of this data provides data on probability of wound closure related to wound size. Using the Kaplan-Meier method report the probability of wound closure at 12 weeks was calculated as 71%, with 3% requiring amputation and 2% with wound-related infections. Smaller wounds were statically more likely to achieve closure with 72.3% of wounds between 0.25-2 $cm^2$ achieving wound closure, declining thereafter with 57.9, 44.9, 37.9 and 27.8% of wounds 2-5, 5-10, 10-25 and >25 $cm^2$ respectively achieving closure by the end of treatment. Wounds with progression during the first 4 weeks were much more likely to close than those that did not show such reduction with 77.8% (95% CI 70.78-83.89) of those with ≥50% reduction by week 4 achieving closure compared to only 22.5% (95% CI 16.6-29.5) that did not show such reduction. Wounds up to 25 $cm^2$ required 8 or less applications with those <2, 2-5, 5-10 and 10-15 requiring a mean of 4, 4, 5 and 8 applications respectively with a range of 3-10. Wounds >25 $cm^2$ (n=18) required a mean of 11 applications with a range of 1-23 with 27.8% achieving closure and median days to closure of 105 (56-187).

Average patient age was 63.7 with mean wound size 5.1 $cm^2$ with 3.9mm depth and 30% were larger than >3 $cm^2$ and 15% had exposed bone or tendon. Mean treatment with vCPM was 89.3 days (median 56.0) and average wound duration was 102 days prior to application of vCPM. They conclude the probability of closure by week 12 was 71% and the number of amputations and wound related infections was 13 (3%) and 9 (2%), respectively. The sub analysis demonstrated that the likelihood of wound closure decreased as wound size increased. "For wounds between 0.25 $cm^2$and 2 $cm^2$, 72.3% achieved complete wound closure, with a median time to closure of 21 days and 4 vCPM applications. However, for wounds larger than 25 $cm^2$ (representing 5% of the wounds in the study), only 27.8% of wounds achieved complete closure, with a median time to closure of 105 days and a median of 11(1-23) vCPM applications". In wounds that did not close 67.6% had a reduction in size by the end of treatment with 9.1% increasing during this period.[95]

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, however despite the limitations the findings were similar to previous RCT.[44] There was no comparison to wounds that did not have vCPM

applied, so results may not be generalizable to other CTPs.

**Grafix CORE**

Frykberg et al.[96] 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 the course of 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.[97] 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).[98] 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.[99] 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.[100]

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.[76] Other investigations (see section on DermACELL), include a Cochrane review analysis[35] and multiple studies investigating the role of the product in tendon repair and breast reconstruction.

**Integra**

Driver et al. 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.[101] 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, short- term follow-up and high risk of bias.

A prospective pilot study evaluated 10 patients treated with Integra bilayer wound matrix for DFU. The authors report 70% (7/10) achieved complete wound healing by 12 weeks.[102] 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.[103] This was a high certainty study, but the results were not applicable to chronic non-healing wounds.

A double-blinded, RCT compared Kerecis Omega3 Wound to porcine small intestinal mucosa (Oasis) for induced wounds. Punch biopsies were performed in 81 subjects of 4-mm size and graft placed over the wound. By day 28 days, 76 of the 80 wounds (95%) treated with fish skin ADM and 79 of the 82 wounds (96.3%) treated with porcine SIS ECM (Oasis) were healed. No autoimmune reaction was detected on serology before and after the study for autoimmune reactions. Application was repeated if material was not noted in the wound on follow-up. The authors conclude non-inferiority of the fish skin graft to the porcine.[104]

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]; significance at p<0 .047).[105] This study was continued to achieve sample size required for statistically significant to include 102 subjects. In the ITT analysis 56.9% of ulcers achieved complete wound closure in the treatment group as compared to 31.4% in the SOC group (p=0.0163) by 12 weeks. Subjects that had <50% closure at 6 weeks were withdrawn for alternative treatments per study protocol. The median number of applications was 6 for the Kerecis Omega3 group. Subjects were followed to 6 months to evaluate for ulcer recurrence with one recurrence in the SOC arm (6.7%) and 3 in the treatment arm (11.1%). Of the recurrences 3 out of 4 patients reported not utilizing appropriate offloading footware.[106] Strength of the study include wash-out phase, 6-month follow-up and reporting of recurrences representing longer term follow-up then most studies in this area. While the investigator was not blinded a blinded assessor was used for confirmation. Limitations include high risk of bias due to missing outcome data, small sample size, and variation in wound size between treatment and SOC group (>15% difference) which raises some concerns with randomization.

A 2024 international RCT of patients with DFU penetrating to bone, joint or tendon were randomized to fish skin graft (n=129) or SOC (n=126). The author reported 44% in fish skin group achieved completed wound closure by 16 weeks as compared to 26% in SOC (p<0.001, unadjusted) with additional healing of 46% and 55% in fish skin group and 32% and 38% in SOC at 20 and 24 weeks respectively. The median number of fish skin graft applications was 9 (8.29,2.47). No adverse events related to treatment were reported. Strength of the study include adequate sample size, prospectively designed end points and limitations include patients and wound care staff were not blinded, short term follow-up, increased weight/BMI in SOC group as compared to treatment group.[107] Risk of bias has some concerns as it is unclear if allocation sequence was concealed, however the randomization was computer generated with well-matched groups so seems to be of little concern, otherwise the study had low risk of bias.

