



Skin Substitutes Clinical Coverage Criteria

Overview

Patients with chronic wounds, such as diabetic foot ulcers and venous leg ulcers, experience loss of function, pain, wound recurrence, and significant morbidity. Care for chronic wounds involves removing necrotic tissue, applying dressings that maintain a moist wound environment, treating wound infections, and restoring blood flow to the wound site. Four weeks of standard of care without achieving a 50% reduction in wound size may signal the need for a change or additional therapies. If chronic wounds fail to respond to standard of care, skin substitutes may be used as an adjunct to established chronic wound care methods to increase the likelihood of complete healing.

There is a lack of clarity in the definition of skin substitutes, also known as skin substitute grafts. For the purpose of this policy, skin substitute grafts will align with the AMA CPT codebook definition “non-autologous human skin (dermal or epidermal, cellular or acellular) grafts (e.g., homograft, allograft), non-human skin substitute grafts (i.e., xenograft), and biological products that form a sheet scaffolding for skin growth.” This surface is not intended to be removed but grows into place or serves as base for new skin to grow.

Policy

This Policy applies to the following Fallon Health products:

- Fallon Medicare Plus)
- MassHealth ACO
- NaviCare HMO SNP
- PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
- Community Care

Prior authorization is required for skin substitutes. Documentation in the medical record specifically addressing circumstances as to why the wound has failed to respond to standard wound care treatment after a minimum of 4 weeks and referencing the specific interventions that have failed is required.

Fallon Health Clinical Coverage Criteria

Fallon Health Clinical Coverage Criteria for skin substitutes applies to Fallon Medicare Plus, NaviCare and Community Care members.

Initial requests for skin substitutes for diabetic foot ulcers and venous leg ulcers will be authorized for up to 4 applications. Authorization for additional 5-8 applications within 16 weeks of the first application require documentation of progression of wound closure: (1) measurable decreased size or depth of ulcer, or (2) Evidence of tissue granulation, epithelialization or progress towards closure.

The usual episode of care for skin substitutes for diabetic foot ulcers and venous leg ulcers 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.

The expectation is that one specific skin substitute graft product will be used for the entire episode of wound care. The rare clinical circumstance necessitating switching to a different product must be clearly supported.

The skin substitute 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 skin substitute 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.

Continued coverage for skin substitutes is contingent upon evidence documented in the plan member's medical record that the wound is improving in response to the wound care being provided. Since it is neither reasonable nor medically necessary to continue a given type of wound care in the absence of wound improvement, it is expected that the wounds response to treatment will be documented in the medical record at least once every 30 days for each episode of wound treatment and made available to the contractor upon request.

Diabetic foot ulcers

1. One of the following skin substitute graft products may be considered medically necessary for the treatment of chronic full-thickness neuropathic diabetic foot ulcers that have failed to achieve at least a 50% reduction in wound area after a minimum of four (4) weeks of standard wound care with documented compliance:¹
 - A2019 Kerecis omega3 Marigen shield, per square centimeter
 - Q4101 Apligraf per sq cm
 - Q4102 Oasis wound matrix, per sq cm
 - Q4105 Integra dermal regeneration template, per sq cm
 - Q4106 Dermagraft, per square centimeter
 - Q4107 Graftjacket, per square centimeter
 - Q4110 Primatrix, per square centimeter
 - Q4121 Theraskin, per square centimeter
 - Q4122 Dermacell, Dermacell AWM or Dermacell AWM porous, per square centimeter
 - Q4128 Flex HD, or Allopatch HD, per square centimeter
 - Q4133 Grafix Prime, GrafixPL Prime, Stravix and StravixPL per square centimeter
 - Q4151 Amnioband or guardian, per square centimeter
 - Q4158 Kerecis Omega3, per square centimeter
 - Q4159 Affinity, per square centimeter
 - Q4160 Nushield, per square centimeter
 - Q4186 Epifix, per square centimeter
 - Q4187 Epicord, per square centimeter
 - Q4203 Derma-Gide, per square centimeter

AND

2. All of the following criteria are met:
 - a. There is adequate circulation to the affected area²,
 - b. There is no sign of clinical infection in the ulcer,

¹ In 2003, Sheehan et al. published the often quoted article supporting the ability of the 4-week healing rate to predict complete healing by 4 weeks. The 4-week 50% wound area reduction has been widely adopted and confirmed as a robust indicator for predicting healing at 12 weeks. Consistent with this premise, wounds failing to achieve a 50% area reduction at this time point need to be reassessed and subsequently considered for advanced therapies in the absence of underlying disease or nonadherence to prescribed basic treatment (Frykberg and Banks, 2015). Current standard of care practices for the treatment of lower extremity diabetic foot ulcers include sharp debridement, wound care dressings that maintain a moist wound-healing environment and manage wound exudates, wound offloading, vascular assessment and infection control (Snyder et al., 2020, Lipsky et al., 2012, Lavery et al., 2016).

² For ABI ≤ 0.90 , referral should be made to a vascular specialist for further arterial evaluation including comprehensive lower extremity arterial Doppler study, arterial imaging, and possible revascularization consideration before therapy (O'Donnell et al., 2014).

- c. The plan member has adequate glycemic control (HbA1C < 12%),
- d. The plan member is willing and able to maintain the required schedule of dressing changes and offloading, and
- e. The plan member is a nonsmoker or has refrained from smoking for at least 6 weeks prior to planned treatment with a skin substitute or has received counseling on the effects of smoking on wound healing and surgical outcomes and treatment for smoking cessation.

Venous leg ulcers

1. One of the following skin substitute graft products may be considered medically necessary for the treatment of chronic partial and full-thickness venous leg ulcers that have failed to respond to a minimum of 4 weeks of standard care with documented compliance³:
 - Q4101 Apligraf per sq cm
 - Q4102 Oasis wound matrix, per sq cm
 - Q4106 Dermagraft, per square centimeter
 - Q4151 Amnioband or guardian, per square centimeter
 - Q4186 Epifix, per square centimeter

AND

2. All of the following criteria are met:
 - a. There is adequate circulation to the affected area,⁴
 - b. There is no sign of clinical infection in the ulcer,
 - c. The plan member has adequate glycemic control (HbA1c < 12%),
 - d. The plan member is will and able to maintain the required schedule of dressing changes and compression, and
 - e. The plan member is a nonsmoker or has refrained from smoking for at least 6 weeks prior to planned treatment with a skin substitute or has received counseling on the effects of smoking on wound healing and surgical outcomes and treatment for smoking cessation.

All other skin substitutes are considered experimental/investigational and not medically necessary for the treatment of diabetic foot ulcers or venous leg ulcers.

Pressure ulcers

RCTs examining skin substitutes in the treatment of pressure ulcers have not demonstrated a clinically significant benefit over standard of care, therefore the use of skin substitutes in the treatment of pressure ulcers is considered investigational.

Medicare Variation

Medicare statutes and regulations do not have coverage criteria for skin substitutes. Medicare does not have an NCD for skin substitutes. National Government Services, Inc., the Part A/B Medicare Administrative Contractor with jurisdiction in the Plan's service area does not have an LCD for skin substitutes (Medicare Coverage Database search 02/16/2026). Coverage criteria for skin substitutes products for the treatment of diabetic foot ulcers and venous leg ulcers are not fully established by Medicare; therefore, the Plan's Clinical Coverage Criteria are applicable.

³ Compression therapy is the standard care for the treatment of venous leg ulcers. The use of a skin substitute in addition to compression therapy is recommended for the treatment of venous leg ulcers that have failed to show signs of healing after standard therapy for 4 to 6 weeks (O'Donnell et al., 2014).

⁴ Mostow et al., 2005 excluded patients with an ankle-brachial index (ABI) <0.80 in the RCT of Oasis Wound Matrix with compression vs. compression alone for the treatment of venous leg ulcers. Falanga et al., 1998 excluded patients with an ABI <= 65 in the RCT of Apligraf with compression vs. compression alone for the treatment of venous leg ulcers.

MassHealth Variation

MassHealth has Guidelines for Medical Necessity Determination for Skin Substitutes (MassHealth website search 11/22/2025), therefore the Plan's Clinical Coverage Criteria are not applicable.

Link: [Guidelines for Medical Necessity Determination for Skin Substitutes](#)

Refer to MassHealth Physician Manual Subchapter 6 Section 604 or Acute Outpatient Hospital Manual Subchapter 6 Section 603, as applicable, for payable skin substitute products for MassHealth members.

Exclusions

- Greater than 8 applications of a skin substitute graft/CTP within an episode of care (up to 16 weeks).
- Repeat applications of skin substitute when a previous application was unsuccessful. Unsuccessful treatment is defined as increase in size or depth of an ulcer, no measurable change from baseline, and no sign of significant improvement or indication that significant improvement is likely (such as granulation, epithelialization, or progress towards closure).
- Application of skin substitute 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).
- Use of surgical preparation services (e.g., debridement), in conjunction with routine, simple or repeat skin replacement therapy with a skin substitute.
- All liquid or gel skin substitute products for ulcer care.
- Placement of skin substitute on infected, ischemic, or necrotic wound bed.

Summary of Evidence

The U.S. Food and Drug Administration (FDA) does not refer to any product or class of products as skin substitutes. Although the term 'skin substitute' has been adopted to refer to this category of products in certain contexts, these products do not actually function like human skin that is grafted onto a wound; they are not a substitute for a skin graft. Instead, these products are applied to wounds to aid wound healing and through various mechanisms of action they stimulate the host to regenerate lost tissue. These products vary in their material composition, intended layer of replacement, and the presence or lack of cellular components (CMS, 2013).

The FDA regulates products commonly referred to as "skin substitutes" under one of four categories, depending on the product's origin and composition: human-derived products regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps); human- and human/animal-derived products regulated through premarket approval (PMA) or as a Humanitarian Use Device (HUD) obtained through a humanitarian device exemption (HDE); or animal-derived products and synthetic products regulated under the 510(k) process. While some skin substitutes have been approved by FDA as medical devices through the PMA process, including Apligraf, Dermagraft, and the Integra skin substitutes, most skin substitutes are regulated as either 510(k) medical devices or HCT/Ps.

Chronic wounds are wounds that fail to proceed through the normal phases of wound healing in an orderly and timely manner. These wounds usually do not close without interventions. Four weeks of standard of care without achieving a 50% reduction in wound size may signal the need for a change or additional therapies (Fryberg and Banks, 2015). A randomized controlled trial (RCT) in patients with diabetic foot ulcers demonstrated that a 50% reduction in wound area at 4 weeks was a strong predictor of wound healing by 12 weeks when standard of care was used (Sheehan et al., 2003). Complete healing of chronic wounds is marked by epidermis reepithelization and dermis repair. Successful healing of chronic wounds depends on critical factors, such as proper blood flow and nutrition to ensure tissue growth, infection control, maintenance of a moist environment, and removal of dead tissue to allow space for new cells and tissue to fill the wound void (Snyder et al., 2020).

Usual care or standard care for established chronic wounds incorporates common principles that apply to managing all wound types:

- Remove necrotic tissue through debridement
- Maintain moisture balance by selecting the proper wound dressing to control exudate.
- Take measures to prevent or treat wound infections.
- Correct ischemia in the wound area.
- For venous leg ulcers, apply some form of compression.
- For diabetic foot ulcers, apply some form of offloading.

The methods for achieving each of these wound management principles varies among clinical practice guidelines and clinical studies (Snyder et al., 2020). Using saline wet-to-dry gauze on any chronic wound is no longer considered part of standard wound care (Ovington LG., 2002). If chronic wounds fail to respond to standard of care, skin substitutes may be indicated as an adjunct to established chronic wound care methods to increase the likelihood of complete healing (Nathoo et al., 2014).

