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.

Policy

This Policy applies to the following Fallon Health products:

☒ Medicare Advantage (Fallon Medicare Plus, Fallon Medicare Plus Central)
☒ MassHealth ACO
☒ NaviCare HMO SNP
☒ NaviCare SCO
☒ 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 of greater than 4 weeks and referencing the specific interventions that have failed is required.

Medicare Advantage (Fallon Medicare Plus, Fallon Medicare Plus Central)
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).

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 or LCA skin substitutes (Medicare Coverage Database search 04/22/2024), therefore the Plan's coverage criteria are applicable.

The Agency for Healthcare Research and Quality completed a **Technology Assessment for Skin Substitutes for Treating Chronic Wounds** at the request of CMS in 2020 (Snyder et al., 2020). The 2020 Technology Assessment is an update of the 2012 AHRQ Technology Assessment (Snyder et al., 2012).

MassHealth ACO
Fallon Health 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.

MassHealth has **Guidelines for Medical Necessity Determination for Skin Substitutes** (MassHealth website search 04/22/2024), therefore the Plan's Clinical Coverage Criteria are not applicable.

NaviCare HMO SNP, NaviCare SCO
For plan members enrolled in NaviCare, Fallon Health first follow's 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.

PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
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.

Fallon Health Clinical Coverage Criteria

Initial coverage for skin substitutes will be authorized for up to 5 applications. 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.

I. Diabetic foot ulcers:
   1. The following skin substitute graft products may be considered medically necessary for the treatment of chronic full-thickness neuropathic diabetic foot ulcers that have not adequately responded to 4 weeks of standard care with documented compliance[1]:
      a. Apligraf (PMA 950032) Q4101, or
      b. Dermagraft (PMA P000036) Q4106, or
      c. Integra Dermal Regeneration Template, marketed as Integra Omnigraft Dermal Regeneration Matrix (PMA P900033) Q4105.

      AND
   2. All of the following criteria are met:

[1] The standard of care in diabetic foot ulcers is sharp debridement, daily wound care dressings, offloading and infection control (Snyder et al., 2010). During the two-week run-in period prior to randomization, 17% of eligible patients (22 of 126) achieved > 20% wound healing with daily dressing changes performed by the patient using collagen-alginate dressings and Camboot offloading and were excluded from the study (Zelen et al., 2016).

a. There is adequate circulation to the affected area[2],
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 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.

II. Venous leg ulcers:
1. The following skin substitute graft products may be considered medically necessary for the treatment of chronic partial and full-thickness venous leg ulcers that have not adequately responded to 4 weeks of standard care with documented compliance[3]:
   a. Apligraf (PMA 950032) Q4101, or
   b. Oasis Wound Matrix (510(k) (K061711) Q4102.

   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.

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.

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.

Exclusions

- Skin substitute products are not considered reasonable and necessary in patients with inadequate control of underlying conditions or exacerbating factors including but not limited to any of the following:
  - Use of skin substitutes in wounds with signs of clinical infection.
  - Use of skin substitutes when there is not adequate circulation to the affected area.
  - Use of skin substitutes in wounds with exposed bone, tendon, or fascia.
  - Use of skin substitutes in plan members with HbA1c >12%.

[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).
[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.

    - Use of skin substitutes in plan members with active Charcot arthropathy of the ulcer extremity
- Continued use of skin substitutes after 6 weeks in any patient whose wound has failed to heal by >/= 50% is not medically necessary
- Treatment with skin substitutes beyond 12 weeks is not typically medically necessary.

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).

Armstrong and colleagues (2021) conducted a retrospective review of Medicare claims for beneficiaries with a diagnosis of diabetes to assess the outcomes in patients receiving advanced

treatment (AT) with skin substitutes for lower extremity diabetic ulcers versus no advanced treatment (NAT). There were four treatment groups defined: AT, NAT, Other treatment, Combination of AT and other treatment. AT was defined as high-cost skin substitute products reported under CPT codes 15271 through 15278 and the applicable Healthcare Common Procedure Coding System (HCPCS) Q-code. CMS designates the HCPCS Q-code to either 'high' or 'low' cost groups under the hospital Outpatient Prospective Payment System (OPPS).12 NAT referred to episodes that were treated without high- or low-cost skin substitutes during the observed episode of care. Other treatments included low-cost skin substitutes, as determined by CMS.