Additional literature includes review papers,[108] case reports, case series, retrospective studies and a prediction model, and additional RCTs are ongoing.[108-110]

**Matriderm**

A 2013 prospective, RCT included 60 subjects with chronic DFUs. In this study subjects had a layer of Matriderm applied followed by split thickness skin graft or split thickness skin graft alone. The investigators reported reduce time to complete wound closure and higher rate of complete closure than skin graft alone. Matriderm's function was to aid in wound healing when placed with a split thickness skin graft and does not meet the definition of skin substitute graft/CTP. This does not provide sufficient evidence that Matriderm is effective as a skin substitute graft/CPT.[111]

Additional literature includes case studies in DFU, VLU, and mixed leg ulcers.[112-115]

**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 1 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 8-week treatment period (p=0.762); complete wound closure at day 70 (p=0.768); or mean time to closure (p=0.523).[9] 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.[116] 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 $cm^2$ (range 0.1 $cm^2$ – 33 $cm^2$); the median wound surface area was 2.1 $cm^2$. 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 3 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 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 limitations included a small sample size, and use of the same clinical investigator who performed all assessments during the study.[116] 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.[117] A literature review of bioactive glass applications introduced the potential of this product and called for further research to understand the clinical role.[118,119] 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 $p = 0.006$).[120] 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 withdrawal in the SOC group (12/20) resulted in high-risk bias due to missing outcome data. While this was per protocol if the wound was not healing it resulted in inadequate number of subjects for confidence in the end result of only 12 patients in the SOC and below the sample size necessary for conclusive results. 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.

Additional literature is in the form of case series and pre-clinical reports.[121-124]

**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) $cm^2$ which was increased to 7.4 ± 5.8 (range: 1.1–28.6) $cm^2$ 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 weeks (60%) and confirmed closure in 10 weeks (50%). Mean healing time was 12.8 ± 4.3 weeks. The average number of applications was 1.5 $\pm$ 0.8 applications (median of 1, range 1–3) over 16 weeks.[125] 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.[126] 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 with 32-59 patients.[127-129] 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 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 of 23 small ulcers, 5 of 15 medium, and 1 of 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.[130] Limitations of the study include the lack of randomization, control group, short term follow-up, small sample size, and risk of bias.

**NuShield**

A prospective, multi-centered, RCT enrolling 218 subjects compares a dehydrated amnion chorion membrane (dACM) product, NuShield + SOC (n=109) to SOC alone (n=109), for complex DFU. The study included subjects with DFU that extended into the dermis, subcutaneous tissue, tendon, capsule, bone or joint. At 12 weeks 50% of the NuShield group achieved wound closure compared to 35% of the SOC alone group (p=0.04) with median time to closure of 84 days. Baseline wound characteristics showed a mean wound size of 4.3±6.67 $cm^2$ and 4.4±7.32$cm^2$. The study has high risk of bias in multiple domains including lack of published protocol, lack of blinding, concerns with accuracy in wound measurements (ruler), and unclear definition and lack of validation of wound closure. The study reports no drop-out. The study is inclusive of a population of difficult wounds, such as exposed bone, which take longer and are more difficult to heal than smaller wounds. [131] While this study has several areas of bias it offers a larger sample size, lack of drop-out and more complex wounds than most similar studies.

Additional literature includes case report[132], retrospective report with 50 wounds,[133] and literature in talar dome lesions.

**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.[134] Limitations include small sample size, short term follow-up and some concerns for bias.

Niezgoda et al. 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.[135]

*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. 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 due to missing outcome with sample size too small to reconcile with ITT analysis. Strengths of the study were comprised of the randomization process and use of a digital wound measurement device.[136] While potential is demonstrated the evidence is not sufficient to determine the efficacy of the product based on small sample size, high risk of bias due to missing outcome data, and lack of any additional supporting literature to confirm findings.

**Phoenix Wound Matrix**

A prospective case series included 38 patients and measured the proportion of healed wounds with a 3D electrospun synthetic polymyer matrix (3DESPM aka Phoenix Wound Matrix) for hard-to-heal wounds with positive outcomes. This report is limited by case series design without controls, blinding, randomization, and short-term outcomes.[137]

**PriMatrix**

Lantis et al. (2021) 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.[138] 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. 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%.[139] Study is limited by observational design without control group.

Additional literature includes a basic science report[140] and a retrospective review.[141,142]

**PuraPly AM**

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.[143] 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.

A prospective non-interventional registry study (RESPOND) was developed to evaluate the clinical effectiveness of Puraply using RWD for management of partial and full thickness wounds. The investigators report wound closure of 49% (n=22) by 24 weeks and 62% (n=28) by 32 weeks.[144] A 2023 report of 3 combined registries using PuraPly for a variety of cutaneous wounds including a 2 single centered study of 41 and 86 patients and the RESPOND registry of 307 patients all of whom received PuraPly AM and followed for up to 48 weeks. The proportion of wounds closed were 72% (VLUs), 52% (DFUs), 63% (PIs), 95% (PSWs), and 67% (other etiologies). While this shows a promising trend for the product the lack of a comparative group precludes an understanding if the results were indeed due to the product or other variables which are not controlled within this study design.[145]

A retrospective non-inferiority study compared 989 DFUs with 325 treated with PuraPly AM and 664 treated with a cadaveric skin allograft (Theraskin). Medical records from 906 patients between 2016-2020 were analyzed. The PCMP versus CCSA frequencies of wound closure were comparable at all study timepoints including week 4 (12% vs 10%), 8 (27% vs 24%), 12 (39% vs 37%), and 24 (60% vs 64%), respectively; $P$ = .95. DFU extending at least through the epidermis into dermis, subcutaneous tissue, muscle, tendon or bone were included and the ulcer sizes ranged from ≥1 to ≤50 $cm^2$. The data analytics conclude non-inferiority of PuraPly to Theraskin.[146] There is not sufficient evidence to be confident in the products effectiveness for wound healing due to lack of control, blinding, and high risk of missing data and wide variability between reviewed patients.

**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.[147] A prospective cohort of 24 subjects with DFU treated with Restrata reported 75% (18/24) achieved complete wound closure by 12 weeks with average closure time 6.4 ± 2.5 weeks and mean application number of 4.3 ± 3.6.[148] 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 the wounds achieved compete closure at 12 weeks.[149] Another retrospective case series with 23 patients with lower extremity wounds reported 96% (22/23) achieved wound closure with mean healing time of 96.1 days and the majority requiring only a single application.[150] 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.