Four weeks of standard of care without achieving a 50% reduction in wound size may signal the need for a change or additional therapies (Frykberg and Banks, 2015). An RCT in patients with diabetic foot ulcers demonstrated that a 50% reduction in wound area at 4 weeks was a strong predictor of wound healing by 12 weeks when standard of care was used (Sheehan et al., 2003). Only 9% of patients who did not meet the 50% reduction at 4-weeks threshold healed by 12 weeks. The positive predictive value was 58%, and the negative predictive value was 91%. For venous leg ulcers, Kantor and Margolis (2000) also showed that percent change in wound area after 4 weeks is predictive of complete wound healing by 24 weeks. The positive predictive value was 68%, and the negative predictive value was 75%. If chronic wounds fail to respond to standard of care, skin substitutes may be used as an adjunct to established chronic wound care methods to increase the likelihood of complete healing (Snyder et al., 2020).

Clinical Trials for Skin Substitute Grafts for Diabetic Foot Ulcers

Affinity® (Organogenesis, Inc.)

Affinity® is an amniotic-derived human allograft tissue that is regulated as a human cells, tissues, and cellular and tissue-based product (HCT/P) as defined by 21 CFR Part 1271. Affinity® is processed by LifeLink® Tissue Bank.

A multicenter, RCT was conducted across 14 centers to investigate the comparative effectiveness of a hypothermically stored amniotic membrane (Affinity®, Organogenesis, Inc.) plus standard of care (SOC) versus SOC alone in the treatment of DFUs over a 16 week study period (12-week treatment phase and a 4 week follow-up phase). SOC consisted of debridement, infection elimination, use of dressings and offloading by total contact casting. After a 2-week screening phase, 76 participants were randomized. The primary analyses were frequency of and time to wound closure by 16 weeks (12 weeks in the treatment phase of the study, 4 weeks in the follow-up phase). Ulcer area (cm²), depth (mm) and volume (cm³) were measured using a digital data collection system. The study population was comprised of subjects with Type I or II diabetes with a DFU of greater than or equal to 4-weeks duration at presentation that was unresponsive to SOC. All included subjects presented with a DFU located below the medial aspect of the malleolus extending at least through the epidermis into dermis, subcutaneous tissue, muscle, or tendon but not into bone. Subjects had well controlled glucose levels with HbA1c <12% and an ulcer between 1 and 25 cm². In both study groups the ulcers were prepared using standard methods that included sharp debridement (by curette or scalpel) to ensure that the ulcer area was free of debris and necrotic tissue. Ulcer beds and peri-ulcer areas were cleansed with normal, sterile saline solution. Affinity was applied directly with the stromal side in contact with the wound per manufacturer specifications on the open ulcer bed at weekly intervals or until healed. This was followed by application of outer dressings. Off-loading was achieved by means of TCC for plantar ulcers, and fixed ankle walker boots (in the case of infection), or other appropriate means at the discretion of the investigator for nonplantar ulcers.

Each subject had one ulcer identified as the index ulcer for treatment in the study (n = 76: 38 Affinity [14 Wagner 1, 24 Wagner 2]; 38 SOC [15 Wagner 1, 23 Wagner 2]). At the first treatment application, the mean ulcer area was 3.12 cm² in the Affinity® group and 3.33 cm² in the SOC group. Ulcers in the Affinity® and SOC groups had mean ulcer depths of 2.5 versus 3.0 mm and mean ulcer volumes of 0.33 versus 0.21 cm³ respectively. 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. The Kaplan-Meier median time to wound closure for Affinity®-treated ulcers was 11 weeks. For SOC-treated ulcers, the Kaplan-Meier median time to wound closure was not attained by 16 weeks (i.e., 50% of patients in the SOC group failed to demonstrate wound closure by the end of study, 16 weeks).

The strengths of this study include rigorous standards of data collection. Additionally, all measurements at all time points were used in a true ITT analysis where all randomized subjects contributed data to the final results. Limitations of this trial included the lack of blinding. This study, like all RCTs, was intended to demonstrate efficacy and as such was conducted under carefully controlled conditions including, required compliance to defined criteria for patient inclusion and exclusion, rigorous monitoring and adherence to the treatment protocol careful selection of participants and standardized treatment protocols. While RCTs are considered level one evidence, there are limitations in the generalizability of the clinical data generated. Clinical evaluations in ordinary settings and in broader populations are recommended.

AmnioBand Membrane (MTF Biologics, Edison, NJ)

AmnioBand Membrane is an aseptically processed amnion and chorion tissue form approved for use as a Human Cellular and Tissue-Based Product (HCT/P) under FDA 21 CFR 1271 and Section 361 of the Public Health Service (PHS) Act.

DiDomenico et al. 2016, conducted a multicenter, RCT comparing a dehydrated human amnion and chorion allograft (AmnioBand Membrane, MTF Biologics, Edison, NJ) used with SOC to SOC alone in the treatment of DFU for up to 12 weeks (ClinicalTrials.gov NCT02399826). All study-eligible wounds were managed with SOC alone for a 2-week screening period before randomization. Surgical debridement was achieved with a 15-blade scalpel or curette to remove all necrotic tissue. Wound offloading was performed using a total contact cast or removable CAM boot. Collagen alginate and a 3-layer dressing were applied daily. During 2-week screening, wounds were assessed and measured weekly. Further debridement was performed as necessary. If the index wound had not reduced by more than 20% in size at the end of the screening period, the patient was then randomized. The trial was conducted between March 23, 2015 and March 23, 2016. Each patient was treated weekly during the study period until the index wound closed or for 12 weeks. The intent-to-treat (ITT) and safety populations comprised randomized patients who received at least 1 treatment. Of 47 patients screened, 40 met the screening criteria and were randomized to AmnioBand plus SOC (n = 20), or SOC alone (n = 20). One subject was lost to follow-up in the SOC group because of a serious adverse event (SAE) that involved bone infection and occurred at week 6. At the primary endpoint (6 weeks), 70% (14/20) of the AmnioBand Membrane plus SOC treated DFUs had healed compared with 15% (3/20) of DFUs treated with SOC alone (P = 0.001). At 6 weeks, 70% (14/20) of the DFU in the AmnioBand plus SOC 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 plus SOC group healed compared with 25% (5/20) in the SOC group (mean time to heal of 36 and 70 days, respectively). At 6 weeks, the mean number of grafts used per wound for the AmnioBand plus SOC group was 3.1 (±1.7). At 12 weeks, the average number of grafts used per healed wound for the AmnioBand plus SOC group was 3.8 ± SD 2.2 (median 3.0). At the 6-week point, 8 patients from the SOC group and 1 patient from the AmnioBand plus SOC group were withdrawn from the study because their wounds failed to reduce in area by at least 50%. Although all DFUs were found still closed 1 week after initial closure in the AmnioBand plus SOC group, 2 DFUs in the SOC group reopened after initial wound closure. Limitations include lack of blinding and withdrawing patients at 6 weeks rather than continuing through 12 weeks of treatment if clinicians judged that their wounds were not sufficiently responding to treatment in order to ensure patient safety and permit other treatment pathways.

DiDomenico et al. 2018, performed a RCT to compare a dehydrated human amnion and chorion allograft (AmnioBand Membrane, MTF Biologics, Edison, NJ) used with SOC to SOC alone in the treatment of DFU for up to 12 weeks (ClinicalTrials.gov NCT02399826). Of the 95 patients screening, 80 met screening criteria following the 2-week screening trial and were randomized 1:1 to AmnioBand (m=80) plus SOC or SOC alone (n=40). 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 the 6-week point, 12 patients from the SOC group and 2 patients from the AmnioBand plus SOC group were withdrawn from the study because their wounds failed to reduce in area by at least 50% and were therefore considered study failures. While all wounds remained closed 1 week after initial closure in the AmnioBand plus SOC group, 2 wounds in the SOC group reopened after initial wound closure. At 6 weeks, 68% (27/40) of the DFU in the AmnioBand plus SOC group achieved healing contrasted to 20% (8/40) of the DFU in the SOC group (p=0.000019). At 12 weeks, 85% (34/40) of the DFU in the AmnioBand plus SOC group achieve healing compared with 33% (13/40) of the DFU in the SOC group (p= 0.000006). The average time to heal within 12 weeks was quicker for the AmnioBand plus SOC 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. Strengths of this study include a larger sample study than the previous study (Domenico et al., 2016), and ITT analysis. Future trials of AmnioBand should consider a comparative arm using an advanced skin substitute for greater strength of evidence.

Glat et al. 2019, conducted a multicenter, RCT comparing a dehydrated human amnion and chorion allograft (AmnioBand Membrane, MTF Biologics, Edison, NJ) and a tissue-engineered skin substitute (Apligraf, Organogenesis, Inc., Canton, MA) in the treatment of DFU (ClinicalTrials.gov NCT02870816). Patients with at least 1 chronic Wagner grade 1 DFU, which had not responded to SOC for at least 4 weeks were randomized 1:1 after a 2-week screening period, and the study was conducted at 5 outpatient wound care centers in the United States between August 31, 2016 and June 14, 2018. During the 2-week screening period, patients underwent debridement, offloading with a removable CAM boot or total contact cast in the instance that the patient could not be fitted with a standard offloading CAM boot. A collagen alginate 3-layer dressing was applied daily. As long as the percent area reduction of the index ulcer was less than or equal to 20% improved during screening and all other inclusion and exclusion criteria were met, the patient was randomized. Post-randomization, patients were seen weekly until the index wound closed or for 12 weeks. Six weeks after randomization, percentage area reduction (PAR) was calculated for the index wound. If the DFU failed to reduce in area by 50% or more, the patient was withdrawn from the study and considered a failure of treatment and allowed to seek other wound care modalities. Healed wounds were defined as complete (100%) epithelialization without drainage and need for dressing, as determined by the site investigator. Any wound that healed was subject to confirmation of wound closure 2 weeks later after initial wound closure (healing validation). The primary endpoint of the study compared time to heal at 6 weeks between the 2 treatment groups. Secondary objectives included comparison of the 2 groups in regard proportion of wounds healed within 12 weeks, time to healing over 12 weeks, and percentage area reduction (PAR) over 12 weeks and comparison of cost to closure and percentage wastage of the grafts. Seventy-two subjects were screened, of whom 60 subjects met the eligibility criteria and were randomized 1:1 to AmnioBand (n=30) or Apligraf (n=30). Two subjects treated with Apligraf exited at weeks 3 and 4 due to serious adverse events (SAEs) (foot infections progressing to osteomyelitis), which by protocol were considered a treatment failure. One subject whose wound was treated with Apligraf initially healed at week 6 but was observed to be re-opened at week 8 at the wound-healing validation visit; therefore, this subject was exited from the study as a treatment failure per protocol. Ten subjects treated with Apligraf and 1 subject treated with AmnioBand were exited from the study at 6 weeks as treatment failures for not meeting the PAR rule. The groups were well matched regarding patient and wound-related parameters without any statistically significant differences. Time to heal (within 6 weeks) for the AmnioBand Membrane group was 24 days (95% CI, 18.9–29.2) compared with 39 days (95% CI, 36.4–41.9) for the Apligraf group (P = 8.0×10⁻⁶). The proportion of wounds closed at 6 weeks for the AmnioBand Membrane group was 77% (23/30) compared with 23% for the Apligraf group

(7/30). By 12 weeks, percentages had increased for both treatment groups with 90% (27/30) of DFUs healed in the AmnioBand Membrane group compared with 40% (12/30) of DFUs healed in the Apligraf group (P = 0.00049). At 12 weeks, the mean time to heal was 32 days for the AmnioBand Membrane group (95% CI, 22.3–41.0) compared with 63 days for the Apligraf group (95% CI, 54.1–72.6) (P = 0.00032). At 12 weeks, the mean PAR was 98% for the AmnioBand group compared with 44% for the Apligraf group. At 12 weeks, the mean number of grafts used per for all AmnioBand-treated wounds was 4.4 (SD: 3.71; median: 2.5). However, the mean number of graft applications for AmnioBand-treated DFUs wounds that healed was 3.7 (SD: 3.05; median: 2). Mean number of graft applications for the Apligraf group at 12 weeks were 7.5 (SD: 3.52; median: 6) for all wounds and for those that healed the mean number of grafts was 6.1 (SD: 2.63; median: 5.5). Study limitations include lack of blinding. Also, withdrawing patients at 6 weeks rather than continuing through 12 weeks of treatment if their wounds were not sufficiently responding to treatment to ensure patient safety and permit other treatment pathways could be considered a limitation as well.