This study was undertaken to redress the paucity of well-controlled clinical trials, unbiased studies and large datasets on which to evaluate care for patients with lower extremity diabetic ulcers. Many guidelines for lower extremity diabetic ulcer treatment exist, yet practice habits vary from clinic to clinic. There is a need to generate better policies, update reimbursement and raise the standard of care for patients with lower extremity diabetic ulcers. This study is a retrospective analysis of the Medicare population which identifies best outcomes for patients with lower extremity foot ulcers receiving AT or NAT and highlights improved outcomes when AT follows parameters for use (FPFU). Claims dates and data were used to determine if parameters for use (PFU) were followed, specifically if treatment began within 30–45 days of lower extremity diabetic foot ulcer diagnosis and continued at seven to 14-day intervals until episode resolution.

The main 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. For the time period from October 1, 2015 through to October 2, 2018, there were 9,738,760 patients with a diagnosis of diabetes, of whom 909,813 had a lower extremity diabetic ulcer.

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. 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-93932 (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 1 (12,676 episodes per cohort),

As a secondary objective, the effect on outcomes when a patient's AT episode follows parameters for use (FPFU) versus when a patient's episode did not FPFU was determined by creating additional propensity-matched groups. Propensity-matched group 1 included 1131 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 (i.e., followed evidence-derived specifications for use highlighted in the Medicare limited data). These patients were defined as AT FPFU and were propensity-matched to delineate Group 2 (AT not FPFU).

In the 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.

There are a growing number of products on the market which qualify as AT. The use of AT improved outcomes, but a further increase in favorable outcomes occurs by merely FPFU. Medicare providers and payors consult various guidelines in the decision to use an AT and the regularity with which the skin substitutes are applied. 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. Nonetheless, such relevant observations may never be fully recognized in the real world if wound care providers are not adequately informed on the optimal parameters for use related to the use of ATs. The recognition of best practices in treating LEDUs needs to be adopted by payors, instituted as policy and followed by providers (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, amnionic 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-blinded, 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-β3 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

Acute Outpatient Hospital and Ambulatory Surgical Center Billing

In the acute outpatient hospital setting, payment for skin substitute products that don't qualify for OPPS pass-through status is packaged into the OPPS payment for the associated skin substitute application procedure. All OPPS pass-through skin substitute products (ASC PI=K2) are billed in combination with one of the skin application procedures for CPT code 15271-15278.

This policy also applies in the ASC payment system. Note that ASCs should not separately bill for packaged skin substitutes (ASC PI=N1) since packaged codes are not reportable under the ASC payment system.

Under Medicare reimbursement methodology (used by Fallon Health for commercial and Medicare members), skin substitute products are divided into two groups for payment purposes:

1. High cost skin substitute products
2. Low cost skin substitute products

High cost skin substitute products should be billed in combination with the performance of one of the skin application procedures described by CPT codes 15271-15278.

Low cost skin substitute products should be billed in combination with the performance of one of the skin application procedures described by HCPCS code C5271-C5278.

The high cost versus low cost assignment is determined by CMS and published annually in the Update of the Hospital Outpatient Prospective Payment System and in the Update of the Ambulatory Surgical Center (ASC) Payment System transmittals.

See Table 21 in CMS Transmittal R12421CP for Skin Substitute Assignments to High-Cost and Low-Cost Groups for CY 2024. Transmittal R12421 is available at: https://www.cms.gov/files/document/r12421cp.pdf.

Excerpt from Table 21 in Transmittal R12421CP:

Calendar Year (CY) 2024 HCPCS Code	CY 2024 Sort Descriptor	CY 2024 High/Low Cost Assignment	CY 2024 High/Low Cost Assignment
Q4101	Apligraf	High	High
Q4102	Oasis Wound Matrix	Low	Low
Q4105	Integra DRT or OmniGraft	High	High
Q4106	Dermagraft	High	High

For MassHealth members, acute outpatient hospitals and ambulatory surgical centers should report the application of skin substitute graft using CPT code range 15271 through 15278. HCPCS code C5271-C5278 are not reimbursable for MassHealth members. Payment for skin substitutes is packaged into the payment for the associated skin substitute application procedure.

Physician Billing

Physicians report the application of skin substitute grafts in the CPT code range 15271 through 15278. In the office setting, skin substitute products are reimbursed separately. If the CMS quarterly ASP Drug Pricing File (available at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice) does not contain pricing for a skin substitute code that is within the Q41XX-Q42XX range, the claim must include the invoice or acquisition cost. Enter the invoice price or acquisition cost and the total amount of product used loop 2400 segment NTE on the electronic claim. If the code is defined as per square centimeter, the units billed must match the size billed in square centimeters. For example, Q4101 is coded as per square centimeter. If you have a product that is 4x4 square centimeters, you would enter as 16 units. Providers must maintain an invoice copy within the patient's file and it must be made available to Fallon Health upon request.