A RCT compared 46 patients with DFU treated with a synthetic electrosun fiber matrix to SOC over a 12-week period. The investigators reported that 56% (25/46) in the treatment group vs. 29% (21/46) in the SOC group. The mean number of applications to closure was 7.0 ± 3.7. The final number of participants analyzed was 37 and below that necessary based on the sample size calculation (40) which was already set at an unreliably low level. The authors acknowledge the small sample as a limitation and the modest results may be impacted by inclusion of larger wounds than some comparator studies in this area. Additional limitations of the study include high risk of bias due to lack of investigator blinding, no validation of outcome measurements by blinded source, and short-term following up.[151]

Additional literature includes retrospective case series and a lab report.[152-155]

**Supra SDRM**

A single centered RCT compares polylactic acid matrix (SUPRA SDRM) +SOC to collagen dressings + SOC for 30 chronic DFU. The study was a pilot study and sample size were not calculated a priori. There were 15 patients in each arm and 12/15 (80%) reported wound closure by 12 weeks in the PLA group compared to 5/15 (33% ) in the collagen dressing arm (p=0.025). No adverse outcomes were reported. The authors acknowledge the major limitation to the study is the sample size as well as a lack of generalizability, blinding, and short duration of follow-up.[156] While the study offers promising preliminary there is insufficient evidence to determine if the improvement is due to the intervention.

**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.[157] 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.[158] Limitations of the study include small sample size, lack of control, short term follow-up, and high risk of bias.

Sanders et al.[86] 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.[86]

Time to healing in the TheraSkin group was 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 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.[86]

Additional literature includes large retrospective matched cohort studies,[159-163] several cost-analysis, retrospective

data analysis,[160,164,165] case series,[166] and animal model studies[167] which are excluded from the analysis.

**Theragenesis (aka Pelnac)**

There is literature published on Theragenesis but not specific to DFU/VFU. There are 3 cases series for use in trauma wounds,[168-170] a retrospective report and case series on use in burns[171,172] a case series on use in necrotizing fasciitis and necrotic skin lesions[173], and an animal study[174]. There is a cases series (n=13) for use in exposed bone or tendon[175] contaminated wounds (n=5),[176] in combination with vacuum-assisted closure (n=14)[177] and a retrospective chart review on decreasing the number of days to apply split-thickness skin graft.[178] There is not sufficient literature for coverage for DFU/VLU.

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

**Amnioband**

Serena et al.[179] 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.[179]

**Apligraf (formerly GraftSkin)**

Falanga et al. (1998) performed a multicenter RCT to evaluate a 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.[180] 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.[181]

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.[182]

**DermACELL**

Cazzell[183] 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 2 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), insufficient criteria for investigators to follow when deciding if a second application would be appropriate, and a short-term follow-up. As an exploratory pilot study there was no expectation of statistical significance. While early results are promising the data is not sufficient for coverage for VLU.

**Dermagraft**

Harding et al.[184] 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.[184]

**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.[185] 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).[186] Limitations of the study include lack of blinding, short term follow up, and high risk for bias.

**Oasis Products**

*Oasis Wound Matrix:*

A 2010 RCT 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.[187]

Mostow and colleagues 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.[188]

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.[189]

*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%)."[3] 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.[190] The final 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.[191]

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.[192] The final results were not identified in the literature and do not appear to have been published, which potentiates the risk for publication bias.

**PuraPly**

The RESPOND registry is a prospective noninterventional study evaluating real world effectiveness of a PHMP (PuraPly) for wound healing. This registry included 28 sites and followed 307 subjects for up to 32 weeks. This included 67 VLU with a mean baseline wound area of 20.07cm2 and achieve wound closure frequency of 42% at 12 weeks and 73% by 32 weeks with median closure time of 22 weeks.[193] While these results are promising lack of a comparative group prohibits confirmation that the results are due to the product and no other factors therefore not sufficient for coverage. This study does provide RWD on a diverse population with large and complex VLU demonstrating the longer duration of time necessary for closure of these large wounds.

**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.[194] 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 reports[195] and a bench papers[196,197], animal models[198,199] and was included in a systematic review[40] (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[200] (RoB2) was used and is described in the Cochrane handbook[201] and utilized in GRADE[202]. This tool is different than the tool used in the AHRQ report[4] and the other systematic reviews published prior to 2019 (see the section addressing Systematic Reviews) when the updated tool was published. The 2024 systematic review by Chen et al. utilizes the Risk of Bias 2 tool.[51] 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 '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 1: Evidence for Covered Products for DFU**

| Skin Substitutes/CTP<br><br>(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).[50] | 1. Low risk [50] |
| 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.[59]<br><br>2. RCT (n=40) reported at 12 weeks 85% of the DFU in the Amnioband group healed compared with 25% in the SOC group.[42]<br><br>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. [43] | 1. High risk due to missing outcome data.[59]<br><br>2. Low risk [42]<br><br>3. Low risk [43] |
| Apligraf | DFU | 1.RCT (n=208) reported wound closure at 12 weeks of 56% for Apligraf and | 1. High risk due to lack of validation of outcome |

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|---|---|---|---|
| | | 38% for SOC.[61]<br><br>2.RCT (n=72) reported on wound closure at 12 weeks of 55.2% for Apligraf and 34.3% for SOC.[62]<br><br>3.RCT (n=82) reported on wound healing at 12 weeks of 51.5% for Apligraf and 26.3% for SOC.[63]<br><br>4.RCT (n=60) reported on wound closure at 6 weeks of 95% for EpiFix, 45% for Apligraft and 35% for SOC.[46] | measurements.[61]<br><br>2. Unable to complete due to pooling data from 2 different studies into one paper.[62]<br><br>3. High risk due to lack of validation of outcome measures.[63]<br><br>4. High risk due to missing outcome data.[46] |
| 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.[75,76]<br><br>2. Prospective study (n=61) of large complex wounds treated with DermACELL with 24.6% closure at 16 weeks.[77] | 1. Some concerns due to randomization.[75,76]<br><br>2. NA |
| Derma-Gide | DFU | 1. RCT (n=40) reported wound closure at 12 weeks of 85% of Derma-Gide group and 30% of SOC group (interim analysis).[79]<br><br>2. RCT (n=105) reported wound closure at 12 weeks of 83% of Derma-Gide group and 45% of SOC group.[80]<br><br>3. Retrospective case series and bench report.[81-83] | 1&2. Some concerns due to randomization.[80] |
| Dermagraft | DFU | 1. RCT (n=314) reported wound closure at 12 weeks of 30% of Dermagraft group and 18.3% in SOC group.[84]<br><br>2. RCT (n=23) reported wound closure at 20 weeks with 90.91% in Theraskin group and 66.67% in Dermagraft group. 86 | 1. Some concerns due to missing outcome data.[84]<br><br>2.High risk due to unclear randomization, potential deviations from intended intervention (no ITT) and lack of validation of outcome measurements. 86 |