DermACELL Acellular Dermal Matrix (LifeNet Health, Virginia Beach, Virginia)

DermACELL Acellular Dermal Matrix (ADM) is a human acellular dermal matrix that is decellularized using Matracell, a proprietary, patented and validated processing technology.

Walters et al., 2016 reported results of an interim analysis for a multicenter, randomized, controlled open-label study to evaluate the safety and efficacy of a human acellular dermal matrix (DermACELL ADM) in patients with full-thickness DFU (Clinicaltrials.gov NCT01970163). Inclusion criteria included the patient having a single, full-thickness target DFU with a Wagner ulcer classification grade of 1 or 2, a wound area of 1 cm² or greater and less than 25 cm², and a wound depth of 9 mm or less. A total of 203 DFU subjects were consented and 35 subjects were removed as screen failures, leaving an intent to treat population of 168 participants who were randomly allocated to treatment arms in a 2:2:1 ratio consisting of 71 subjects in the DermACELL ADM group, 69 subjects in the conventional care group, and 28 in the Graftjacket group. Patients in the dermal matrix groups received 1 or 2 applications of the graft, the second application at the discretion of the investigator. Weekly follow-up visits occurred until full wound closure was observed (100% reepithelialization) or the 16th week follow-up visit was reached. If wound closure was observed, a second visit occurred 2 weeks later to confirm wound closure and was considered the termination visit if the wound was still closed. Otherwise, the patient continued weekly follow-up visits until wound closure was observed or 16 weeks was reached. Throughout the course of the study, 18 patients in the DermACELL ADM arm, 13 patients in the conventional care arm, and 5 patients in the Graftjacket withdrew early for either an adverse event or significant noncompliance. Fifty-three Dermacell ADM patients, 56 conventional care patients, and 23 Graftjacket patients whose ulcer healed or reached the 12-week follow-up visit and were included in this interim per protocol analysis. At 16 weeks, the DermACELL group had a significantly higher proportion of completely healed ulcers than the conventional care group (67.9% vs 48.1%; p=0.0385) and a nonsignificant higher proportion than the Graftjacket group (67.9% vs 47.8%; p= 0.1149). The DermACELL group also exhibited a greater average percent reduction in wound area than the conventional care group (91.4% vs 80.3%; P = 0.0791) and the Graftjacket group (91.4% vs 73.5%; P = 0.0762). There were no serious AEs related to the graft reported. A common limitation in this and other wound-healing studies is the absence of a blinded analysis.

This same study population was reported by Cazzell et al., 2017, after subjects were followed for 24 weeks. In the intent to treat population, single application DermACELL ADM (n=50) demonstrated significantly greater healing over conventional care through endpoints at Week 16 (66.0% vs. 37.7%; p = 0.0093) and Week 24 (70.0% vs. 49.3%; p = 0.0442). No other statistically significant differences were observed.

Cazzell et al., 2019 conducted a prospective single arm, multicenter open label trial designed to evaluate the safety and efficacy of DermACELL Acellular Dermal Matrix (ADM) in healing large, complex DFUs with exposed bone or tendon on the lower extremities (Clinicaltrials.gov NCT03044132). Sixty-one participants were screened, and all were enrolled in the study as the intent-to-treat population. The two sites were located in Fresno, California (n = 45), and Rocky

Mount, North Carolina (n = 16). The ulcers were deep, with 59 of 61 probing to bone, and all wounds scored a Wagner grade 3 or 4. The average wound area was 29.0 ± 21.0 cm² (maximum, 113.6 cm²). More than half of the DFUs had an area greater than 25 cm², which is a common upper limit cutoff in published clinical studies. Most of the ulcers were located on the dorsal and plantar forefoot areas. The treatment plan includes surgical debridement, the addition of a cellular and/or tissue-based product (CTP) (DermACELL ADM), offloading with a boot, weekly office visits, and negative-pressure wound therapy (NPWT), if geographically available, until 100% granulation is achieved. Dressings were standardized across both sites. The primary endpoint was the time in weeks required for 100% wound granulation, which was defined as complete coverage of the exposed tendon and/or bone with collagen-rich connective tissue. Granulation was determined by the site investigator. Secondary endpoints were percent wound area reduction at 16 weeks, percent complete wound closure at 16 weeks, and the number of applications of DermACELL ADM required to achieve 100% wound granulation. Debridement was performed in the operating room per standard of care. The NPWT was permitted starting the day of the debridement procedure to achieve 100% granulation, but it was prescribed at only one study site. Many patients from the North Carolina site lived in rural areas where home health support services, such as NPWT, are not available. The DermACELL ADM was applied either in the operating room or the wound care clinic after debridement per the clinician's standard of care. Bolster dressings were used for larger wounds to prevent the central area of the graft from tenting away from the wound bed. The bolster and outer layer dressings were allowed to be reapplied if dressing changes were required between weekly clinic visits. Offloading with a removable boot was prescribed for all participants except one with a dorsal wound. At investigator discretion, one additional application of DermACELL ADM was allowed if (1) the wound required further coverage for exposed deep tissue, (2) there was less than 75% granulation tissue present. A validated laser measurement device was used to photograph and measure the wound at every visit. At after 4 weeks, or (3) less than 50% granulation tissue was present after 8 weeks. All participants whose wounds had not yet healed were released from the study at the 16-week visit. If the wound healed at the 15- or 16-week visit, the participant remained in the study for a confirmatory visit 2 weeks later. Fourteen participants did not complete the full 16 weeks of the study. Of these, 9 were withdrawn by an investigator for nongraft-related adverse events (8 of these participants required a surgical intervention that impacted the target wound area), 1 was nonadherent to the visit schedule and instructions, 1 withdrew consent to move out of state, 2 were lost to follow-up, and 1 died of an unrelated cause. In the intention to treat group 90.2% achieved 100% granulation by 16 weeks with 24.6% of wounds completely healed by 16 weeks. The mean time to achieve 100% granulation was 4.1 ± 2.1 weeks. The average number of applications was 1.2 ± 0.4 . In this study, 14.8% of target ulcers were infected. Infected ulcers not only take longer to heal but also have a higher risk of amputation. The amputation rate for noninfected DFUs in this study was 1.6%. In contrast, of the nine participants with infected DFUs in the present study, the amputation rate was only 11.1% over 16 weeks. Although none of the infected ulcers healed completely by 16 weeks, the safety of DermACELL ADM with excellent limb salvage rates in the study timeframe was encouraging. The North Carolina site, which did not use NPWT, had 70.0% of wounds heal, whereas the California site, which did use NPWT through granulation, had 21.6% healed wounds. There was no significant difference in wound size or time to granulation between the sites. However, the sample size for the North Carolina site had fewer participants enrolled, precluding generalization. A limitation of this study was the lack of a control arm. Another limitation was that the study follow-up terminated after 16 weeks, which provided an insufficient length of time for the extremely large ulcers to heal. Future studies that include Wagner grades 3 and 4 DFUs would benefit from a longer study duration.

Derma-Gide (Geistlich Pharma AG, Switzerland)

Derma-Gide is a porcine-derived, purified reconstituted bilayer wound matrix, with FDA 510(k) clearance (K182838; Product Code KGN, Date: November 8, 2018).

Armstrong et al., 2022, reported interim results of a multicenter, randomized controlled trial (RCT) evaluating treatment of full-thickness non-infected, non-ischemic (Wagner 1) DFUs with Derma-Gide or standard of care (SOC). The trial was performed at multiple specialty wound care centers between February 2019 and April 2023. The SOC dressing was a moisture retentive,

conformable collagen alginate dressing (Fibracol Plus, KCI). The primary study endpoint was a comparison of wound closure rates at 12 weeks. Secondary endpoints included comparisons of time to heal at 6 and 12 weeks, percentage wound area reduction at 6 and 12 weeks, and patient-reported quality of life outcomes. Cost to closure was calculated for Derma-Gide based on product list prices and the total number and size of grafts used. The primary endpoint was evaluated by a Fisher exact test using an intent-to-treat (ITT) analysis of all randomized patients. Time to heal within 6 and 12 weeks was analysed using Kaplan–Meier log-rank test, while PAR at 6 and 12 weeks analysed using the Mann–Whitney test. Participants were screened over a 14-day run-in period to determine eligibility. The run-in preceded randomization to eliminate those patients in whom a short course of routine therapy would demonstrate effectiveness as measured by a >20% reduction in wound area. All wounds were managed during run-in using a standard protocol including cleaning, appropriate sharp debridement, infection management, dressing, and offloading using a diabetic offloading boot or when the patient's foot could not be accommodated with the offloading boot, a total contact cast was used. Study visits were performed weekly until either complete healing of the index ulcer or for 12 weeks, whichever came first. At the time of reporting the interim results, forty-six patients were screened, with 40 randomised to treatment with either Derma-Gide (n=20) or SOC (n=20). Using an ITT approach, after 12 weeks of treatment, the Derm-Gide arm had 85% (17/20) of ulcers healed compared with 30% (6/20) in the SOC arm ($P < 0.001$) with all patients analyzed. When evaluated per protocol (PP), the PRBM arm demonstrated 94% (16/17) wound closure compared with 30% (6/20) in the SOC Arm ($P < .001$). On average, wounds treated with Derma-Gide healed completely in 37 days (95% CI: 26–48, median 21 days) compared to the SOC group averaging 67 days ($P = 0.002$; 95% CI: 55–78, median inestimable). The mean percent area reduction (PAR) at 6 and 12 weeks for wounds treated with Derma-Gide was 95% (SD: 8%) and 96% (SD: 10%), respectively, compared with 24% (SD: 82) and 9.8% (SD: 89%) for wounds in the SOC group. A mean of 5.2 (SD: 3.5; median 4; range 1–12) Derma-Gide grafts was applied to achieve wound healing. Mean per-patient Derma-Gide cost to closure was \$1731 (SD: \$1308; median \$1050). Smaller grafts were applied as wound area decreased, minimizing cost and product waste. The investigators evaluated the wound quality of life (Wound-QoL) and patients in the PRBM arm reported a 47% improvement in mean Wound-QoL scores from baseline compared with a 23% improvement in the SOC arm. The difference, however, between the two arms did not reach the level of statistical significance. Similarly, patients in both groups reported generally decreasing VAS pain scores over time, with the PRBM arm reporting a mean reduction of 0.4 and the SOC group a mean reduction of 0.6 over the 12-week study, but the difference also was not statistically significant.