Application of skin substitute grafts

To be properly performed, every surgical procedure in this CPT/HCPCS code range requires the use of a skin substitute. These surgical procedures include preparation of the wound and application of the skin substitute product through suturing or various other techniques. The skin substitutes themselves are identified by a HCPCS code in the range Q4101-Q42XX. Claims reporting skin substitute grafts must contain the presence of an appropriate surgical procedure CPT or HCPCS code.

Use of surgical preparation services in conjunction with skin substitute application codes will be considered not reasonable and necessary.

Note: These procedures are not to be reported for application injected skin substitutes.

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)
C5271	Application of low cost 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 *Not covered for MassHealth members*
C5272	Application of low cost 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 *Not covered for MassHealth members*
C5273	Application of low cost 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 *Not covered for MassHealth members*
C5274	Application of low cost 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 *Not covered for MassHealth members*
C5275	Application of low cost 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 *Not covered for MassHealth members*
C5276	Application of low cost 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 *Not covered for MassHealth members*
C5277	Application of low cost 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 *Not covered for MassHealth members*
C5278	Application of low cost 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 *Not covered for MassHealth members*

Skin substitutes covered for the treatment of diabetic foot ulcers:

Code	Description
Q4101	Apligraf, per sq cm

Q4105	Integra dermal regeneration template, per sq cm
Q4106	Dermagraft, per sq cm

Skin substitutes covered for the treatment of venous leg ulcers:

Code	Description
Q4101	Apligraf, per sq cm
Q4102	Oasis wound matrix, per sq cm

Skin substitutes considered experimental and investigational). If a service lacks scientific evidence regarding safety and efficacy and is considered experimental or investigation, the service is noncovered as not medically necessary (not reasonable and necessary) to treat illness or injury.

A2001	Innovamatrix AC, per sq cm
A2002	Mirragen 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

Q4100	Skin substitute, not otherwise specified
Q4103	Oasis burn matrix, per sq cm
Q4104	Integra bilayer matrix wound dressing (BMWD), per sq cm
Q4107	GraftJacket, per sq cm
Q4108	Integra Matrix, per sq cm
Q4110	PriMatrix, 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
Q4121	TheraSkin, per sq cm
Q4122	DermACELL, per sq cm
Q4123	AlloSkin RT, per sq cm
Q4124	Oasis ultri tri-layer wound matrix, per sq cm
Q4125	ArthroFlex, per sq cm
Q4126	MemoDerm, DermaSpan, TranZgraft or IntéguPly, per sq cm
Q4127	Talymed, per sq cm
Q4128	FlexHD, AlloPatchHD, or MatrixHD, per sq cm
Q4130	Strattice TM, per sq cm
Q4132	Grafix Core and GrafixPL Core, per sq cm
Q4133	Grafix Prime, GrafixPL PRIME, Stravix and Stravix PL, 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
Q4151	AmnioBand or Guardian, 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
Q4158	Kerecis Omega3, per sq cm
Q4159	Affinity, per sq cm
Q4160	Nushield, 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
Q4210	Axolotl Graft or Axolotl DualGraft, 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-DUALl, per sq cm
Q4220	BellaCell HD or Surederm, per sq cm
Q4221	Amnio Wrap2, per sq cm
Q4222	ProgenaMatrix, per sq cm
Q4224	Human Health Factor 10 Amniotic Patch (HHF10-P), 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
Q4277	WoundPlus membrane or E-Graft, 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