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| | | 3. RCT (n=50) on wound closure at 12 weeks with 50% for Dermagraft and 8% SOC group.[85] | 3. High risk due to missing outcome data, lack of validation of outcome and unclear randomization.[85] |
| Epicord | | 1. RCT (n=155) reported wound closure at 12 weeks of 70% for EpiCord and 48% for SOC.[91] | 1. Low risk[91] |
| Epifix | DFU | 1. RCT (n=25) reported wound healing at 6 weeks in EpiFix group of 92% and 8% in SOC group.[45]<br><br>2. RCT (n=104) reported wound closure 12 weeks of 73% for Apligraf, 97% for EpiFix and 51% for SOC. [47]<br><br>3. RCT (n=110) reported on wound closure at 12 weeks of 70% EpiFix and 50% SOC in the ITT analysis.[48]<br><br>4. RCT (n=60) reported on wound closure at 6 weeks of 95% for EpiFix, 45% for Apligraft and 35% for SOC.[46] | 1. High risk due to lack of validation of outcome measurements.[45]<br><br>2. High risk due to unbalanced and missing outcome data.[47]<br><br>3. Low risk[48]<br><br>4. High risk of bias due to missing outcome data.[46] |
| FlexHD or AllopathHD | 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[203]<br><br>2. Literature also in breast reconstruction, rotator cuff repair, hernia repair, and lab research[56-58] and a retrospective report[55] | 1. High risk due to missing data outcomes.[203]<br><br>2. NA |
| Grafix stravix prime pl | DFU | 1. RCT (n=97) reported wound closure at 12 weeks was 62% in Grafix group and 21% in SOC group.[44]<br><br>2. Retrospective report (n=441).[95] | 1. High risk as randomization was not described, and missing outcome data. [44]<br><br>2. NA |

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| Graftjacket | DFU | 1. RCT (n=40) reported on wound healing at 12 weeks with a 67.4% reduction with Graftjacket and 34% with SOC.[97]<br><br>2. RCT (n=28) reported on wound closure at 16 weeks of 85.71% in Graftjacket arm and 28.57% in SOC.[98]<br><br>3. RCT (n=86) reported on mean wound healing time of 12 weeks was 30.4% with Graftjacket and 53.9% with SOC.[99]<br><br>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.[75,76]<br><br>5. These studies were included in a meta-analysis[100] and Graftjacket in another.[204] | 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.[97,98]<br><br>3. High risk due to unclear randomization, lack of validation of outcome measurements.[99]<br><br>4. Low risk[75,76]<br><br>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.[101] | 1. High risk due to missing outcome data.[101] |
| Kerecis Omega3/ Kerecis omega3, MariGen shield | DFU | 1. RCT (n=170) for healing in punch biopsy site.[103]<br><br>2.RCT (n=49) reported wound closure at 12 weeks of 67% for Kerecis and 32% for SOC.[105]<br><br>3. RCT (n=102) reported 56.9% wound closure by 12 weeks in Keracis group and 31.4% in the SOC group.[106]<br><br>4. RCT (n=255) wound closure by 16 weeks of 44% in Kerecis group and 26% in SOC.[107] | 1. NA<br><br>2. High risk of bias due to missing outcome data.[105,106]<br><br>3. Some concerns due to randomization.[107] |

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| NuShield | DFU | 1. RCT (n=218) reported on wound closure at 12 weeks with 50% closure for Nushield and 35% for SOC alone.[131]<br><br>Additional literature is case report[132], retrospective report with 50 wounds,[133] and literature in talar dome lesions. | 1. High risk of bias due to blinding and lack of validation of wound measurements.[131] |
| Oasis wound matrix | DFU | 1. RCT (n=26) reported no difference in closure time for Dermagraft (84.6% or Oasis Wound Matrix (76.9%).[134]<br><br>2. RCT (n=73) reported on wound healing at 12 weeks of 49% for Oasis wound matrix and 28% for Regranex gel.[135]<br><br>Additional literature on pressure ulcers. | 1. Some concerns due to no validation of wound measurements. [134]<br><br>2. Some concerns due lack of validation of outcome measurements.[135] |
| PriMatrix | DFU | 1. RCT (n=161) reported wound closure at 12 weeks of 59.5% for PrimMatrix arm and 35.4% for SOC arm.[138]<br><br>2. Prospective trial(n=55)[139], retrospective[141,142] and lab[140] | 1. High risk due to lack of blinding and analysis of outcome measures. [138]<br><br>2. NA |
| Theraskin | DFU | 1. RCT (n=50) reported on wound healing at 12 weeks was 76% for TheraSkin and 36% for SOC.[157]<br><br>2. RCT (n=23) reported wound closure at 20 weeks with 90.91% in Theraskin group and 66.67% in Dermagraft group.[86]<br><br>3. A small prospective study (n=29),[158] retrospective cohort studies,[159,160] and lab study.[205] | 1. Low risk[157]<br><br>2. High risk[86]<br><br>3. NA |