Armstrong et al., 2024 reported the final efficacy and safety results of the multicenter, RCT to evaluate the treatment of full-thickness non-infected, non-ischemic (Wagner 1) DFUs with Derma-Gide or standard of care (SOC) (interim results were reported by Armstrong et al., 2022). A total of 123 patients were screened and 105 were randomized to treatment with either Derma-Gide (n=54) or SOC (n=51). Wound closure rate was significantly higher in the Derma-Gide arm than the SOC arm. Using an ITT approach, at 12 weeks of treatment, 83% of the patients in the Derma-Gide arm (45/54 DFUs) presented with healed wounds, compared to 45% in the SOC group (23/51 DFUs). This was significant at $p = 0.00004$. The secondary endpoints also showed that ulcers healed significantly faster for those patients in the Derma-Gide group. For the ITT cohort the time to heal within 12 weeks was a mean of 42 days (95% CI: 35–49, median 42 days) among PRBM patients while in the SOC group this was a mean of 62 days (95% CI: 55–70, median 77 days), which was statistically significant ($p = 0.00074$). The Kaplan–Meier plot of healing illustrates early divergence in the healing probability between the groups. Analysis of time to heal within 6 weeks for the ITT cohort showed a significant difference between study arms. The Derma-Gide-treated wounds healed in a mean of 31 days (95% CI: 27–34) compared with a mean of 66.5 days (95% CI: 59–74) for wounds in the SOC arm ($p = 0.007$). The healing rate in the Derma-Gide arm at the 6-week mid-study point was 56% compared with 29% in the SOC arm and was also significant ($p = 0.0098$). The PAR values for the ITT cohort also showed a significant difference between the treatment arms. At week 6, the Derma-Gide group had a mean PAR of 90.3 (SD:17.42) while in the SOC this was 52.6 (SD: 60.14) ($p = 0.00074$). Likewise, the week 12 mean values for PAR were 93.6 (SD:18.83) in the Derma-Gide cohort compared to 50.5

(SD: 69.07) in the SOC cohort ($p = 0.0023$). There was a mean of 5.7 (SD:3.55) graft applications per patient, with a mean cost to closure of \$1982 per patient (range \$283 - \$1442). The costs calculated here are slightly higher than the mean graft cost to closure that had been reported, \$1731.00, in the interim data of this study (Armstrong et al., 2022) which is likely attributable to the variation of a much larger cohort. Specific to safety, there were 13 SAEs, six in the Derma-Gide group (five patients) and seven in the SOC group (six patients). There were no instances of a causal relationship between the SAE and either the Derma-Gide or the SOC. With regard to Wound QoL, for the ITT cohort the patients in the Derma-Gide cohort presented with a mean score of 1.2 (SD:0.90) at baseline, which decreased to 0.8 (SD:0.73) at the end of study, and this was similar to the SOC patients, with a change from 1.4 (SD:1.08) to 1.0 (SD:0.91), thus there was no significant difference ($p = 0.89$). Similarly, the change in the VAS for pain from baseline to end of treatment were quite comparable for both groups. Limitations of this study include small sample size, the inclusion of only full-thickness, noninfected, non-ischemic (Wagner 1) wounds, and lack of longer-term follow-up. The Agency for Healthcare Research and Quality Technology Assessment (Snyder et al., 2020) suggests a need for studies evaluating patients with more serious comorbidities. Therefore, future trials should consider a real-world patient population with more complex wounds, including deeper wounds.

EpiCord (MiMedx Group, Inc., Marietta, GA)

EpiCord is a dehydrated human umbilical cord allograft comprised of an extracellular matrix of hyaluronic acid (HA) and collagen.

Tettelbach et al., 2018, reported results of a multicenter, RCT conducted at 11 centers in the United States between August 2016 and March 2018 (Clinicaltrials.gov NCT02844660). Individuals with a confirmed diagnosis of Type 1 or Type 2 diabetes presenting with a 1 to 15 cm² ulcer located below the ankle that had been persisting for at least 30 days were eligible for the 14-day study run-in phase. A total of 202 subjects were screened and met the inclusion/exclusion criteria for entry into the study for the 2-week run-in period. During the run-in period, subjects received weekly debridement, moist wound therapy, and offloading. Those with > 30% wound area reduction were no longer eligible for study inclusion ($n=33$). At the conclusion of the run-in period, there were 47 patients no longer eligible for study and a total of 155 subjects were randomised in a 2:1 ratio to receive a weekly application of EpiCord ($n = 101$) or standardized therapy with alginate wound dressing, non-adherent silicone dressing, absorbent non-adhesive hydrolymer secondary dressing, and gauze bandage roll ($n = 54$). All wounds continued to have appropriate offloading during the treatment phase of the study. Study visits were conducted for 12 weeks. At each weekly visit, the DFU was cleaned and debrided as necessary, with the wound photographed pre- and post-debridement and measured before the application of treatment group-specific dressings. A follow-up visit was performed at week 16. The primary efficacy end point examined was the percentage of subjects in the ITT population, with complete closure of the study ulcer within 12 weeks of treatment initiation. Twelve-week healing rates were also examined in subjects completing the study per protocol (PP) and for only those wounds determined to have received consistent, adequate debridement. In the ITT population, at the end of the 12-week treatment phase, 70% (71/101) of EpiCord-treated ulcers had completely healed, a significantly greater number of healed ulcers compared with 48% (26/54) in the alginate group ($P = 0.0089$). Of the 71 healed ulcers treated with EpiCord during the 12-week treatment phase, 68 of 71 (96%) remained closed at week 16 follow up, while 22 of the 26 ulcers healed with alginate dressings (85%) had remained closed. At the 16-week follow-up visit, in the ITT population, 74 of 101 (73%) of EpiCord-treated ulcers were healed, compared with 29 of 54 (54%) of alginate-treated ulcers, $P = 0.0199$. A Kaplan-Meier plot of time to heal within 12 weeks by study group in the ITT population demonstrated a superior wound-healing trajectory for EpiCord-treated vs alginate-treated (SOC) ulcers ($P=0.0152$). Overall, 69% (107/155) of study ulcers were determined to have received adequate debridement. Adequate debridement occurred in 67 of 101 (66.3%) and 40 of 54 (74.1%) of EpiCord and alginate-treated ulcers, respectively, $P = 0.3653$. For those ulcers that received adequate debridement ($n = 107$), 64 of 67 (96%) of the adequately debrided and EpiCord-treated ulcers healed completely within 12 weeks, compared with 26 of 40 (65%) of adequately debrided and alginate-treated ulcers, $P < 0.0001$. The median number of EpiCord allografts applied per healed wound was 7 (range 2-12). Average cost per

EpiCord-healed ulcer was \$3250.99 ± \$2898.48. Seventy-five subjects experienced at least one adverse event, with a total of 160 adverse events recorded. There were no adverse events related to either EpiCord or alginate dressings. The use of alginate dressings in the control group, instead of simple wet-to-dry gauze dressings, may have reduced the treatment effect compared with EpiCord. A healing rate of 48% for wounds treated with alginate dressings in the ITT population compared with expected healing rates of approximately 24% reported with wet-to-dry dressings 20 years ago speaks to the overall advances being made in treating chronic wounds with contemporary management. Yet the results of the current study provide strong evidence that, while healing rates may be improved when more advanced dressings such as alginates are used, the clinician's role in adequate wound bed preparation continues to exist.

AlloPatch Pliable (MTF Biologics, Edison, NJ)

AlloPatch is an acellular dermal matrix comprised of human cells, tissues, and cellular and tissue-based products (HCT/PS) and regulated under section 361 of the PHS Act.

Zelen et al., 2017, reported results of a multicenter, randomized controlled trial (RCT), comparing (ADM) AlloPatch Pliable, MTF Biologics, Edison, NJ) plus standard of care (SOC) to SOC alone in the management of diabetic foot ulcers at 6 weeks (Clinicaltrials.gov NCT02331147). The primary endpoint of this study was to compare the proportion (%) of ulcers completely healed between treatment groups at 6 weeks. Secondary endpoints were comparison between treatment groups of the proportion of wounds healed at 12 weeks, time to heal within 6 and 12 weeks, numbers of grafts used, graft wastage and graft cost to closure. All eligible participants meeting inclusion and exclusion criteria were treated with SOC alone for a 2-week screening period prior to randomization. Patients whose index wound had not healed greater than 20% at 2 weeks were then randomised to the ADM plus SOC or SOC alone groups. Patients were examined and treated weekly during the study period until the index wound closed, for up to 12 treatment weeks or if the patient did not achieve greater than 50% closure at 6 weeks, they were withdrawn from the study at that time. A total of 45 subjects were screened, with 40 meeting the screening criteria followed by randomization to ADM plus SOC (n=20) or SOC alone (n=20). At 6 weeks, 65% (13/20) of the ADM-treated wounds had healed compared with 5% (1/20) of the SOC alone (P=0.00028). The percentage of wound area reduction between the groups changed substantially over time, with a mean time to heal within 6 weeks of 28 days (95% confidence interval (CI): 22–35 days) for the ADM group compared with 41 days (95% CI: 40–43 days) for the SOC group. After adjusting for area of wound at randomization, the hazard ratio (HR) for ADM compared with SOC was 168 (95% CI: 10–2704), P=0.00036. Ten patients from the SOC group (50%) and one patient from the HR-ADM group (5%) exited from the study at 6 weeks per protocol because their wounds failed to reduce in area by at least 50%. At 12 weeks, 80% (16/20) of the ADM-treated wounds had healed compared with 20% (4/20) of the wounds that received SOC alone (P=0.00036). Mean time to heal within 12 weeks was 40 days (95% CI: 27–52 days) for the ADM group compared with 77 days (95% CI: 70–84 days) for the SOC group (P=0.00014). The mean number of ADM grafts used to achieve closure per wound was 4.7 (SD =3.3). The mean and median graft costs to heal (healed wounds only) were \$1475 (SD: \$1528; n=16) and \$963, respectively. The mean percentage of wastage (healed wounds only) was 51.7% (SD: 10.7; n=16).

The study initially reported on by Zelen et al., 2016 (Clinicaltrials.gov NCT02331147), was extended to 40 additional patients (80 in total) to validate and extend the original findings. Zelen et al., 2018, reported on the results of entire cohort of 80 patients (ADM group n=40, SOC group n=40). All subjects received their assigned intervention and were included in the ITT analysis. This study took place from December 16, 2014 to March 29, 2017. At 6 weeks, a significantly higher number, 68% (27/40), of the ADM-treated ulcers had healed compared with 15% (6/40) of the ulcers treated with SOC alone (P = 0.0000027). At 12 weeks, a significantly higher number, 80% (32/40), of the HR-ADM-treated ulcers had healed compared with 30% (12/40) of the ulcers treated with SOC alone (P = 0.0000084). Mean time to heal at the 6-week time point was 27 days (95% CI: 23- 32 days) for the ADM group and 41 days (95% CI: 39- 42 days) for the SOC group (P = 0.00000099). Mean time to heal at the 12-week time point was 38 days (95% CI: 29-47 days) for the ADM group and 72 days (95% CI: 66-79 days) for the SOC group (P = 0.00000039).

Two patients from the ADM group (5%) and 19 patients from the SOC group (48%) were withdrawn from the study at 6 weeks per protocol because their ulcers did not decrease in area by at least 50%. The difference in mean percentage area reduction (PAR) at 6 weeks between study groups was statistically significant ($P = 0.000027$) ADM: 62% (SD: 160) vs SOC: 50% (SD: 41). From week 6 to week 12, the median PAR remained consistent at 100% for the ADM group, whereas it continued to slightly fluctuate in a decreasing trend for the SOC group. At 12 weeks, mean PARs were similar to 6 weeks: ADM: mean: 64% (SD: 160); SOC: mean: 52% (SD: 43) ($P = 0.00001$). The mean number of ADM grafts applied per ulcer to achieve closure by 6 weeks was 3.4 and at 12 weeks was 4.7. Mean product cost to heal a closed ulcer ($n = 27$) at 6 weeks was \$800 (SD: \$687; median: \$675; IQR: \$850). The corresponding cost at 12 weeks was \$1200 (SD: \$1209; median: \$675; IQR: \$994; $n = 32$). The mean wastage at 12 weeks was 57% (SD: 11; $n = 32$).

Grafix (Osiris Therapeutics, Inc., Columbia, MD; acquired by Smith & Nephew in 2019)

Grafix is a cryopreserved placental membrane regulated under section 361 of the PHS Act.