References

1. Centers for Medicare & Medicaid Services (CMS). Medicare and Medicaid Programs: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems and Quality Reporting Programs Calendar Year 2014 Final rule with comment period (CMS-1601-FC). December 10, 2013. Available at: https://www.govinfo.gov/content/pkg/FR-2013-12-10/pdf/2013-28737.pdf.
2. Snyder DL, Sullivan N, Schoelles KM. Skin substitutes for treating chronic wounds. Final report. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2012 Dec 18. 203 p. (Technology assessment report; Also available: http://www.ahrq.gov/research/findings/ta/skinsubs/HCPR0610_skinsubst-final.pdf.
3. Ovington LG. Hanging wet-to-dry dressings out to dry. *Adv Wound Care*. 2002 Mar-Apr;15(2):79-86.
4. Eisenbud D, Huang NF, Luke S, et al. Skin substitutes and wound healing: current status and challenges. *Wounds*. 2004;16(1):2–17.
5. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. *Adv Wound Care (New Rochelle)*. 2015 Sep 1;4(9):560-82.
6. Berlowitz D, VanDeusen Lukas C, Parker V, et al. Preventing pressure ulcers in hospitals: a toolkit for improving quality of care. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2014. 156 p. Also available: http://www.ahrq.gov/research/ltc/pressureulcertoolkit/putoolkit.pdf.
7. Nathoo R, Howe N, Cohen G. Skin substitutes: an overview of the key players in wound management. *J Clin Aesthet Dermatol*. 2014 Oct;7(10):44-8.
8. Snyder DL, Sullivan N, Margolis DJ, Schoelles K. Skin substitutes for treating chronic wounds. Technology Assessment Program Project ID No. WNDT0818. (Prepared by the ECRI Institute-Penn Medicine Evidence-based Practice Center under Contract No. HHSA 290-2015-00005-I) Rockville, MD: Agency for Healthcare Research and Quality. February 2020. Available at: http://www.ahrq.gov/research/findings/ta/index.html.

9. Center for Biologics Evaluation and Research (CBER). Guidance for industry: chronic cutaneous ulcer and burn wounds — developing products for treatment. Rockville (MD): U.S. Food and Drug Administration, Center for Drug Evaluation and Research; 2006 Jun. 22 p. Also available: http://www.fda.gov/cder/guidance/index.htm#clinical%20medicine.
10. Clayton, Jr W, Elasy, TA. A review of the pathophysiology, classification, and treatment of foot ulcers in diabetic patients. *Clin Diabetes*. 2009;27(2):52-8.
11. Eklöf B, Rutherford RB, Bergan JJ, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg*. 2004 Dec;40(6):1248-52.
12. Carter MJ, Fife CE, Walker D, et al. Estimating the applicability of wound care randomized controlled trials to general wound-care populations by estimating the percentage of individuals excluded from a typical wound-care population in such trials. *Adv Skin Wound Care*. 2009 Jul;22(7):316-24.
13. Driver VR, Lavery LA, Reyzelman AM, et al. A clinical trial of Integra Template for diabetic foot ulcer treatment. *Wound Repair and Regeneration*. 2015;23:891-900.
14. Snyder RJ, Kirsner RS, Warriner III RA, et al. Consensus Recommendations on Advancing the Standard of Care for Treating Neuropathic Foot Ulcers in Patients with Diabetes. *Ostomy Wound Management.* 2010;56(Suppl 4):S1-S24.
15. Brown-Etris M, Milne CT, Hodde JP. Anextracellular matrix graft (Oasis(®) wound matrix) for treating full-thickness pressure ulcers: a randomized clinical trial. *J Tissue Viability*. 2019;28:21-26.
16. Veves A, Falanga V, Armstrong DG, Sabolinski ML; Apligraf Diabetic Foot Ulcer Study. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care*. 2001 Feb;24(2):290-5.
17. Marston WA, Hanft J, Norwood P, Pollak R; Dermagraft Diabetic Foot Ulcer Study Group. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care*. 2003 Jun;26(6):1701-5.
18. Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. *Arch Dermatol*. 1998 Mar;134(3):293-300.
19. O'Donnell TF Jr, Passman MA, Marston WA, et al.; Society for Vascular Surgery; American Venous Forum. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum. *J Vasc Surg*. 2014 Aug;60(2 Suppl):3S-59S.
20. Zaulyanov L, Kirsner RS. A review of a bi-layered living cell treatment (Apligraf) in the treatment of venous leg ulcers and diabetic foot ulcers. *Clin Interv Aging*. 2007;2(1):93-98.
21. Hankin CS, Knispel J, Lopes M, Bronstone A, Maus E. Clinical and cost efficacy of advanced wound care matrices for venous ulcers. *J Manag Care Pharm*. 2012 Jun;18(5):375-84.
22. Zelen CM, Serena TE, Gould L, Le L, Carter MJ, Keller J, Li WW. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. *Int Wound J*. 2016 Apr;13(2):272-82.
23. Sheehan P, Jones P, Caselli A et al. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care*. 2003; 26(6):1879– 1882.
24. Atkin L, Bućko Z, Montero EC et al. Implementing TIMERS: the race against hard-to-heal wounds. *J Wound Care.* 2019; 28 Sup3a:S1–S50.
25. Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *Int Wound J*. 2013 Oct;10(5):502-7.
26. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix([R]) for the treatment of chronic diabetic foot ulcers: results of a multi-Centre, controlled, randomised, blinded, clinical trial. *Int Wound J*. 2014;11(5):554-560.
27. Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-Centre comparative effectiveness study of healing using dehydrated human

amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. *Int Wound J*. 2015;12(6):724-732.
28. DiDomenico LA, Orgill DP, Galiano RD, et al. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. *Plast Reconstr Surg Glob Open*. 2016;4(10):e1095.
29. Mohajeri-Tehrani MR, Variji Z, Mohseni S, et al. Comparison of a bioimplant dressing with a wet dressing for the treatment of diabetic foot ulcers: a randomized. *Controlled Clinical Trial Wounds*. 2016;28 (7):248-254.
30. Snyder RJ, Shimozaki K, Tallis A, et al. A prospective, randomized, multicenter, controlled evaluation of the use of dehydrated amniotic membrane allograft compared to standard of care for the closure of chronic diabetic foot ulcer. *Wounds: A Compendium of Clinical Research and Practice*. 2016;28(3):70-77.
31. Tettelbach W, Cazzell S, Reyzelman AM, Sigal F, Caporusso JM, Agnew PS. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: a prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. *Int Wound J*. 2019;16(1):19-29.
32. Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. *Int Wound J*. 2019;16(1):122-130.
33. Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multicentre comparative study examining clinical efficacy and cost. *Int Wound J*. 2016;13(2):272-282.
34. Kirsner RS, Sabolinski ML, Parsons NB, Skornicki M, Marston WA. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. *Wound Repair Regen*. 2015;23(5):737-744.
35. U.S. Food and Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use-Guidance for Industry and Food and Drug Administration Staff. Center for Biologics Evaluation and Research. Center for Devices and Radiological Health. Office of Combination Products. July 2020. Available at: https://www.fda.gov/media/109176/download.
36. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg*. 2016 Feb;63(2 Suppl):3S-21S.
37. Veves A, Falanga V, Armstrong DG, Sabolinski ML; Apligraf Diabetic Foot Ulcer Study. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care*. 2001 Feb;24(2):290-5.
38. Niezgoda JA, Van Gils CC, Frykberg RG, Hodde JP. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care*. 2005 Jun;18(5 Pt 1):258-66.
39. Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *Int Wound J*. 2009 Jun;6(3):196-208.
40. Marston WA, Hanft J, Norwood P, Pollak R; Dermagraft Diabetic Foot Ulcer Study Group. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care*. 2003 Jun;26(6):1701-5.
41. Hanft JR, Surprenant MS. Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. *J Foot Ankle Surg*. 2002 Sep-Oct;41(5):291-9.
42. Lavery LA, Davis KE, Berriman SJ, et al. WHS guidelines update: Diabetic foot ulcer treatment guidelines. *Wound Repair Regen*. 2016 Jan-Feb;24(1):112-26.
43. Marston W, Tang J, Kirsner RS, Ennis W. Wound Healing Society 2015 update on guidelines for venous ulcers. *Wound Repair Regen*. 2016 Jan-Feb;24(1):136-44.

44. Rayman G, Vas P, Dhatariya K, et al. International Working Group on the Diabetic Foot (IWGDF). Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020 Mar;36 Suppl 1:e3283.
45. Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ, Lipsky BA; IWGDF Editorial Board. Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020 Mar;36 Suppl 1:e3266.
46. Gordon AJ, Alfonso AR, Nicholson J, Chiu ES. Evidence for Healing Diabetic Foot Ulcers With Biologic Skin Substitutes: A Systematic Review and Meta-Analysis. *Ann Plast Surg*. 2019 Oct;83(4S Suppl 1):S31-S44.
47. Ontario Health (Quality). Skin Substitutes for Adults With Diabetic Foot Ulcers and Venous Leg Ulcers: A Health Technology Assessment. *Ont Health Technol Assess Ser*. 2021 Jun 4;21(7):1-165
48. Santema TB, Poyck PP, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev*. 016;2(2):CD011255.
49. Armstrong DG, Tettelbach WH, Chang TJ, et al. Observed impact of skin substitutes in lower extremity diabetic ulcers: lessons from the Medicare Database (2015-2018). *J Wound Care*. 2021 Jul 1;30(Sup7):S5-S16.
50. Tettelbach WH, Armstrong DG, Chang TJ, et al. Cost-effectiveness of dehydrated human amnion/chorion membrane allografts in lower extremity diabetic ulcer treatment. *J Wound Care*. 2022;31(Sup2):S10-S31.
51. Tettelbach W, Forsyth A. Specialty specific quality measures needed to improve outcomes in wound care. Int Wound J. 2023 May;20(5):1662-1666.

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).

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.