**Table 2: Evidence for covered Products for VFU**

| Skin Substitutes/CTP (Per sq cm unless otherwise stated) | Ulcer Type | Literature | Risk-of-bias Assessment |
|---|---|---|---|
| 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.[179] | 1. Low risk[179] |
| Apligraf | VLU | 1.RCT (n=275) reported on wound closure at 6 months of 63% for Apligraf and 49% for SOC.[206]<br><br>2. RCT (n=120) reported on wound closure at 24 weeks of 47% for Apligraf and 19% SOC.[181]<br><br>3. RCT (n=31) reported on wound healing at 12 weeks of 93.3% for | 1. Some concerns due to potential deviations from intended intervention (no ITT).[206]<br><br>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.[181]<br><br>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 |

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|---|---|---|---|
| | | Theraskin and 75% for Apligraf.[182] | planned sample size.[182] |
| Dermagraft | VLU | 1. RCT (n=366) reported on wound closure at 12 weeks of 34% for Dermagraft and 31% for SOC.[184] | 1. Some concerns due to high dropout rate (missing outcomes), and lack of validation of outcome measurements.[184] |
| Epifix | VLU | 1. RCT (n=53) reported wound reduction in 4 weeks was 62% for EpiFix and 32% for SOC.[185]<br><br>2. RCT (n=109) reported wound closure at 16 weeks for VLU was 71% for EpiFix and 44% for SOC.[186] The follow-up report included ITT analysis reported similar results with 50% in EpiFix group and 31% in SOC.[207] | 1. Low risk[185]<br><br>2. The 2018 paper was high risk due to potential deviations from intended intervention (no ITT) and missing outcome data[186] while the 2019[207] was high only due to missing outcome data. |
| Oasis wound matrix | VLU | 1. RCT (n=48) reported wound closure at 8 weeks of 80% for Oasis wound matrix and 65% for SOC.[187] | 1. Some concerns due to randomization process.[187]<br><br>2. High risk due to missing outcome data, lack of validation of |

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| | | 2. RCT (n=120) reported on wound healing at 12 weeks of 55% in Oasis group and 34% in SOC.[188]<br><br>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.[190]<br><br>4. RCT (n=84) reported on wound closure at 12 weeks of 71% Oasis and 46% SOC.[192] | outcome measurements.[188]<br><br>3. High risk of bias due to per-protocol analysis only.[190]<br><br>4. High risk due to per-protocol analysis, missing outcome data and uncertain method for outcome measurements or blinding protocol.[192] |

**Table 3: Evidence for Non-Covered Products**

| Skin Substitutes<br><br>(Per sq cm unless otherwise stated) | Evidence<br><br>(Published, peer reviewed literature to support use in chronic DFU/VFU) | Comment |
|---|---|---|
| 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 | |

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|---|---|---|
| Alloskin, Alloskin ac | Evidence in burn and orthopedics | Insufficient evidence for DFU/VLU |
| Allowrap DS or DRY | Literature in tarsal tunnel, thoracic outlet syndrome, proctectomy, and burns | Insufficient evidence for DFU/VLU |
| 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[44] | Insufficient evidence (see LCD section Amnioexcel) |
| Amniomatrix or Biomatrix, injectable, 1 cc | No literature identified | |

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|---|---|---|
| Amnio-maxx or amnio-maxx lite | No literature identified | |
| Amniorepair or Altiply | No literature identified | |
| Amniotext patch | Case report[127] | Insufficient evidence |
| Amniotext, per cc | No literature identified | |
| Amnio-tri-core amniotic | No literature identified | |
| Amniowrap2 | No literature identified | |
| Amniply, for topical use only | No literature identified | |
| Apis | Retrospective comparative study of 47 wounds[65], case serie[66] | Insufficient evidence (see section Apis) |
| Architect ecm px fx | No literature identified | |
| Artacent ac, 1 mg | No literature identified | |
| Artacent am | Observational study (n=26) [70] | Insufficient evidence |
| Artacent cord | No literature identified | |
| Artacent wound | Observational study (n=26)[70] | 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 | Case report[209] | |

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|---|---|---|
| Axolotl graft or axolotl dualgraft | Case report[210], literature in Mohs surgery | |
| 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[71], case series[72] | 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 | |

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|---|---|---|
| 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 | No literature identified | |
| Corplex, per cc | No literature identified | |
| Cryo-cord | No literature identified | |
| Cygnus | No literature identified | |
| Cygnus dual | No literature identified | |
| Cygnus, matrix | Lab study[211] | Insufficient evidence |
| Cymetra, injectable, 1 cc | No literature identified | |
| Cytal (formerly Matristem) | One RCT[9] and 2 case series [212,213] | 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 [214], Retrospective comparative report (n=18).[215] | Insufficient evidence |

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|---|---|---|
| Dermapure | Retrospective review (n=37)[88], Observational study (n=20)[87] | Insufficient evidence |
| Dermavest, plurivest | Case series[216], Lab study[217] | Insufficient evidence |
| Derm-maxx | No literature identified | |
| Impax, Impax dual layer membrane, Impax dual layer amniotic graft | 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, 0.1cc | Lab paper[218] | Insufficient evidence |
| EZ-derm | Evidence in burn. | Insufficient evidence for DFU/VLU |
| 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 | Bench[219]/ case report | Insufficient evidence |

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|---|---|---|
| Genesis amniotic membrane | No literature identified | |
| Grafix core, grafixpl core | Prospective study in 31 complex wounds achieving 59% closure.[96]<br><br>Retrospective report (n=441)[95]<br><br>Case series for VFU [220] | Insufficient evidence (see LCD section GrafixCORE) |
| Grafix plus | No literature identified | |
| Graftjacket Xpress, injectable, 1 cc | Lab study[97] | Insufficient evidence |
| Helicoll | Literature for split-thickness graft donor sites. | Insufficient evidence for DFU/VLU |
| Hmatrix | Evidence in breast surgery, head and neck, and hand/arm reconstruction, and abdominal wall closure. | Insufficient evidence for DFU/VLU |
| Hyalomatrix | Evidence in burns, trauma, skin cancer. Evidence in ulcer management includes case series[221-224] and a review article.[2254] | Insufficient evidence |
| Innovaburn or Innovamatrix xl | Review paper[226] | Insufficient evidence |
| Innovamatrix ac, Innovamatrix fs | No literature identified | |
| Innovamatrix pd 1mg | No literature identified | |
| Integra bilayer dermal matrix wound dressing | No literature identified | |