Lavery et al., 2014 reported on the results of a multicenter, randomised controlled trial that evaluated the safety and efficacy of Grafix, a cryopreserved placental membrane, for the treatment of chronic DFUs. Patients were enrolled from May 2012 through April of 2013. During screening, 139 patients were evaluated. Ninety-seven patients were subsequently randomised, with 50 subjects randomized to the Grafix plus standard wound therapy group and 47 to the standard wound therapy group. Following a 1-week screening period, patients were randomised to the Grafix or control group in a 1:1 ratio. Patients randomized to Grafix treatment received an application of Grafix once a week (± 3 days) for up to 84 days (blinded treatment phase). Patients in the control group received standard wound therapy once a week (± 3 days) for up to 84 days. All wounds were appropriately cleaned and surgically debrided to remove all non-viable soft tissue from the wound by scalpel, tissue nippers and/or curettes at each weekly visit. Wounds in both groups received standard wound care that included surgical debridement, off-loading and non-adherent dressings. All patients received a non-adherent dressing: Adaptic® (Systagenix, Gatwick, UK) and either saline moistened gauze or Allevyn® (Smith & Nephew, London, UK) for moderately draining wounds. Patients were evaluated weekly at the clinical site. Patients who achieved complete wound closure then continued to be evaluated during the follow-up phase, twice during the first month and then monthly for two additional visits). Control patients whose wounds were not closed by the end of the blinded treatment phase were able to receive Grafix in the open-label treatment phase, in which Grafix was applied weekly for up to 84 days. Outcome and safety assessments occurred at each visit during the blinded treatment phase, follow-up visits, as well as during the open-label treatment phase. The primary endpoint of the study was evaluation of complete wound closure of the index wound. Confirmation of wound closure was confirmed at an initial follow-up visit 2 weeks later. The proportion of patients who achieved complete wound closure was significantly higher in patients who received Grafix (31 of 50, 62.0%) compared with controls (10 of 47, 21.3%, $P=0.0001$). The odds ratio for complete healing for a Grafix patient compared with control was 6.037 (95% CI 2.449–14.882). The Grafix group had significantly faster median time to complete wound closure compared with controls (42.0 versus 69.5 days, $P=0.019$), among the wounds that closed in both groups. The Kaplan–Meier analysis illustrated a statistically greater probability of complete wound healing during the 12-week evaluation period for Grafix. The probability of closure for the Grafix group was 67.1% compared with 27.1% for the standard care group (Log-Rank, $P<0.0001$). Grafix patients also required fewer study visits (i.e. applications) to achieve closure compared with patients in the control arm (6 versus 12, $P<0.001$). Comparison of patients with at least a 50% reduction in wound size by day 28 showed that 31 of 50 patients (62.0%) in the Grafix group achieved this reduction versus 19 of 47 (40.4%) in the control group ($P=0.035$). There were 8 (16%) patients who withdrew from the study prior to completion in the Grafix group versus 11 (23.4%) patients who withdrew from the control group. Wound recurrence of DFUs closed during the initial 12-week study period was assessed. Follow-up every 4 weeks for an additional 12 weeks showed that ulcers remained closed in 82.1% of patients (23 of 28 patients) in the Grafix group versus 70.0% (7 of 10 patients) in the control group ($P=0.42$). Patients in the control arm who failed to heal during the initial 12-week treatment period could cross over to receive up to 12 weeks of

Grafix therapy (n=26). After receiving treatment with Grafix, the probability of closure was 67.8% with a mean time to closure for these patients of 42 days. Overall, fewer Grafix patients experienced at least one adverse events compared with control patients (44.0% versus 66.0%, P=0.031). Among the patients randomised to Grafix, there were significantly fewer patients with wound-related infections (Grafix, 9 of 50, 18.0%, versus control, 17 of 47, 36.2%, P=0.044) and fewer hospitalizations related to infections in the Grafix group than control (6% versus 15%, P=0.15).

Graftjacket Regenerative Tissue Matrix (Wright Medical Technology, Inc., Arlington, TN)

Graftjacket is a human acellular dermal matrix (allograft), regulated under PHS 361: Human cells, tissues, and cellular and tissue-based products.

Brigido et al (2004) reported a (N=40) randomized pilot study comparing Graftjacket with conventional treatment for chronic nonhealing diabetic foot ulcers.(35) Control patients received conventional therapy with debridement, wound gel with gauze dressing, and offloading. Graftjacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the Graftjacket group. Preliminary one month results showed that, after a single treatment, ulcers treated with Graftjacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs 15%), width (50% vs 23%), area (73% vs 34%), and depth (89% vs 25%), respectively. With follow-up to four weeks, no data were reported on the proportion with complete closure or the mean time to heal. All grafts were incorporated into the host tissue.

Brigado SA (2006) reported results of a 16-week pilot study conducted to evaluate the safety and efficacy of Graftjacket Regenerative Tissue Matrix, an acellular dermal matrix, in DFU management with 40 subjects comparing Graftjacket to gauze dressings with a suggested potential role in ulcer management. The percent change in wound area over a 4-week period has been shown to be a good indicator of complete healing in a 12-week study. It was therefore hypothesized that after 12 weeks, 18 of the 20 Graftjacket-treated patients would be healed compared with two of the 20 debridement-only-treated patients. 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. 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). Limitations of both studies included a small sample size and high risk of bias.

Reyzelman et al., 2009, reported results of a multicenter 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. 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.

Reyzelman and Bazarov (2015) reported results of an industry-sponsored meta-analysis that pooled results from the three studies described above comparing Graftjacket to SOC (n=154) 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.

Real World Evidence

Armstrong and colleagues (2021) conducted a retrospective review of Medicare claims for the time period from October 1, 2015 through to October 2, 2018 to assess outcomes in patients receiving advanced treatment with skin substitutes for lower extremity diabetic ulcers versus no advanced treatment. Patients were followed from the time of diagnosis through to completion of the episode of care.

Advanced treatment (AT) was defined as treatment with high-cost skin substitute products reported with CPT codes 15271-15278 and the applicable HCPCS code. No advanced treatment (NAT) referred to episodes that were treated without high- or low-cost skin substitutes during the observed episode of care.

The primary objective was to compare the effectiveness of treating lower extremity diabetic foot ulcers with AT versus NAT. Outcomes tracked included length of treatment, the frequency of major and minor amputations, ED visits and hospital readmissions.

In the analyzed dataset, 9,738,760 patients had a diagnosis of diabetes, of which, 909,813 had a confirmed diagnosis of lower extremity diabetic ulcer, totaling 1,336,415 treatment episodes.

Assessing a provider's adherence or compliance with AT PFU is challenging in a retrospective study. To address this, claims data was used to assign the date of AT initiation and reapplication, and categorized as "follows parameters for use" (FPFU) or not FPFU.

There were 12,313 patients who received AT and were propensity-matched to 12,510 patients who received NAT to establish propensity-matched Group 1. Propensity-matched group 1 included 1,131 patients (9.2%) who started AT treatment within 30-45 days of diagnosis and were treated at regular intervals within the specified 7-14 day range thereafter. These patients were defined as FPFU and were propensity matched to create group 2.

In the propensity-matched group 1 (AT versus NAT), patients with diabetes who were treated with AT for a lower extremity diabetic ulcer were noted to have undergone significantly fewer minor amputations and a 50% reduction in major amputations compared with those treated with NAT (AT: n=490 (3.9%), NAT: n=551 (4.3%), p=0.0367 and AT: n=197 (1.6%), NAT: n=402 (3.2%), p<0.0001, respectively). They were also observed to have significantly fewer readmissions (AT: n=508 (4.0%), NAT: n=805 (6.4%), p<0.0001 and ED visits (AT: n=2322 (18.3%), NAT: n=3932 (23.1%), p<0.0001) compared with those treated with NAT. The median length of treatment for patients in propensity-matched group 1 was similar; 71 days for AT versus 63 days for patients who received NAT (p<0.0001). Providers in propensity-matched group 1 initiated AT 69.4 days on average (standard deviation (SD): 83.3) into the episode of care and used 3.7 applications on average.

In propensity-matched Group 2 (NAT versus AT FPFU versus AT not FPFU), minor and major amputations were observed to be reduced by >50% with AT when FPFU compared with NAT (AT: n=22 (1.9%), NAT: n=47 (4.2%), p=0.0040 and AT: n<11 (<1%), NAT: n=30 (2.7%), p=0.0008, respectively). Using AT FPFU was also associated with significantly reduced hospital readmissions (AT: n=27 (2.4%), NAT: n=73 (6.5%), p<0.0001) and ED visits compared with NAT (AT: n=161 (14.2%), NAT: n=237 (21.0%), p=0.0004). Major amputations were similar between AT FPFU and AT not FPFU (AT FPFU: n<11 (<1%), AT not FPFU: n=18 (1.6%), p=0.1006), while minor amputations were reduced with AT FPFU (AT FPFU: n=22 (1.9%), AT not FPFU: n=51 (4.5%), p=0.0020). The median length of treatment for patients in propensity-matched Group 2 was statistically similar for the NAT and AT FPFU cohorts; 60 days versus 68 days (p=0.0836). AT not FPFU resulted in a significant increase in the median length of treatment to 76 days, compared with AT FPFU, with 69.4 days (p=0.0027). Episodes in propensity-matched Group 2 initiated AT FPFU at 34.7 days on average (SD: 5.7 days) using 4.9 applications, while episodes using AT not FPFU initiated at 77.2 days on average (SD: 88.0) using 3.5 applications.

AT that does not PPFU outperforms NAT by many metrics. While better outcomes were observed with AT PPFU, the exception was a numerical increase in minor amputations in the AT not PPFU compared with the NAT cohort. Frequently, minor amputations are performed to save a limb and an increase in prophylactic amputations may be indicative of this. Additionally, the length of treatment for AT PPFU and NAT were similar, although both were shorter than AT not PPFU. The preponderance of providers who do not PPFU (~90.8%) when using AT may lead to skewed opinions of the performance and cost-benefits of AT in the healthcare system. Notably, AT had demonstrably better outcomes and statistically equivalent lengths of treatment.

Sheehan et al. (2003) identified four weeks for 50% or greater DFU wound closure as the inflection point to choose an alternative to SOC. Tracking propensity-matched Group 1 episodes via a hazard plot, highlighted the divergence in outcomes upon the decision to use or not use an AT. Patients who reached the four-week inflection point and continued to receive NAT began a steeper rate of amputations compared with patients who began AT.

The use of AT improved outcomes, but a further increase in favorable outcomes occurs by merely PPFU. This analysis of three years of Medicare-approved treatment outcomes for patients with lower extremity diabetic foot ulcers demonstrates statistically significant reductions in the rates of major and minor amputations, ED visits and hospital readmissions when AT was used in accordance with existing parameters for use versus NAT (Armstrong et al., 2021).

Systematic Reviews

In 2012 the Agency for Healthcare Research and Quality (AHRQ) published a technology assessment for Skin Substitutes for Treating Chronic Wounds for the Centers for Medicare & Medicaid Services (CMS). AHRQ identified 57 skin substitute products available in the United States that are used to manage or treat chronic wounds and regulated by FDA. Eighteen RCTs met inclusion criteria. Twelve studies examined diabetic foot ulcers, and six studies examined vascular leg ulcers. One RCT of pressure ulcers was identified but did not meet inclusion criteria. Of the 57 skin substitute products identified for this report, only seven skin substitutes were examined in RCTs that met inclusion criteria. Overall applicability of the evidence base is limited to a small number of skin substitutes used to treat diabetic foot ulcers and venous leg ulcers, and to patients in generally good health. Patients were generally excluded from studies if their health was suboptimal, they were taking medication that would interfere with wound healing, their wounds were infected, or the blood flow to the affected area was poor. Excluding these types of patients means that the outcomes reported in these studies address the efficacy (the capacity to produce a desired effect) of skin substitutes rather than the effectiveness (create an effect in real world practice) of skin substitutes and raises questions about the applicability of the results of these studies to the general population affected by chronic wounds (Carter et al., 2009). All the studies in the evidence base reported some benefit of skin substitutes over the control treatments when number of wounds completely healed was measured between 8 and 16 weeks but the reported results varied widely across studies. Two studies comparing different skin substitutes reported no significant differences in wound healing rates. This is significant given the wide variation in cost for skin substitutes.^{5,6} Because of the differences in product components and healing properties, the results obtained from studies of a single product cannot be extrapolated to other skin substitutes. Similarly, results from studies of diabetic foot ulcers cannot be applied to venous leg ulcers or pressure ulcers because of the differences in etiology and pathophysiology

⁵ In a review of the clinical and cost efficacy of targeted skin substitutes for the treatment of venous leg ulcers, Hankin et al., 2012, found that the most expensive skin substitute for the treatment of venous leg ulcers did not appear to provide the greatest comparative clinical or cost efficacy. Conclusions must be tempered by the small number of studies and limitations in study quality. Given the wide variation in costs for skin substitutes, payers must carefully compare cost efficacy when determining the relative value of these products. More high-quality head-to-head comparisons to guide coverage and reimbursement determinations for these products are needed.

⁶ A cost-effectiveness review of three skin substitutes (Oasis Wound Matrix, Apligraf and Dermagraft) conducted by Carter et al., 2014, found that Oasis Wound Matrix was the most cost-effective skin substitute when used in the management of venous leg ulcers as an adjunct to standard care.

(CBER, 2006). Clinical evidence from RCTs demonstrating effectiveness for the majority of the skin substitutes identified in this technology assessment was not available.

In 2020, the Agency for Healthcare Research and Quality (AHRQ) published an update of their previous technology assessment for Skin Substitutes for the Treatment of Chronic Wounds for the Centers for Medicare & Medicaid Services (CMS). This report includes human placental/amniotic membrane products which were not included in the earlier AHRQ report. In the 2020 report, AHRQ identified 76 commercially available skin substitutes. Three systematic reviews and 22 RCTs that met inclusion criteria. Any studies that used saline wet-to-dry gauze as the comparator were excluded. Sixteen skin substitutes were examined in the treatment of diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Of the 22 RCTs, 16 studies compared standard of care to 13 skin substitutes. Seven studies reported statistically significant differences in number of wounds healed and time to heal favoring the intervention over standard of care in the treatment of diabetic foot ulcers. One study reported statistically significant differences in number of wounds healed and time to heal favoring the intervention over standard of care in the treatment of venous leg ulcers. The only RCT examining a skin substitute compared to standard of care in the treatment of pressure ulcers found no statistically significant differences in pressure ulcers healed at 12 weeks or 6 months. The remaining six RCTs compared one skin substitute with another skin substitute in the treatment of diabetic foot ulcers or venous leg ulcers. Of the six head-to-head comparative studies, findings from five studies did not indicate significant differences between skin substitutes in outcomes measured at the latest follow-up. One head-to-head study in diabetic foot ulcers reported significantly shorter time to healing and significantly higher rate of complete healing at 12 weeks for EpiFix vs. Apligraf (Zelen et al., 2016).

AHRQ concluded that the evidence base remained insufficient to determine whether one skin substitute product is superior to another and that the clearest implications of this assessment are the lack of studies examining the effectiveness of most skin substitute products and the need for better-designed and better-reported studies providing more clinically relevant data (Snyder et al., 2020). Clinical evidence for the majority of skin substitutes is lacking. Well-designed studies are needed to determine whether one skin substitute product is superior to another. Trial design should be standardized to facilitate comparisons across studies. Published studies seldom reported wound recurrence which is an important outcome.

A Cochrane Review conducted by Santema et al. (2016) examined the benefits and harms of skin grafting and tissue replacement for treating foot ulcers in people with diabetes. Primary outcomes of interest included incidence of complete closure of the foot ulcer (healing rate), time to complete closure of the foot ulcer, and total incidence of lower limb amputations. Secondary outcomes included recurrence rate of ulcers, change in ulcer area, incidence of infection, quality of Life, safety and cost of treatment. Seventeen randomized controlled trials with a total of 1655 randomized participants were included in this review. The authors identified 5 ongoing clinical trials (NCT01693133; NCT02070835; NCT02120755; NCT02331147; NCT02399826). Study size ranged from 23 to 314 included patients. Thirteen studies compared a skin graft or tissue replacement with standard care. Four studies investigated the effectiveness of two different types of grafts. Inclusion and exclusion criteria were clearly listed in most trials (15/17). Two publications lacked a complete description of the selected patients. The majority of studies (15/17) excluded patients with an infection of the target ulcer. Adequate arterial perfusion of the foot was required for inclusion in all fifteen trials that described their inclusion and exclusion criteria. More than half of the studies (10/17) included chronic, or hard-to-heal ulcers that were present for at least four to six weeks. The follow-up period ranged from six weeks to 14 months, but most trials (11/17) reported a follow-up period of 12 weeks. An a priori sample size calculation was described in only three studies. In only one of these trials the chosen effect size was clearly described. In this trial they calculated a sample size of 78 participants to detect a difference in healing rate after 30 days with 70% of ulcers healing in the intervention group and 30% of ulcers healing in the control group. None of the included studies described blinding of personnel. Participants were blinded to the treatment allocation in three of the included studies. and therefore these three studies were classified as a low risk of bias for this domain. Nine studies were considered to be at a high risk of bias for this domain because they were described

as open-label or single-blinded studies. The remaining five studies provided no information regarding blinding of participants and personnel and were classified as having an unclear risk of bias for this domain.

Thirteen studies compared a skin graft or tissue replacement with standard wound care and reported on incidence of complete closure of the ulcer. Compared products were Apligraf or Graftskin, Dermagraft, EpiFix, Graftjacket, Hyalogra 3D Kaloderm and OrCel. Pooling of the results was possible because all trials reported on incidence of complete closure at similar time points.

- For the outcome of time to complete closure: Eleven trials reported on incidence of complete closure after 12 weeks, one after 11 weeks, one after 16 weeks and one after six weeks. Pooling of these results by using a random-effects model yielded a significant effect in favor of the intervention group (risk ratio (RR) 1.55, 95% CI 1.30 to 1.85, low quality of evidence. One study compared a living skin equivalent (Dermagraft) with an extracellular collagen wound dressing (OASIS). In this trial no significant differences were found as to the incidence of complete ulcer closure (RR 1.10, 95% CI 0.75 to 1.60).
- For the outcome of ulcer healing One study reported a higher incidence of ulcer healing after 20 weeks in the TheraSkin group (66.7%) compared with the Apligraf group (46.1%), although this difference was not statistically significant (RR 0.71, 95% CI 0.37 to 1.34). One study reported a higher incidence of ulcer healing after 12 weeks in the TheraSkin group (63.6%) compared with the Dermagraft group (33.3%), but this difference was not statistically significant (RR 1.91, 95% CI 0.76 to 4.77).
- For the outcome of incidence of amputations: Only two studies reported on the total incidence of amputations. By pooling the results of these two studies, there were fewer lower limb amputations after 12 weeks in the intervention group; this is a small but statistically significant difference (RR 0.43, 95% CI 0.23 to 0.81, very low quality of evidence).
- For the outcome of recurrence of foot ulcers: Six studies reported on recurrence rates of foot ulcers. Four of these studies found no differences in ulcer recurrence rates between the study groups. One study reported one recurrent ulcer in the Apligraf group (1/15, 7.0%) and one recurrent ulcer in the control group (1/10, 10%). One study reported a recurrence percentage of 5.9% in the Graftskin group (3/112) and 12.9% in the control group (4/96) during the first six months. One study showed an ulcer recurrence rate of 6.3% in the intervention group (1/16) and 6.7% in the control group (1/15) among patients who were monitored for 6 months. One study reported that none of the healed ulcers (n = 11 intervention group, n = 1 control group) had recurred during the follow-up period (mean 14 months, range two to 22 months). Pooling of the results of these four studies showed no statistically significant difference in recurrence rates between intervention and control groups (RR 0.69, 95% CI 0.22 to 2.22).
- For the outcome of reduction in ulcer area: Nine studies reported on change or reduction in ulcer area in various ways, which precluded meta-analysis.
- For the outcome of incidence of infection: In general, the incidence of infection was poorly reported as a separate outcome.
- For the outcome of quality of life: No studies reported on this outcome.
- For the outcome of safety/adverse events: No study reported a statistical difference in the occurrence of adverse events between the intervention and the control group.
- For the outcome of cost of treatment: Only one study included a comparison of costs. This study estimated the total costs for the treatment by multiplying the average number of dressings necessary for complete healing and the costs per dressings. On average, treatment with Dermagraft was four times more expensive than treatment with OASIS. In the cost effectiveness analysis, the predicted 12-week cost per diabetic foot ulcer was USD \$2522 for OASIS and USD \$3889 for treatment with Dermagraft.

Overall, the therapeutic effect of skin grafts and tissue replacements, in conjunction with standard care, shows an increase in the healing rate of foot ulcers and slightly fewer amputations in people with diabetes compared with standard care alone. However, the data available was insufficient to draw conclusions on the effectiveness of different types of skin graft or tissue replacement therapies, and evidence of long-term effectiveness is lacking. Furthermore, the potential benefits

of skin grafts and tissue replacements should be weighed against the high costs of these products. Finally, it is important to note that skin grafts and tissue replacements cannot be seen as a treatment on their own, but should always be part of the multidisciplinary approach to this complex, chronic disease.

Clinical Practice Guidelines

The Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine (Hingorani et al., 2016)

The committee made specific practice recommendations using the Grades of Recommendation Assessment, Development, and Evaluation system. This was based on five systematic reviews of the literature. Specific areas of focus included (1) prevention of diabetic foot ulceration, (2) off-loading, (3) diagnosis of osteomyelitis, (4) wound care, and (5) peripheral arterial disease.

For DFUs that fail to demonstrate improvement (>50% wound area reduction) after a minimum of 4 weeks of standard wound therapy, we recommend adjunctive wound therapy options. These include negative pressure therapy, biologics (PDGF), living cellular therapy, extracellular matrix products, amniotic membrane products), and hyperbaric oxygen therapy. Choice of adjuvant therapy is based on clinical findings, availability of therapy, and cost-effectiveness; there is no recommendation on ordering of therapy choice. Re-evaluation of vascular status, infection control, and off-loading is recommended to ensure optimization before initiation of adjunctive wound therapy (Grade 1B).

Adjunctive therapies for the healing of DFUs should be considered after all standard of care measures have been implemented. Standard, comprehensive care should include wound off-loading, local wound debridement, control of edema, control of bioburden, and wound moisture balance with appropriate dressings. Standard of care for diabetic foot ulcerations will lead to improvement in the majority of cases, and only in those cases without improvement should adjunctive modalities be used. The cost of these therapies can be high, and the evidence supporting their use is not sufficiently strong to justify their use as primary therapy without an attempt at lower cost, evidence-based methods. Failure to demonstrate improvement after 4 weeks of treatment should lead the clinician to reassess the adequacy of and compliance with debridement/wound care, proper offloading of the DFU, and adequacy of the arterial perfusion of the foot before considering adjunctive treatment options. Re-evaluation of the patient and wound should be performed before the use of adjuvant therapies to ensure that offloading is implemented, bioburden is well controlled, vascular supply is optimized, and exudate is not excessive.

Recommendation 8. We suggest consideration of living cellular therapy using a bilayered keratinocyte/fibroblast construct or a fibroblast-seeded matrix for treatment of DFUs when recalcitrant to standard therapy (Grade 2B).