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|---|---|---|
| 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 | Insufficient evidence |
| Keroxx (2.5G/CC), 1 cc | No literature identified | |
| Lamellas xt, Lamellas | No literature identified | |
| Matriderm | One RCT[111] and case series[112-115] | Insufficient evidence for DFU/VLU (see LCD section Matriderm). |
| Matrion | No literature identified | |
| Matristem micromatrix, 1 mg, MAtristem wound matrix, Matristem burn matrix | One RCT[9] and 2 case series [212,213] | Insufficient evidence for DFU/VLU (see LCD section Matristem). |
| Mediskin | Evidence for split-thickness graft donor sites. | Insufficient evidence for DFU/VLU |
| Membrane graft or membrane wrap | No literature identified | |
| Membrane wrap-hydro | No literature identified | |
| Memoderm, Dermaspan, Tranzgraft, or Integuply | Case report[227] | Insufficient evidence |
| Mgl-complete | No literature identified | |

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|---|---|---|
| Microlyte, Matrix | Prospective observational study in 35 chronic wounds with 91% healing or improved at 12 weeks.[116] | Insufficient evidence (see LCD section Microlyte Matrix) |
| Miro3d | No literature identified | |
| Miroderm | Prospective pilot study in 7 wounds, [228] and prospective observational study of 38 ulcers[229] | Insufficient evidence |
| Mirragen adv wnd matrix | Bench papers[117,118]/ case series[121], small RCT [120]/ review paper[119] | 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 | No literature identified | |
| Neox cord 1K, Neox Cord rt, or Clarix cord 1K | Prospective trail (n=32)[125,126]basic science report, case series and small retrospective reports.[127-129] | Insufficient evidence (see LCD section Neox cord 1K). |
| Neox Flo or Clarix Flo, 1 mg | Case series[230] | Insufficient evidence |
| Novachor | No literature identified | |
| Novafix, Novafix dl | No literature identified | |

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|---|---|---|
| Novosorb Synpath Dermal Matrix | Book chapter (bench studies)[231] (review article[232] | Insufficient evidence |
| Nudyn dl or nudyn dl mesh, Nudyn sl or nudyn slw | No literature identified | |
| Oasis burn matrix | No literature identified | |
| Oasis tri-layer wound | 1. RCT (n=82) reported on wound closure at 12 weeks with 54% for Oasis Tri-layer and 32% for SOC.[136] | Insufficient evidence (see LCD section Oasis). |
| Omeza collagen matrix, per 100 mg | Bench papers[233-235] | 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 | Case series[137] | |
| Polycyte, for topical use only, per 0.5cc | No literature identified | |
| Porcine implant, Permacol | Evidence in hernia repair | Insufficient evidence for DFU/VLU |
| Procenta, per 200 mg | No literature identified | |
| Progenamatrix | Case series | |

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| Puraply, Puraply xt | Prospective, noninterventional study (n=307)[143] | Insufficient evidence (see LCD section Puraply) |
| Puraply, am | Prospective, noninterventional study (n=307)[143], case series.[236-238] | Insufficient evidence (see LCD section Puraply) |
| Rebound matrix | No literature identified | |
| Reguard, for topical use | No literature identified | |
| Relese | No literature identified | |
| Repriza | 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 | RCT (n=46) with complete wound closure over 12 weeks in 56% (25/46) in the treatment group vs. 29% (21/46) in the SOC group.[151]<br><br>Retrospective review 82 wounds[149] | 1. High risk of bias due to blinding and outcome measures.[151]<br><br>2. Insufficient evidence due to low certainty |
| Revita | No literature identified | |
| Revitalon | No literature identified | |
| Revoshield + amniotic barrier, per sq cm | No literature identified | |
| Sanopellis | No literature identified | |

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|---|---|---|
| Signature apatch | No literature identified | |
| Skin Sub, NOS | | |
| Skin substitute, FDA cleared as a device, not otherwise specified | | |
| Skin te | No literature identified | |
| Strattice TM | Evidence in abdominal wall closure/hernia repair | Insufficient evidence for DFU/VLU |
| Supra sdrm | One RCT[156] | Insufficient evidence for DFU/VLU (see LCD section supra sdrm) |
| 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 | Evidence in breast surgery | Insufficient evidence for DFU/VLU |
| Surgraft | No literature identified | |
| Symphony | No literature identified | |
| Tag | No literature identified | |

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| Talymed | One RCT[194], one case report[195], literature on use in bone wound healing[239] and lab reasearch.[240] | Insufficient evidence (see LCD section Talymed) |
| Tensix | Case reports[227] | Insufficient evidence |
| Theragenesis | Retrospective report, case series,animal studies, evidence in trauma, burn, necrotizing fascititis and other conditions but not specific to DFU/VLU.[168-171,173-178] | Insufficient evidence for DFU/VLU |
| Transcyte | Literature in burns | Insufficient evidence for DFU/VLU |
| Truskin | No literature identified | |
| Unite biomatrix | Abstract and case report[241] | 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)[242] | Insufficient evidence |
| Woundfix, Biowound, Woundfix plus, biowound plus, Woundfix xplus or biowound xplus | No literature identified | |
| Woundplus membrane or e-graft | No literature identified | |

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|---|---|---|
| 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 | No literature identified | |
| Zenith amniotic membrane | No literature identified | |