- Apligraf (Organogenesis, Canton, Mass) is a cultured bilayer skin substitute originating from neonatal foreskin. Apligraf was studied in a prospective randomized multicenter trial for the treatment of DFUs (Veves et al., 2001). At 24 centers, 208 patients were treated with standard DFU care (debridement, foot off-loading) and saline-moistened gauze or standard DFU care and Apligraf application. After 12 weeks of treatment, 56% of Apligraf-treated wounds were closed, compared with 38% in the control group. The odds ratio for complete healing was 2.14 (95% CI, 1.23-3.74). The incidence of osteomyelitis was significantly less frequent in Apligraf-treated patients (2.7%) than in controls (10.4%; $P = .04$). Ipsilateral toe or foot amputation was also significantly less frequent in the Apligraf group (6.3%) than in the control group (15.6%). Cost-effectiveness analysis revealed 12% reduction in costs during the first year of treatment compared with standard wound care alone (Redekopp et al., 2003) The increased ulcer-free time coupled with a reduced risk of amputation to a large extent offset the initial costs of the product.
- Dermagraft (Organogenesis) is an allogeneic dermal fibroblast culture derived from human neonatal foreskin samples and grown on a biodegradable scaffold. The pivotal study of Dermagraft in DFUs was a single-blind, randomized, controlled investigation at 35 centers enrolling 314 patients comparing standard DFU care with standard care plus the weekly

application of Dermagraft for up to 8 weeks (Marston et al., 2003). Clinical studies evaluating Dermagraft and Apligraf were not double blinded because the unique characteristics of the devices preclude the use of a placebo that cannot be distinguished from the true product. Standard care in both groups consisted of routine sharp debridement, pressure off-loading, and saline-moistened gauze dressings. Of the 314 patients enrolled, 245 evaluable patients completed the study. Results showed that treatment with Dermagraft produced a significantly greater proportion (30%) of healed ulcers compared with the control group (18%). The number of ulcer-related adverse events (local wound infection, osteomyelitis, cellulitis) was significantly lower in the Dermagraft-treated patients (19%) than in the control patients (32%; $P = .007$). Similar findings were noted in a smaller clinical trial ($n = 28$) with more ulcers closed, faster closure, higher percentage of ulcers closed by week 12, and fewer infections than in the control patients (Hanft and Suprenant, 2002).

Recommendation 9. We suggest consideration of the use of extracellular matrix products employing acellular human dermis or porcine small intestinal submucosal tissue as an adjunctive therapy for DFUs when recalcitrant to standard therapy (Grade 2C).

A variety of tissue constructs have recently become available, approved through the 510K mechanism as adjunctive therapies for the healing of chronic wounds including DFUs. This includes products incorporating human tissue (acellular dermis, amniotic membrane, cryopreserved skin, others) or animal tissue (bladder tissue, pericardial tissue, intestinal submucosa). Of the multitude of these products, only two have been found to provide benefit compared with standard DFU treatment. A porcine small intestinal submucosa (SIS) construct (OASIS; Cook Biotech, West Lafayette, Ind) has been tested in a prospective randomized trial. In this study, 73 patients with DFUs were randomized to treatment with standard care and SIS compared with standard care and becaplermin. More wounds in the SIS-treated group healed at 12 weeks (49% vs 28% treated with becaplermin; $P = .055$). Although it is not statistically superior to treatment with PDGF, it seems reasonable to consider the use of SIS, given the previous trials demonstrating improved healing rates with becaplermin compared with standard DFU therapy (Niezgoda et al., 2005).

An acellular human dermal matrix (Graftjacket; Wright Medical Technology, Memphis, Tenn) was studied in a prospective randomized multicenter trial in 87 patients with DFUs compared with standard care. Significantly more wounds treated with the human dermal matrix healed at 12 weeks (69.6%) than with control (46.2%; $P = .03$) (Reyzelman et al., 2009)

It must be stressed that these adjunctive therapies are not a substitute for the standard principles of wound healing. If the wound is not well prepared before application of a growth factor or living tissue substitute, there is little potential for wound stimulation or accelerated healing. Strict wound off-loading is required for maximum benefit.

Wound Healing Society (WHS) Update: Diabetic Foot Ulcer Treatment Guidelines (Lavery et al., 2016)

The objectives of the WHS DFU guidelines are to systematically evaluate the medical literature to assist clinicians in making health care decisions, identify areas that need additional research, and to clarify controversial diagnosis and treatment strategies.

Guideline # 7.2.2: Cellular and Acellular skin equivalents improve DFU healing. (Level I)

Principle: Healthy living skin cells assist in healing DFUs by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed.

Wound Healing Society 2015 Update on Guidelines for Venous Ulcers (Marston et al., 2016)

Guideline #7b.1: There is evidence that a bioengineered bilayered living human cellular construct, used in conjunction with compression bandaging, increases the incidence of healing and speed of healing for venous ulcers compared with compression and a simple dressing (Level I).

Principle: Various skin substitutes or biologically active dressings are emerging that provide temporary wound closure and serve as a source of stimuli (e.g., growth factors) for healing of venous ulcers. One of these, a cellular construct made using living neonatal fibroblasts and

keratinocytes, was found to heal significantly more wounds than compression alone in a randomized clinical trial. We recommend that prior to the application of any biologically active dressing, adequate wound bed preparation should be completed including complete.

Guideline#7b.3: There is evidence that a porcine small intestinal submucosal construct may enhance healing potential of venous ulcers. (Level II)

Principle: Numerous tissue constructs are available for use in chronic wounds that employ either human tissue (amniotic membrane, cryopreserved skin) or animal tissue (bladder, fetal bovine skin, others). Some are reported to contain active growth factors or other attributes that might be beneficial to healing venous leg ulcers. Of the multitude of such products currently marketed, only porcine small intestinal submucosa has prospective randomized data supporting its utilization to accelerate venous ulcer closure.

International Working Group on the Diabetic Foot (IWGDF) Practical Guidelines on the Prevention and Management of Diabetic Foot Disease (Schaper et al., 2020)

Foot ulcers will heal in the majority of patients if the clinician bases treatment on the principles outlined in these Guidelines, including pressure offloading, restoration of tissue perfusion, treatment of infection, metabolic control and treatment of comorbidities, local ulcer care, and patient education. Offloading is a cornerstone in treatment of ulcers that are caused by increased biomechanical stress. However, even optimum wound care cannot compensate for continuing trauma to the wound bed, or for inadequately treated ischemia or infection. Patients with an ulcer deeper than the subcutaneous tissues often require intensive treatment, and, depending on their social situation, local resources, and infrastructure, they may need to be hospitalized.

International Working Group on the Diabetic Foot (IWGDF) Guidelines on Use of Interventions to Enhance Healing of Chronic Foot Ulcers in Diabetes (Rayman et al., 2019)

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999.

9. Consider the use of placental derived products as an adjunctive treatment, in addition to best standard of care, when the latter alone has failed to reduce the size of the ulcer (weak; low).

Rationale: Human placental membranes contain a combination of growth factors, collagen-rich extracellular matrix, and cells including mesenchymal stem cells, neonatal fibroblasts, and epithelial cells that provide the necessary mechanisms for coordinated wound healing. Multiple growth factors and proteins including TGF- β 3 and human growth factor, antimicrobial proteins and angiogenic factors (VEGF, PDGF, and basic fibroblast growth factor) are present in the matrix. A number of products derived from different components of the placental and umbilical cord have been developed to enhance healing in a variety of tissues including diabetic foot skin wounds. Cryopreserved preparations contain living cells as well as growth factors whereas dehydrated products which are easier to store, and handle contain growth factors but no living cells. The previous review reported a single study of an amniotic membrane wound graft but commented that the study was of high risk of bias and the conclusions marred by the low rate of healing in the comparator group (Zelen et al., 2013) In the relatively short period of time since that study, interest in this type of therapy has developed rapidly as shown by the number of new placental-derived products available and the publication of eight RCTs and a cohort registry study.

Analysis of Evidence (Rationale for Determination)

Skin substitutes 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).

Studies are lacking for many skin substitutes which are essential to evaluate effectiveness and the impact that the product has on health outcomes. Evidence is needed to show that the product improves health outcomes or provide benefits relative to established alternatives or standard of care. Many of the current studies are noted to be funded by industry, which presents concerns regarding bias for these studies.

Systematic reviews have found that skin substitutes increase in the healing rate of foot ulcers and slightly fewer amputations in people with diabetes compared with standard care alone. However, the data available is insufficient to draw conclusions on the effectiveness of different types of skin substitutes, and evidence of long-term effectiveness is lacking. It is important to note that skin substitutes cannot be seen as a treatment on their own but should always be part treatment protocol that includes pressure offloading and ulcer protection, restoration of tissue perfusion, monitoring for infection, metabolic control and treatment of comorbidities, local ulcer care and patient education.

Despite the lack of high quality randomized controlled studies, skin substitutes are recommended as an adjunct to the established standard of care treatment protocols for wound care to increase the chances of healing in diabetic foot ulcers and venous leg ulcers by Clinical Practice Guidelines.

Coding

Application of skin substitute grafts (CPT 15271-15278)

To be properly performed, every code in this CPT code range requires the use of a skin substitute graft. These codes include preparation of the wound and application of the skin substitute graft product through suturing or various other techniques. The skin substitute grafts themselves are identified separately by a HCPCS code. Effective 1/1/2026, the HCPCS codes for the skin substitute products are considered add-on codes and cannot be reported without CPT 15271, 15273, 15275 or 15277).

Removal of current graft and/or simple cleansing of the wound is included, when performed. Do not report CPT 97602. Use of surgical preparation services in conjunction with skin substitute application codes will be considered not reasonable and necessary.

Debridement is considered a separate procedure only when gross contamination requires prolonged cleansing, when appreciable amounts of devitalized or contaminated tissue are removed, or when debridement is carryout out separately without immediate primary closure.

Note: CPT 15271-15278 are not to be reported for application of non-graft wound dressings (e.g., gel, powder, ointment, foam, liquid) or injected skin substitutes. Application of non-graft wound dressings is not separately reportable.

Code	Description
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)

15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)

Skin substitutes covered for Medicare HMO Plus, NaviCare, PACE and Community Care members for the treatment of diabetic foot ulcers effective for dates of services on or after January 1, 2026

Must be reported with a CPT code for application of skin substitute grafts.

Code	Description
A2019	Kerecis omega3 Marigen shield, per square centimeter
Q4101	Apligraf, per sq cm
Q4102	Oasis wound matrix, per sq cm
Q4105	Integra dermal regeneration template, per sq cm
Q4106	Dermagraft, per sq cm
Q4107	Graftjacket, per square centimeter
Q4110	Primatrix, per square centimeter
Q4121	Theraskin, per square centimeter
Q4122	Dermacell, Dermacell AWM or Dermacell AWM porous, per square centimeter
Q4128	Flex HD, or Allopatch HD, per square centimeter
Q4133	Grafix Prime, GrafixPL Prime, Stravix and StravixPL, per square centimeter
Q4151	Amnioband or Guardian, per square centimeter
Q4158	Kerecis Omega3, per square centimeter
Q4159	Affinity, per square centimeter
Q4160	Nushield, per square centimeter
Q4186	Epifix, per square centimeter
Q4187	Epicord, per square centimeter
Q4203	Derma-Gide, per square centimeter

Skin substitutes covered for Medicare HMO Plus, NaviCare, PACE and Community Care members for the treatment of venous leg ulcers effective for dates of service on or after January 1, 2026

Must be reported with a CPT code for application of skin substitute grafts.