**Application changes**

Establishing application limits is challenging and reflects the shortcomings of the current evidence including lack of standardized protocol, missing data on frequency of application, and lack of studies directed at this specific area. Many reports do not include information on consistent outcome measures, co-morbidities, or other risk factors that may impact application frequency. This is further complicated as products have set parameters for weekly application changes, despite lack of evidence to support this labeling so the true number of applications necessary for the product may not be known. Some products remain in place with 1-2 applications per episode of care. Other products are reapplied weekly or biweekly and some studies report changes only when there has been a slowed progression of healing. Because the labeled use for the products is left to manufacturer discretion and not based on evidence, this creates a dilemma on understanding what factors should be considered regarding when to reapply products and what application frequency is optimal for wound healing. This is exemplified by EpiFix, which is the most extensively studied product. The label recommends weekly applications, yet subsequent research demonstrates weekly application is not always necessary to achieve wound healing. In fact, a median of 2.5 applications in 12 weeks has been reported to complete wound healing. 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 decrease in wound healing.[37]

The following retrospective reports are reviewed in the Real-World Evidence Section of this LCD in greater detail. A 2021 retrospective cohort study by Armstrong et al. utilizing Medicare Limited Dataset by Armstrong et al. patients report the average number of applications was 3.7(3.6) in Group 1 (n=12,313). In Group 2 (n=1131) the average number of applications was 4.9(3.8) in the following parameter group and 3.5(3.3) in the not following parameter group.[22] This report demonstrates the average number of applications is 4, but that additional application are common up to 8 applications.[22]

A 2024 retrospective review (n=257) offers specific data on application frequency. They report a reduction in wound size is exponentially greater during the first 5 applications (28.12->67.87% between applications 1-5 for DFU and 23.21->64.5% between applications 1-5 for VLU) with minimal change after 7 applications (77.88->80.21->80.01% after applications [8, 9, 10] respectively for DFU and 76.05->78.01->81.37% after applications [8, 9, 10] respectively

for VLU).[21] The episode of care was 16-weeks for closure.

**Societal Input**

**National Institute for Health and Care Excellence (NICE) Diabetic foot problems: prevention and management**[243]

The clinical guideline on diabetic foot problems developed by multidisciplinary foot care service providers considers dermal or skin substitute grafts as an appropriate addition to SOC in treating diabetic foot ulcers only when healing has not progressed with SOC treatment.

**International Working Group on the Diabetic Foot (IWGDF)**[13]

IWGDF recommends the consideration of placental-derived products as an adjunctive treatment to the best standard of care when SOC 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).

IWGDF commissioned an updated systematic review published in 2024 which demonstrates low quality evidence for skins substitute products (see Systematic Review section). The IWGDF/EWMA has published 21-point checklist of reporting standards of studies and papers representing markers of quality research in DFU which may aid future investigators for high quality study designs.[244]

**Wound Healing Society (WHS)**[5,12]

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.[5]

**Society for Vascular Surgery/American Podiatric Medical Association/Society for Vascular Medicine (SVS/APMA/SVM)**[8]

The SVS/APMA/SVM published a joint evidence-based guideline using GRADE system for the management of patients with diabetes, including treatment of diabetes related chronic foot ulcers.

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)**[11]

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 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 function 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.

**Journal of Wound Care International Consensus Document**[24]

A consensus document was published by the Journal of Wound Care which included an international panel of experts and the recommendations scrutinized by an expert review board. This project was sponsored by multiple manufacturers of skin substitute graft/CTP products, and their evidence reviewed was not conducted through systematic review although they provide an excellent summary of SR/MA conducted on CAMPS for wound healing. They utilize the term CAMP rather than skin substitute graft or CTP and provide the definition as "cellular, acellular

and matrix-like product, also referred to as a cellular/tissue product (CTP)." They define scaffolding as "three-dimensional extracellular matrix analogues— natural, synthetic or a combination of the two—that contribute to cell adhesion, proliferation and differentiation and are compatible with neovascularization (an essential process for keeping cells alive)." The document provides an extensive review on wound healing mechanisms and addresses the challenges in making decisions about which product to use for a particular indication due to limitations in the current literature. They explain there are few comparative studies demonstrating superiority of one CAMP over another or systematic reviews comparing classes of products to each other. "Differences in product composition and the proprietary processing methods used by manufacturers make each CAMP unique, creating a need for more comparative studies." They state CAMPs may be used on wounds of all etiologies after failure to respond to SOC and risk factors and co-morbidities optimized. They promote early application and defined treatment goals. The document provides best practice guidelines for wound preparation, application, and follow-up. They explain "based on clinical experience, a CAMP is typically left in place after the first application for 7–14 days, or as needed, depending on the product. However, the time period needs to be individualized, based on holistic assessment of the patient, and wound and the manufacturer's recommendation for use." They also provide specific measures for interval reassessment which should be done at every subsequent visit and if there is not progression of closure new treatment goals determined. The document states, "reapplication often occurs weekly or every other week, based on the wound's closure rate and appearance and the manufacturer's recommendations" and prior to reapplication wound care and determining if reapplication is appropriate (e.g., not if there is no improvement in hard-to-heal wounds) is necessary. They conclude with an understanding "there needs to be ongoing support for research to better understand the physiological effect and modes of action of CAMPs, and "research studies need to have longer follow-up periods to determine the full patient and cost benefits of CAMPs" They acknowledge "this level of evidence is critical to obtain universal acceptance and availability of the products".

**The Wound Care Collaborative Community (WCCC)**

The WCCC developed a Wound Care Expert/FDA- Clinical Endpoints Project (WEF-CEP) to develop meaningful outcome endpoints for measuring wound healing. A survey, including providers and patients, combined with literature for data were published in 3 manuscripts. These documents support 15 wound care endpoints. The priority wound care endpoints are percentage area reduction in 4-8 weeks, percentage volume reduction by study end, time to heal, increased physical function/ambulation, cost effectiveness, reductions in odor, social isolation, analgesic use, recurrence, depression, infection, bioburden, cost of treatment, pain, and amputation.[245-247]

**Analysis of Evidence (Rationale for Determination)**

The overall evidence to support skin substitute graft/CTP is low quality.[4,51] Many factors contribute to the heterogeneity of randomized controlled trials including poor study designs, small sample sizes, lack of comparators or standardization of practices, lack of long-term efficacy and safety data, high risk of bias, inconsistent definitions and outcome measures, and lack of blinding. Therefore, this evidence is challenged by a low level of certainty in the estimated wound-healing effect attributable to these products and studies must be interpreted with caution. Potential risks with these products are not adequately addressed due to lack of long-term safety data. 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). Given the low confidence of evidence and moderate to high risk of bias in most studies the overall effectiveness of these products is still uncertain. Efforts to provide guidance and education to enhance the quality of studies has been published including AHRQ Technical assessment[17], the Journal of Wound Care International Consensus Document[24], International Working Group on the Diabetic Foot[244], and Serena et al. consensus principles for wound care research.[248]

This is compounded by the majority studies being sponsored by the manufacturer of products. A non-industry

sponsored trial comparing a cellular and acellular wound matrix to SOC for DFU followed for 28 weeks reported no difference in wound closure or percentage area reduction between the three groups.[190] Unlike most studies which report a higher outcome for the skin substitute graft/CTP after 12 weeks they did not find superiority to the SOC arm which had a notably higher healing rate (73.7%) than most industry sponsored trials. The higher healing rate in the SOC arm was comparable to those found by a European Study Group (77%).[249] This highlights the need for high-quality studies comparative studies to investigate how these products compare to each other, as classes of products, and how skin substitute graft/CTP compared to other wound treatment modalities to determine optimal care for patients suffering from these debilitating conditions.

Despite the limitations, a promising trend within the literature towards outcome improvement with few adverse events is identified. It is well established these wounds are difficult to treat and are responsible for significant morbidity and even mortality. Therefore, given the potential benefits in a high-risk population a limited coverage position for skin substitute graft/CTP in specific patient populations was taken to facilitate access to these products with clinically meaningful net-positive clinical outcome(s) validated by evidentiary review. Specifically, wound closure attributable to the individual product(s) proven in clinical trials with meaningful degree of certainty is required. This contractor aligned recommendations from AHRQ, IWGDF and SVS/APMA/SVM. However, given the heterogenicity and low quality of studies reviewed in their analyses, we employed a standardized tool, RoB2[200], to provide assessment of each RCT using the same criteria and measures to evaluate if the individual product had meaningful level of supporting evidence that it is effective for wound healing. Additionally, we looked for at least one additional clinical trial that showed equivalent healing rates to the RCT confirming the utility of each product. To be considered for coverage, each product must have published clinical trial(s) that evaluate a well-defined patient population of sufficient sample size and use a robust study design to convey confidence in the results.

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/CTP.

Retrospective data provide data on application frequency and suggest the mean closure time is approximately 4 applications within 12 weeks with an upper range of 8 applications in 16 weeks. In the largest reported cohort of 12,313 ulcers treated with skin substitute grafts/CTP the mean number of applications was 3.7 with a standard deviation of 3.6.[22] A retrospective cohort which offers data specific to application frequency reported a mean number of applications to achieve closure was 5.77 ± 2.71 $cm^2$ with 6.06 ± 2.74 for DFU and 5.57 ± 2.69 $cm^2$ for VLU. They also found the reduction in wound closure was exponentially greater during the first 5 applications with minimal change after 7 applications.[21] Another report shows smaller wounds were more likely to achieve closure than larger ones, and those that achieved ≥50% closure by week 4 have the greatest potential for complete closure. The larger the wound the more applications received but the majority was still used 8 or less. The longest interval in the report for wound closure was wounds >25 $cm^2$ and the median in this group was 105 days for wound closure (when it was achieved) supporting the upper time limit of 16 weeks.[95] Moreover, products evaluated in the evidence review also reported a similar number of applications and time duration. These reports suggest that wounds that have slowed or have prolonged healing are less likely to achieve closure with additional applications/time and other treatment modalities may be optimal and warrants further investigation into optimal treatment of these wounds. Based on this evidence most ulcers would be expected to close within a maximum of 8 applications within 16 weeks establishing the limitations set within the policy to be consistent with current evidence and stakeholder and provider input provided during the open comment period.

Due to proprietary processing each product has unique features. There is a lack of comparative studies to understand if and how products within the same class share similar function. There is not sufficient evidence that a class of products or predicate devices are equal in terms of effectiveness for wound closure. Both the 2012 and 2020[4] AHRQ reports that conclude due to processing variations each product must be studied in a "properly conducted clinical trial". A 2024 SR/MA[31] concludes "enough evidence is still lacking to determine a statistical difference between broad categories of CAMPs; and hence decision makers should consider published head-head comparative studies, real-world evidence and cost-effectiveness evidence between individual CAMPs to decide on which to use in practice." The International Consensus Document[24] in the Journal of Wound Care explains "differences in product composition and the proprietary processing methods used by manufacturers make each CAMP unique, creating a need for more comparative studies."

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. Given the rapid growth the intent is this policy will be reviewed every 12 months with updates to products/coverage as indicated.

# General Information

**Associated Information**

NCD 20.29 Hyperbaric Oxygen Therapy

270.3 Blood-Derived Products for Chronic Non-Healing Wounds

270.4 Treatment of Decubitus Ulcers

270.5 Porcine Skin and Gradient Pressure Dressings

L34032 Debridement Services

L39575 Amniotic and Placental Derived Product Injections and/or Applications for Musculoskeletal Indications, Non-Wound

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N/A

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# Revision History Information

| REVISION HISTORY DATE | REVISION HISTORY NUMBER | REVISION HISTORY EXPLANATION | REASONS FOR CHANGE |
|---|---|---|---|

# Associated Documents

**Attachments**

N/A

**Related Local Coverage Documents**

**Articles**

A59618 - Billing and Coding: Skin Substitutes Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

A59941 - Response to Comments: Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

**LCDs**

DL39756 - Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers

**Related National Coverage Documents**

N/A

**Public Versions**

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