Code	Description
Q4101	Apligraf per sq cm
Q4102	Oasis wound matrix, per sq cm
Q4106	Dermagraft, per square centimeter
Q4151	Amnioband or guardian, per square centimeter
Q4186	Epifix, per square centimeter

Skin substitutes considered experimental and investigational effective for dates of service on or after January 1, 2026

Code	Description
A2001	Innovamatrix AC, per sq cm
A2002	Mirrugen Advanced Wound Matrix, per sq cm
A2003	Bio-Connekt Wound Matrix, per sq cm

A2004	XCelliStem, per sq cm
A2005	Microlyte matrix, per sq cm
A2006	NovoSorb SynPath dermal matrix, per sq cm
A2007	Restrata, per sq cm
A2008	TheraGenesis, per sq cm
A2009	Symphony, per sq cm
A2010	Apis, per sq cm
A2011	Supra SDRM, per sq cm
A2012	Suprathel, per sq cm
A2013	InnovaMatrix FS, per sq cm
A2014	Omeza Collagen Matrix, per sq cm
A2015	Phoenix Wound Matrix, per sq cm
A2016	PermeaDerm B, per sq cm
A2017	PermeaDerm Glove, each
A2018	PermeaDerm C, per sq cm
A2019	Kerecis OmegaS MariGen Shield, per sq cm
A2020	ACS Advance Wound System (ACS)
A2021	NeoMatriX, per sq cm
A2022	Innova Burn or InnovaMatrix XL, per sq cm
A2023	InnovaMatrix PD, 1 mg
A2024	Resolve Matrix, per sq cm
A2025	Miro3D, per sq cm
A4100	Skin substitute, FDA-cleared as a device, not otherwise specified
C9358	Dermal substitute, native, non-denatured collagen, fetal bovine origin (Surgimend collagen matrix), per 0.5 square centimeters
C9360	Dermal substitute, native, non-denatured collagen, neonatal bovine origin (Surgimend collagen matrix), per 0.5 square centimeters
C9363	Skin substitute, integra meshed bilayer wound matrix, per square centimeter
Q4100	Skin substitute, not otherwise specified
Q4103	Oasis burn matrix, per sq cm
Q4104	Integra bilayer matrix wound dressing (BMWWD), per sq cm
Q4108	Integra Matrix, per sq cm
Q4111	GammaGraft
Q4112	Cymetra, Injectable, 1 cc
Q4113	GraftJacket Xpress, Injectable, 1 cc
Q4114	Integra flowable wound matrix, Injectable, 1 cc
Q4115	AlloSkin, per sq cm
Q4116	AlloDerm, per sq cm
Q4117	HyaloMatrix, per sq cm
Q4118	MatriStem micromatrix, 1 mg
Q4123	AlloSkin RT, per sq cm
Q4124	Oasis ultra tri-layer wound matrix, per sq cm
Q4125	ArthroFlex, per sq cm

Q4126	MemoDerm, DermaSpan, TranZgraft or InteguPly, per sq cm
Q4127	Talymed, per sq cm
Q4130	Strattice TM, per sq cm
Q4132	Grafix Core and GrafixPL Core, per sq cm
Q4134	Hmatrix, per sq cm
Q4135	Mediskin, per sq cm
Q4136	E-Z Derm, per sq cm
Q4137	AmnioExcel or BioDExCel, per sq cm
Q4138	BioDFence, DryFlex, per sq cm
Q4139	AmnioMatrix or BioDMatrix, Injectable, 1 cc
Q4140	BioDFence, per sq cm
Q4141	AlloSkin AC, per sq cm
Q4142	XCM biologic tissue matrix, per sq cm
Q4143	Repriza, per sq cm
Q4145	EpiFix, Injectable, 1 mg
Q4146	Tensix, per sq cm
Q4147	Architect, Architect PX, Architect FX, extracellular matrix, per sq cm
Q4148	Neox Cord 1k, Neox Cord RT, or Clarix Cord 1K, per sq cm
Q4149	Excellagen, 0.1cc
Q4150	AlloWrap DS or dry, per sq cm
Q4152	DermaPure, per sq cm
Q4153	Dermavest and Plurivest, per sq cm
Q4154	Biovance, per sq cm
Q4155	Neox Flo or Clarix Flo 1 mg
Q4156	Neox 100 or Clarix 100, per sq cm
Q4157	Revitalon, per sq cm
Q4161	Bio-Connekt wound matrix, per sq cm
Q4162	WoundEx Flow, BioSkin Flow, 0.5 cc
Q4163	WoundEx, Bioskin, per sq cm
Q4164	Helicoll, per sq cm
Q4165	Keramatrix or Kerasorb, per sq cm
Q4166	Cytal, per sq cm
Q4167	Truskin, per sq cm
Q4168	AmnioBand, 1 mg
Q4169	Artacent wound, per sq cm
Q4170	Cygnus, per sq cm
Q4171	Interfyl, 1 mg
Q4172	Puraply or Puraply AM, per sq cm
Q4173	PalinGen or PallinGen XPlus, per sq cm
Q4174	PalinGen or ProMatriX, 0.36 mg per 0.25 cc
Q4175	Miroderm, per sq cm

Q4176	NeoPatch or therion, per sq cm
Q4177	FlowerAmnioFlo, 0.1 cc
Q4178	FlowerAmnioPatch, per sq cm
Q4179	FlowerDerm, per sq cm
Q4180	Revita, per sq cm
Q4181	Amnio Wound, per sq cm
Q4182	Transcyte, per sq cm
Q4183	Surgigraft, per sq cm
Q4184	Cellesta or Cellesta Duo, per sq cm
Q4185	Cellesta Flowable Amnion (25 mg per cc); per 5 cc
Q4186	EpiFix, per sq cm
Q4187	Epicord, per sq cm
Q4188	AmnioArmor, per sq cm
Q4189	Artacent AC, 1 mg
Q4190	Artacent AC, per sq cm
Q4191	Restorigin, per sq cm
Q4192	Restoragin, 1 cc
Q4193	Coll-e-Derm, per sq cm
Q4194	Novachor, per sq cm
Q4195	PuraPly, per sq cm
Q4196	PuraPly AM, per sq cm
Q4197	PuraPly XT, per sq cm
Q4198	Genesis Amniotic Membrane, per sq cm
Q4199	Cygnus matrix, per sq cm
Q4200	Skin TE, per sq cm
Q4201	Matrion, per sq cm
Q4202	Keroxx (2.5g/cc), 1 cc
Q4203	Derma-Gide, per sq cm
Q4204	XWRAP, per sq cm
Q4205	Membrane Graft or Membrane Wrap, sq cm
Q4206	Fluid Flow or Fluid GF, 1 cc
Q4208	Novafix, per sq cm
Q4209	SurGigraft, per sq cm
Q4211	Amnion Bio or AxoBioMembrane, per sq cm
Q4212	AlloGen, per cc
Q4213	Ascent, 0.5mg
Q4214	Cellesta Cord, per sq cm
Q4215	Axolotl Ambient or Axolotl Cryo, 0.1mg
Q4216	Artacent Cord, per sq cm
Q4217	WoundFix, BioWound, WoundFx Plus, BioWound Plus, WoundFix Xplus, BioWound Xplus, per sq cm
Q4218	SurgiCORD, per sq cm

Q4219	SurgiGRAFT-DUALI, per sq cm
Q4220	BellaCell HD or Surederm, per sq cm
Q4221	Amnio Wrap2, per sq cm
Q4222	ProgenaMatrix, per sq cm
Q4225	AmnioBind or DermaBind TL, per sq cm
Q4226	MyOwn Skin, includes harvesting and preparation procedures, per sq cm
Q4227	AmnioCore, per sq cm
Q4229	Cogenex Amniotic Membrane, per sq cm
Q4230	Cogenex Flowable Amnion, per 0.5 cc
Q4231	Corplex P, per cc
Q4232	Corplex, per sq cm
Q4233	SurFactor or NuDyn, per 5 cc
Q4234	XCellerate, per sq cm
Q4235	Amniorepair or AltIPly, per sq cm
Q4236	CarePATCH, per sq cm
Q4237	Cryo-Cord, per sq cm
Q4238	Derm-Maxx, per sq cm
Q4239	Amnio-Maxx or Amnio-Maxx Lite, per sq cm
Q4240	CoreCyte, for topical use only, per 5 cc
Q4241	PolyCyte, for topical use only, per 5 cc
Q4242	AmnioCyte Plus, per 0.5 cc
Q4244	Procenta, per 22 mg
Q4245	AmnioText, per cc
Q4246	CoreText or ProText, per cc
Q4247	Amniotext patch, per sq cm
Q4248	Dermacyte Amniotic Membrane Allograft, per sq cm
Q4249	AMNIPLY, per sq cm
Q4250	AmnioAmp-MP per sq cm
Q4251	Vim, per sq cm
Q4252	Vendaje, per sq cm
Q4253	Zenith Amniotic Membrane, per sq cm
Q4254	Novafix DL, per sq cm
Q4255	REGUaRD, topical use only, per sq cm
Q4256	MLG-Complete, per sq cm
Q4257	Release, per sq cm
Q4258	Enverse, per sq cm
Q4259	Celera Dual Layer or Celera Dual Membrane, per sq cm
Q4260	Signature APatch, per sq cm
Q4261	TAG, per sq cm
Q4262	Dual Layer Impax Membrane, per sq cm
Q4263	SurGraft TL, per sq cm

Q4264	Cocoon Membrane, per sq cm
Q4265	NeoStim TL, per sq cm
Q4266	NeoStim Membrane, per sq cm
Q4267	Neo Stim DL, per sq cm
Q4268	SurGraft FT, per sq cm
Q4269	SurGraft XT, per sq cm
Q4270	Complete SL, per sq cm
Q4271	Complete FT, per sq cm
Q4272	Esano A, per sq cm
Q4273	Esano AA, per sq cm
Q4274	Esano AC, per sq cm
Q4275	Esano ACA, per sq cm
Q4276	Orion, per sq cm
Q4278	Epieffect, per sq cm
Q4279	Vendaje AC, per sq cm
Q4280	Xcell Amnio Matrix, per sq cm
Q4281	Barrera SL or Barrera DL, per sq cm
Q4282	Cygnus Dual, per sq cm
Q4283	Biovance Tri-Layer or Biovance 3L, per sq cm
Q4284	DermaBind SL, per sq cm
Q4285	NuDYN DL or NuDYN DL MESH, per sq cm
Q4286	NuDYN SL or NuDYN SLW, per sq cm
Q4287	DermaBind DL, per sq cm
Q4288	DermaBind CH, per sq cm
Q4289	RevoShield + Amniotic Barrier, per sq cm
Q4290	Membrane Wrap-Hydro, per sq cm
Q4291	Lamellas XT, per sq cm
Q4292	Lamellas, per sq cm
Q4293	Amnio Quad-Core, per sq cm
Q4295	Amnio Tri-Core Amniotic, per sq cm
Q4296	Rebound Matrix, per sq cm
Q4297	Emerge Matrix, per sq cm
Q4298	AmnioCore PRO, per sq cm
Q4299	AmnioCor Pro+, per sq cm
Q4300	Acesso TL, per sq cm
A4301	Activate Matrix, per sq cm
Q4302	Complete ACA, per sq cm
Q4303	Complete AA, per sq cm
Q4304	Grafix plus, per sq cm
Q4305	American amnion ac tri-layer, per square centimeter
Q4306	American amnion ac, per square centimeter

Q4307	American amnion, per square centimeter
Q4308	Sanopellis, per square centimeter
Q4309	Via matrix, per square centimeter
Q4310	Procenta, per 100 mg

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Policy history

Origination date:	06/01//2021
Review/Approval(s):	Technology Assessment Committee: 12/08/2020 (policy origination), 07/10/2021 (Added clarifying language related to Medicare Advantage, MassHealth ACO, NaviCare and PACE under policy section), 04/23/2024 (annual review; updated MassHealth information under Policy section, added Summary of Evidence and Analysis of Evidence (Rationale for Determination; updated References, updated Coding), 11/25/2025 (annual review, no changes to coverage criteria, updated list of covered skin substitute products, added new sections for Medicare and MassHealth Variation, updated Coding). Utilization Management Committee: 12/16/2025: (annual review, approved with no changes to coverage criteria, approved updated list of covered skin substitute products), 02/17/2026 (update due to withdrawal of National Government Services, Inc. LCD for Skin Substitutes; Medicare coverage criteria for skin substitutes are not fully established therefore the Plan's coverage criteria are applicable).

Instructions for Use

Fallon Health complies with CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations for Medicare Advantage members. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health may create internal coverage criteria under specific circumstances described at § 422.101(b)(6)(i) and (ii).

Fallon Health generally follows Medical Necessity Guidelines published by MassHealth when making medical necessity determinations for MassHealth members. In the absence of Medical Necessity Guidelines published by MassHealth, Fallon Health may create clinical coverage criteria in accordance with the definition of Medical Necessity in 130 CMR 450.204.

For plan members enrolled in NaviCare, Fallon Health first follows CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with

jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, or if the NaviCare member does not meet coverage criteria in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health then follows Medical Necessity Guidelines published by MassHealth when making necessity determinations for NaviCare members.

Each PACE plan member is assigned to an Interdisciplinary Team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans.