MEDICAL POLICY

Medical Policy Title	**Bioengineered Tissue Products for Wound Treatment and Surgical Interventions**
Policy Number	**7.01.35**
Current Effective Date	**January 1, 2027**
Next Review Date	**August 2027**

Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service.
(Link to Product Disclaimer)

POLICY STATEMENT(S)

This policy does not address fibrin sealants (e.g., Tisseel) or repair of ocular defects.

I. The following bioengineered tissue products are considered **medically appropriate** for the listed indications, when criteria are met:

A. Diabetic Foot Ulcers (AlloPatch, Apligraf, AmnioBand Membrane, Biovance, Dermagraft, EpiCord, EpiFix, Grafix CORE, Grafix PRIME, Integra, Integra Dermal Regeneration Matrix (Omnigraft), Oasis Wound Matrix, TheraSkin) when meeting **ALL** of the following criteria:

1. The patient has adequate arterial blood supply as evidenced by ankle-brachial index (ABI) of 0.65 or greater in the limb being treated;
2. The patient is competent or has support system required to participate in follow-up care associated with treatment with a bioengineered tissue product;
3. Ulcers are full thickness, extend through the dermis but without tendon, muscle, capsule, or bone exposure, and of greater than three (3) weeks' duration for which standard wound therapy has failed;
4. Patient has adequate treatment of underlying disease process(es) contributing to the ulcer;
5. Ulcers are located on foot or toes and are free of infection, redness, drainage, underlying osteomyelitis, surrounding cellulitis, tunnels and tracts, eschar, or any necrotic material that would interfere with adherence of a bioengineered tissue product and wound healing;
6. Patient's current HbA1C does not exceed 12%; and
7. Absence of the following contraindications:
   a. Known hypersensitivity to bovine collagen, silicone, or chondroitin materials;
   b. Pregnancy;
   c. Clinically diagnosed infected wounds.

B. Venous Ulcers (Apligraf, AmnioBand, EpiFix, Oasis Wound Matrix, TheraSkin) when meeting

ALL of the following criteria:

1. The patient has adequate arterial blood supply as evidenced by ankle-brachial index (ABI) of 0.65 or greater in the limb being treated;
2. The patient is competent or has support system required to participate in follow-up care associated with treatment with a bioengineered tissue product;
3. Ulcers are partial or full thickness and have failed to respond to conservative measures of at least one (1) month duration that have, at a minimum, included regular dressing changes, debridement of necrotic tissue, and standard therapeutic compression. ("Failure to respond" is defined as increase in size or depth or no change in size or depth with no sign or indication that improvement is likely, such as granulation, epithelialization, or progress toward closing);
4. Patient has adequate treatment of the underlying disease process(es) contributing to the ulcer; and
5. Ulcers are free of infection, redness, drainage, underlying osteomyelitis, surrounding cellulitis, tunnels and tracts, eschar or any necrotic material that would interfere with adherence of a bioengineered tissue product and wound healing.

C. Breast Reconstruction (Alloderm, AlloMax/Cortiva, DermACELL AWM, DermaMatrix, FlexHD, GraftJacket, Surgimend)
   1. Breast reconstruction surgery following surgical mastectomy
      a. Evidence on acellular dermal matrix (ADM) in post-mastectomy expander/implant breast reconstruction is varied and conflicting. Surgeons should evaluate each clinical case individually and objectively determine the use of ADM.

D. Nasal Repairs (Alloderm)
   1. Septal repair, septal perforation repair, or reconstructive septorhinoplasty

E. Non-Primary Hernia Repair (Alloderm)
   1. When chronic infection contraindicates the use of mesh or other conventional repair

F. Parotidectomy (Alloderm)

G. Burns
   1. Integra Dermal Regeneration Matrix (Omnigraft) when meeting **ALL** of the following criteria:
      a. Insufficient autograft is available at the time of burn excision; **and**
      b. When used for **ANY** of the following indications:
         i. post excisional treatment of a full thickness or deep partial thickness burn;
         ii. for repair of scar contractures secondary to third-degree burns;
   2. Biobrane

a. When used as a temporary covering for clean, debrided superficial and partial thickness burns and donor sites;

3. Epicel
    a. deep dermal or full thickness burns over greater than 30% of the body;
4. TransCyte
    a. When used for temporary covering of a surgically excised deep partial or full thickness burn wound as a covering prior to autografting.

II. After initial treatment has been completed, reinitiated treatment on the same wound site less than one (1) year after successful treatment is considered treatment failure and **not medically appropriate**.

III. **ALL** other bioengineered tissue products are considered **investigational** for **ANY** indication.

RELATED POLICIES

Corporate Medical Policy

1.01.38 Negative Pressure Wound Therapy (Vacuum Assisted Closure)

2.01.24 Platelet Rich Plasma and Growth Factor Treatments

9.01.20 Amniotic Membrane Grafting/Transplantation (AMG/AMT) for Ophthalmologic Conditions

10.01.01 Breast Reconstruction Surgery

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

I. Specific products should only be used in accordance with US Food and Drug Administration (FDA) product approval and when the above policy criteria are met.

II. If a product is not FDA approved for the indication for which it is being used (i.e.., “off label” use), documentation of a shared decision-making process and informed consent is required.

III. The FDA requests prompt reporting of adverse effects associated with bioengineered tissue products through MedWatch, the FDA Safety Information and Adverse Event Reporting Program.

IV. If a wound has not responded to standard of care by achieving a 50% or better wound reduction after four weeks of standard of care, a single application of a bioengineered tissue product was thought to be all that was required to affect wound healing in wounds likely to be improved by this treatment. Based on clinical input from wound specialists, refractory wounds rarely heal with one graft application and may require additional graft applications, no more frequently than once per week, until the wound heals. Re-application of a product is appropriate only if there has been measurable response to the first application.

V. Treatment of venous stasis ulcers that extend above the malleoli is beyond the scope of practice of podiatrists.

DESCRIPTION

Bioengineered tissue products are cellular (contain living cells) or acellular (no biological component) matrices that can be derived from human tissue (autologous or allogeneic), nonhuman tissue (xenographic), synthetic materials, or a composite of these materials. Manufacturing processes vary, but generally involve seeding selected cells onto a matrix, where they receive proteins and growth factors necessary for them to develop into the desired tissue. The tissue may then be used for a variety of procedures, including breast reconstruction, treatment of severe burns, and healing of diabetic and venous ulcers.

SUPPORTIVE LITERATURE

Diabetic Foot Ulcers (AlloPatch, Apligraf, AmnioBand Membrane, Biovance, Dermagraft, EpiCord, EpiFix, Grafix CORE, Grafix PRIME, Integra, Integra Dermal Regeneration Matrix (Omnigraft), Oasis Wound Matrix)

Tettelbach et al (2018) conducted a multicenter prospective randomized controlled comparative parallel study at 11 centers in the United States. The aim of this study was to determine the safety and effectiveness of dehydrated human umbilical cord allograft (EpiCord) compared with alginate wound dressings for the treatment of chronic, non-healing diabetic foot ulcers (DFU). 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. After 14 days of weekly debridement, moist wound therapy, and off-loading, those with ≤30% wound area reduction post-debridement (n = 155) were randomized 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 hydropolymer secondary dressing, and gauze bandage roll (n = 54). Study visits were conducted for 12 weeks. Data for randomized subjects meeting study inclusion criteria were included in an intent-to-treat (ITT) analysis. Additional analysis was conducted on a group of subjects (n = 134) who completed the study per protocol (PP) (EpiCord, n = 86, alginate, n = 48) and for those subjects receiving adequate debridement (EpiCord, n = 67, alginate, n = 40). ITT analysis showed that DFUs treated with EpiCord were more likely to heal within 12 weeks than those receiving alginate dressings, 71 of 101 (70%) vs 26 of 54 (48%) for EpiCord and alginate dressings, respectively, P = 0.0089. Healing rates at 12 weeks for subjects treated PP were 70 of 86 (81%) for EpiCord-treated and 26 of 48 (54%) for alginate-treated DFUs, P = 0.0013. For those DFUs that received adequate debridement (n = 107, ITT population), 64 of 67 (96%) of the EpiCord-treated ulcers healed completely within 12 weeks, compared with 26 of 40 (65%) of adequately debrided alginate-treated ulcers, P < 0.0001. 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 authors conclude these results demonstrate the safety and efficacy of EpiCord as a treatment for non-healing DFUs.

A review article (Zelen 2015a) addresses the use of human amnion/chorion membrane (dHACM) for lower extremity repair. The article states:

Although there is limited data available regarding most amniotic membrane-based products, there is substantial preclinical and clinical evidence supporting the rationale and effectiveness of dHACM allograft as a treatment modality. The rapidly growing body of evidence suggests that the properties inherent in dHACM promote tissue regeneration and healing, recruiting patients' own stem cells into

the wounded area. Randomized controlled trials evaluating dHACM now include more than 200 patients collectively and the results consistently show improved healing. Use of dHACM has been shown to be more clinically effective and cost-effective than other frequently used advanced wound care products. This cost-effectiveness results from dHACM showing higher healing rates and more rapid healing than other advanced wound care products. Cost-effectiveness is also enhanced through the availability of grafts of multiple sizes, which reduces wastage, and through ease of handling and storage for clinical use. Ongoing and future studies will further define and establish the value of amniotic membrane for chronic tissue repair and regeneration.

A small, industry-sponsored, non-blinded, RCT comparing the use of EpiFix (n=13) with SOC (moist wound therapy, n=12) for diabetic foot ulcers of at least four weeks' duration (Zelen 2013). EpiFix was applied every two weeks if the wound had not healed, with weekly dressing changes consisting of non-adherent dressing, moisture retentive dressing, and a compression dressing. Standard moist wound dressing was changed daily. After four weeks of treatment, EpiFix-treated wounds had reduced in size by a mean of 97.1%, compared with 32.0% for the SOC group. Healing rate (complete epithelialization of the open area of the wound) was 77% for EpiFix, compared with 0% for SOC. After six weeks of treatment, wounds were reduced by 98.4% with EpiFix treatment, compared with -1.8% for SOC. The healing rate was 92% with EpiFix, compared with 8% with standard treatment alone.

Treatment with EpiFix, Apligraf, or standard wound care was compared in a multicenter randomized, controlled study (Zelen2015b). Sixty patients with chronic lower extremity diabetic ulcers were randomized to treatment with Epifix (dehydrated human amniotic membrane), Apligraf (human skin allograft with living fibroblasts and keratinocytes), or standard wound care. Although the patient and site investigator could not be blinded due to differences in products, wound healing was verified by three independent physicians who evaluated photographic images. The median wound size was 2.0 cm^2 (range, 1.0-9.0), and the median duration of the index ulcer was 11 weeks (range, 5-54). After six weekly treatments, the mean percent wound area healed was 97.1% for EpiFix, 80.9% for Apligraf, and 27.7% for standard care; 95% of wounds had healed in the EpiFix group compared with 45% treated with Apligraf and 35% who received standard wound care ($p<0.003$). The estimated median time to wound closure, based on Kaplan-Meier analysis, was 13 days for EpiFix, compared with 49 days for both Apligraf and SOC ($p<0.001$).

In 2015, Kirsner et al reported an industry-sponsored observational study comparing the effectiveness of Apligraf and EpiFix for the treatment of diabetic foot ulcers in a real-world setting. Data were obtained from a wound care–specific database from 3000 wound care facilities. The database included 1458 diabetic ulcers treated for the first time in 2014 with Apligraf (n=994) or EpiFix (n=464). After study inclusion criteria, data were included on the treatment of 226 diabetic foot ulcers from 99 wound care centers. Foot wounds were included with size between 1 cm2 and 25 cm2, duration of one year or less, and wound reduction of 20% or less in the 14 days prior to treatment. Although wounds for the two groups were comparable at baseline, the rationale for using a particular product was not reported. There were 163 wounds treated with Apligraf (mean, 2.5 applications) and 63 treated with EpiFix (mean, 3.5 applications, p=0.003). By week 24, 72% of wounds treated with Apligraf and 47% of wounds treated with EpiFix had closed (p=0.01).

Treatment with Grafix or standard wound care was compared in a small, multi-centered RCT for

diabetic foot ulcers (Lavery 2014). Although the results were positive, the sample size was small, with 50 treated with Grafix and 47 in the control group treated with SOC. The primary end point was complete wound closure by 12 weeks. Grafix patients who achieved full closure was 62% versus 21% in the control group receiving SOC. Ananian et al (2018) reported a prospective, randomized, single-blind study comparing the efficacy of Grafix with Dermagraft. The end result of this study was measured by wound closure and showed that Grafix (48.4% closure) is non-inferior to Dermagraft (38.7% closure).

AmnioBand was compared to SOC for treatment of non-healing diabetic foot ulcers in an industry-sponsored, multi-center study (DiDomenico 2016). Forty patients were randomized to SOC or SOC with AmnioBand for up to 12 weeks. Complete healing by six weeks was observed for 70% of wounds treated with SOC and AmnioBand versus 15% treated with SOC alone. At 12 weeks, complete healing was observed in 85% of the SOC and AmnioBand group versus 25% treated with SOC alone. Limitations of the study were small sample size, a drop-out rate of 9/40, and the wound area in the control group was larger than in the treatment group.

Smiell et al (2015) reported on an industry-sponsored, multicenter registry study of Biovance d-HAM for the treatment of various chronic wound types; about a third (n=47) were diabetic foot wounds. Of those treated, 28 ulcers had failed prior treatment with advanced biologic therapies. For all wound types, 41.6% closed within a mean time of 8 weeks and a mean of 2.4 amniotic membrane applications.

AlloPatch, which is a pliable human reticular, acellular dermis, was compared to SOC in the treatment of diabetic foot ulcers in an industry-sponsored, multicenter trial (Zelen 2017). The trial was powered to detect a 45% difference between groups in percentage healing at six weeks with 20 patients per group. Evaluation of the outcome measures was not blinded. At six weeks, 65% (13/20) of wounds treated with AlloPatch had healed, compared to 5% (1/20) in the SOC-alone group ($p<0.001$). After adjusting for wound area at baseline, the hazard ratio for healing was 168 (95% CI, 10 to 2704; $p<0.001$), indicating a lack of precision in the estimate. Per protocol, 10 patients in the SOC group and one in the AlloPatch group exited the study at six weeks because their wounds failed to reduce in area by at least 50%. According to ITT analysis with last observation carried forward, the percentage of wounds healed at 12 weeks was 80% in the AlloPatch group, compared to 20% in the SOC group. However, because there was a high (50%) withdrawal rate in the SOC group, this result has a high risk of bias.

Integra Dermal Regeneration Template, marketed as Omnigraft, randomized, controlled studies have been shown to improve healing of chronic, non-healing diabetic foot ulcers with the use of Omnigraft (Driver 2015). The Foot Ulcer New Dermal Replacement (FOUNDER) multicenter study on the use of Integra Dermal Regeneration Template for chronic, non-healing diabetic foot ulcers was conducted under an FDA-regulated investigational device exemption. A total of 307 patients with at least one chronic diabetic foot ulcer were randomized to treatment with the Integra Template or a control condition (0.9% sodium chloride gel). Treatment was given for 16 weeks or until wound closure. There was a modest increase in wound closure with the Integra Template (51% versus 32%) and a shorter median time to closure (43 days versus 78 days). There was a strong correlation between investigator-assessed and computerized planimetry assessment of wound healing ($r=0.97$). Kaplan-Meier analysis showed the greatest difference between groups in wound closure up to 10 weeks, with

diminishing differences after 10 weeks. Strengths of the study included adequate power to detect an increase in wound healing of 18%, which was considered to be clinically significant, as well as secondary outcomes of wound closure and time to wound closure by computerized planimetry and intention-to-treat (ITT) analysis.

The Oasis Wound Matrix (Cook Biotech) is a xenogeneic collagen scaffold derived from porcine small intestinal mucosa. Niezgoda et al (2005) compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with the OASIS Wound Matrix (an acellular wound care product) to Regranex Gel. This industry sponsored, multicenter RCT was conducted at nine outpatient wound care clinics and involved 73 patients with at least one diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix (n=37) or Regranex Gel (n=36) and a secondary dressing. Wounds were cleansed and debrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks, 18 (49%) Oasis-treated patients had complete wound closure, compared with 10 (28%) Regranex-treated patients. Oasis treatment met the noninferiority margin, but the study did not demonstrate that healing in the Oasis group was statistically superior (p=0.055). Post hoc subgroup analysis showed no significant difference in incidence of healing in patients with type 1 diabetes (33% versus 25%) but showed a significant improvement in patients with type 2 diabetes (63% versus 29%). There was also an increased healing of plantar ulcers in the Oasis group (52% versus 14%).

TheraSkin was reported in a small (n=23), industry-funded, randomized comparison of TheraSkin (human skin allograft with living fibroblasts and keratinocytes) to Dermagraft (human-derived fibroblasts cultured on mesh) for diabetic foot ulcers (Sanders 2014). Wound size at baseline ranged from 0.5 to 18.02 cm^2; the average wound size was about 5 cm^2 and was similar for the two groups (p=0.51). Grafts were applied according to the manufacturer's instructions over the first 12 weeks of the study until healing, with an average of 4.4 TheraSkin grafts (every two weeks) compared with 8.9 Dermagraft applications (every week). At week 12, complete wound healing was observed in 63.6% of ulcers treated with TheraSkin and 33.3% of ulcers treated with Dermagraft (p<0.049). At 20 weeks, complete wound healing was observed in 90.9% of the TheraSkin-treated ulcers, compared with 66.67% of the Dermagraft group (p=0.428).

Venous Ulcers (Apligraf, Oasis Wound Matrix)

Hankin et al (2012) explains venous leg ulcers (VLUs) are commonly associated with substantial disability, impaired quality of life, and high economic costs. Compression therapy, which has remained the standard care for VLUs over several decades, is often insufficient to heal VLUs in a timely manner. VLU-related treatment costs are directly related to time to achieve complete wound closure. Advanced wound care matrices (AWCMs) developed to stimulate wound healing may reduce VLU-related costs associated with delayed healing.

Mostow et al (2005) conducted a prospective, randomized, controlled multicenter trial to compare the effectiveness of Oasis wound matrix with compression vs compression alone in healing chronic leg ulcers within 12 weeks. Participants included 120 patients with at least one (1) chronic leg ulcer, randomly assigned to receive either weekly topical treatment of Oasis plus compression therapy (n = 62) or compression therapy alone (n = 58). Ulcer size was determined at enrollment and weekly throughout the treatment. Healing was assessed weekly for up to 12 weeks. Recurrence after 6 months was recorded. The primary outcome measure was the proportion of ulcers healed in each

group at 12 weeks. After 12 weeks of treatment, 55% of the wounds in the Oasis group were healed, as compared with 34% in the standard-care group (P = .0196). None of the healed patients treated with Oasis wound matrix and seen for the 6-month follow-up experienced ulcer recurrence. The authors concluded the study showed Oasis wound matrix, as an adjunct therapy, significantly improves healing of chronic leg ulcers over compression therapy alone.

A prospective, head-to-head, single site randomized clinical trial pilot study evaluated the effectiveness of two (2) biologically active grafts, TheraSkin and Apligraf, in conjunction with compression therapy (Towler 2018). The study was not industry-sponsored and was designed and conducted to assess differences in healing rates, adverse outcomes, and treatment costs. Although there were higher venous leg ulcer (VLU) healing rates with the TheraSkin cohort compared with the Apligraf cohort at both 12 weeks (93.3% vs 75.0%) and 20 weeks (93.3% vs 83.3%), these healing rate differences were not statistically significant. There was no statistically significant difference in the number of grafts required to achieve wound closure within limitations of the small sample size presented and there were no adverse outcomes. There was a statistically significant 42.2% decrease in cost for the appropriate graft sizes in the TheraSkin cohort ($2495.33/subject) compared with the Apligraf cohort ($4316.67/subject), even though the initial wound sizes were not significantly different between groups. This suggests that TheraSkin may provide equivalent or superior outcomes to Apligraf while reducing costs though the authors concluded that the use of either of these biologics in conjunction with compression therapy is a safe and effective way to treat VLUs.

Landsman et al (2011) published a study examining TheraSkin for safety and efficacy in the treatment of venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs). The objective was to determine if TheraSkin could serve as a safe and effective alternative to bioengineered skin substitutes such as Apligraf and Dermagraft. The authors conducted a retrospective study of 214 consecutive patients seen at the Inova Wound Center (Mt Vernon, Virginia), with either a DFU or a VLU. After excluding patients who did not meet the study criteria, the final eligible cohort consisted of 188 subjects, with 134 VLUs and 54 DFUs. Multivariate logistic regression was used to evaluate the relationship between baseline wound size and the proportion of healed wounds after 12 and 20 weeks from initial allograft application. The authors found that by the 12th week, DFUs closed 60.38% of the time and VLUs closed 60.77% of the time. After 20 weeks, the number of closed DFUs increased to 74.1% and the number of VLUs increased to 74.6%. The mean wound size in the DFU group was 6.2 cm (2) (±11.8) and 11.8 cm (2) (±22.5) in the VLU group. The mean number of TheraSkin allografts required ranged from 1 to 8, with an average of 2.03 (±1.47) at the 12-week point and an average of 3.23 (±2.77) at the 20-week point. Multivariate logistic regression was used to calculate the odds of wound healing by week 12 and week 20 in each group. The authors also analyzed adverse events and found TheraSkin to be noncontributory to any adverse events, verifying the safety of TheraSkin in this study population. The authors concluded, TheraSkin has been shown to be highly effective for the treatment of both VLUs and DFUs with an acceptable safety profile.

A randomized, controlled, multicenter clinical trial was conducted to evaluate the efficacy of dehydrated human amnion/chorion membrane (EpiFix) allograft as an adjunct to multilayer compression therapy for the treatment of non-healing full-thickness venous leg ulcers (Bianchi 2018). The authors randomly assigned 128 subjects initially though only 109 subjects finished the trial. They received EpiFix and multilayer compression (n = 52) or dressings and multilayer compression therapy

alone (n = 57). Patients were recruited from 15 centers around the United States and were followed up for 16 weeks. The primary end point of the study was defined as time to complete ulcer healing. Participants receiving weekly application of EpiFix and compression were significantly more likely to experience complete wound healing than those receiving standard wound care and compression (60% versus 35% at 12 weeks, P = 0·0128, and 71% versus 44% at 16 weeks, P = 0·0065). A Kaplan-Meier analysis was performed to compare the time-to-healing performance with or without EpiFix, showing a significantly improved time to healing using the allograft (log-rank P = 0·0110). Cox regression analysis showed that subjects treated with EpiFix had a significantly higher probability of complete healing within 12 weeks (HR: 2·26, 95% confidence interval 1·25-4·10, P = 0·01) versus without EpiFix. The authors concluded these results confirm the advantage of EpiFix allograft as an adjunct to multilayer compression therapy for the treatment of non-healing, full-thickness venous leg ulcers.

Bianchi et al (2019) published further analysis on the previously mentioned cohort of patients in a follow-up study. The purpose of this study is to report intention-to-treat (ITT) results on all 128 randomized subjects and assess if both ITT and per-protocol (PP) data analyses arrive at the same conclusion of the efficacy of EpiFix as a treatment for VLU. Rates of healing for the ITT and PP populations were, respectively, 50% and 60% for those receiving EpiFix and 31% and 35% for those in the standard care cohort. Within both ITT and PP analyses, these differences were statistically significant; P = 0.0473, ITT and P = 0.0128, PP. The Kaplan-Meier plot of time to heal within 12 weeks for the ITT and PP populations demonstrated a superior wound-healing trajectory for EpiFix compared with VLUs treated with standard care alone. The authors concluded that these data provide clinicians and health policymakers with an additional level of assurance regarding the effectiveness of EpiFix.

An open label randomized controlled trial including patients with chronic venous leg ulcers was conducted at eight (8) wound care centers across the United States (Serena 2022). This industry sponsored trial evaluated the safety and effectiveness of weekly and biweekly applications of dehydrated human amnion and chorion allograft (dHACA) (AmnioBand Membrane; MTF Biologics) plus standard of care compared to standard of care alone on chronic venous leg ulcers. The primary endpoint was the proportion of healed ulcers at 12 weeks. Secondary endpoints included the proportion of ulcers achieving 40 percent closure at 4 weeks and the incidence of adverse events. Among 101 patients screened for eligibility, 60 were eligible and enrolled. At 12 weeks, significantly more venous leg ulcers healed in the two dHACA-treated groups (75 percent) than in the standard-of-care group (30 percent) (p = 0.001) even after adjustment for wound area (p = 0.002), with an odds ratio of 8.7 (95 percent CI, 2.2 to 33.6). There were no significant differences in the proportion of wounds with percentage area reduction greater than or equal to 40 percent at 4 weeks among all groups. The adverse event rate was 63.5 percent. Among the 38 adverse events, none were graft or procedure related, and all were resolved with appropriate treatment. The authors concluded, dHACA and standard of care, either applied weekly or biweekly, significantly healed more venous leg ulcers than standard of care alone, suggesting that the use of aseptically processed dHACA (AmnioBand Membrane; MTF Biologics) is advantageous and a safe and effective treatment option in the healing of chronic venous leg ulcers.

Breast Reconstruction (Alloderm, AlloMax/Cortiva, DermACELL AWM, DermaMatrix, FlexHD,

GraftJacket, Surgimend)

A prospective study was completed which evaluated limited submuscular direct-to-implant technique utilizing AlloMax where only the upper few centimeters of the implant is covered by the pectoralis, whereas the majority of the implant including the middle and lower poles are covered by acellular dermal matrix (Brichacek 2017). Nineteen consecutive patients with 37 reconstructed breasts were studied and followed up to six (6) months postoperatively. Average age was 50 years, average BMI was 24.3, ptosis ranged from grade 0-III, and average cup size was B (range, A-DDD). Early minor complications included one (1) seroma, three (3) minor postoperative hematomas managed conservatively, and 3 minor wound healing problems. Three breasts experienced mastectomy skin flap necrosis and were managed with local excision. There were no cases of postoperative infection, red breast syndrome, grade III/IV capsular contractures, or implant loss. A single patient complained of animation postoperatively. One patient desired fat grafting for rippling. The limited submuscular direct-to-implant technique utilizing AlloMax appears to be safe with a low complication rate at 6 months. This technique minimizes the action of the pectoralis on the implant, reducing animation deformities but still providing muscle coverage of the upper limit of the implant. Visible rippling is reduced, and a vascularized bed remains for fat grafting of the upper pole if required.

Zheng et al (2025) reported a single, academic institution's experience with two (2) ADM brands in breast reconstruction and provides data on clinical and financial outcomes. A retrospective chart review of patients who underwent two-staged breast reconstruction with Cortiva Allograft Dermis was matched with a cohort who received AlloDerm RTU. Comparison of clinical outcomes, such as complications and revision surgeries, in addition to a cost analysis was completed. The study cohort included 24 patients who received Cortiva and 24 patients who received AlloDerm. There were no statistical differences in demographics or breast-specific characteristics between the cohorts. Major complications were not statistically increased with Cortiva use [Hazard Ratio 1.78 (0.421-7.66)], but the rate of revision following second-stage reconstruction trended toward significance with Cortiva use [3.41 (0.99-11.80), p=0.05]. The material base cost and total cost following surgeries were lower for Cortiva (44% of the AlloDerm costs), but the incremental costs did not display significant difference secondary to comparable complication and revision rates. The authors concluded that the use of Cortiva Allograft Dermis was shown to have a decreased cost in base material and total cost associated with surgery while also displaying comparable clinical outcomes and complication rate.

A single-blinded randomized controlled trial comparing Cortiva with AlloDerm in prepectoral and subpectoral immediate prosthetic breast reconstruction was performed at two (2) academic hospitals from March of 2017 to December of 2021 (Keane 2024). Reconstructions were direct to implant (DTI) or tissue expander (TE). Primary outcome was reconstructive failure, defined as TE explantation before planned further reconstruction, or explantation of DTI reconstructions before 3 months postoperatively. Secondary outcomes were additional complications, patient-reported outcomes (PROs), and cost. There were 302 patients including: 151 AlloDerm (280 breasts), 151 Cortiva (277 breasts). The majority of reconstructions in both cohorts consisted of TE (62% versus 38% DTI), smooth device (68% versus 32% textured), and prepectoral (80% versus 20% subpectoral). Reconstructive failure was no different between ADMs (AlloDerm 9.3% versus Cortiva 8.3%; P = 0.68). There were no additional differences in any complications or PROs between ADMs. Seromas occurred in 7.6% of Cortiva but 12% of AlloDerm cases, in which the odds of seroma formation were

two-fold higher (odds ratio, 1.93 [95% CI, 1.01 to 3.67]; P = 0.047). AlloDerm variable cost was 10% to 15% more than Cortiva, and there were no additional cost differences. The authors concluded, when assessing safety, clinical performance, PROs, and cost, Cortiva is noninferior to AlloDerm in immediate prosthetic breast reconstruction, and may be less expensive, with lower risk of seroma formation.

Kaplan HY and Rysin R (2025) published a retrospective study evaluating a patient cohort that underwent primary or revisional breast reconstruction (DTI) utilizing DermaCell, from Jan 2017 to Jan 2024 by a single surgeon. A total of 230 consecutive patients, 410 breasts, and 801 DermaCell sheets were evaluated. All were DTI breast reconstructions. Complication rate was described per breast. A total of 92 cases of complication occurred (22.4%). Rippling was seen in 18 breasts (4.39%), skin ischemia in 21 breasts (5.12%), hematoma in 5 (1.21%), and seroma in 9 (2.19%). Seventeen breasts experienced capsular contraction. In the nonirradiated group, capsular contracture (CC), Baker grade 3 to 4, was seen in 4 breasts (1.11%), with 9 (18%) in the irradiated group. The postoperative follow-up period was 18 months (range: 6-84 months). BREAST-Q satisfaction with the breast increased by a mean of 10.45. Satisfaction with the implant was 6.61 out of 8. The authors concluded that DermaCell ADM offers a safe and reliable option and is an important component in prepectoral breast reconstruction, contributing to better results, an improved complication profile, and patient satisfaction.

Glynou SP et al (2024) conducted a network meta-analysis to compare outcomes of different ADMs that are commonly used during implant-based reconstruction (IBR). A total of 51 studies were captured by the search, of which 27 were included in the network meta-analysis. Alloderm was the most used ADM (54%), followed by Porcine (17%), Bovine (11%), Dermacell (11%), and FlexHD (7%). The mean follow-up was 27.8 months. The complication rates varied. Porcine ADMs had the highest rate of seroma formation (10.3%) and of hematoma formation (2.7%). AlloDerm FD had the highest rate of wound dehiscence (3.1%). Implant failure was highest in AlloDerm FD ADMs (11.8%), followed by Porcine ADMs (11.2%). Infections were most common in Porcine (11.2%) and AlloDerm FD ADMs (11.0%). Capsular contracture was rare across all ADM types, with no significant differences observed. In the network meta-analysis (NMA), AlloDerm FD showed significantly higher risks of infection, explantation, and wound dehiscence compared to AlloDerm RTU. The overall complication profiles of ADMs used in IBR are similar, except for the higher risks associated with AlloDerm FD compared to RTU. These findings suggest that the choice of ADM may not significantly impact overall outcomes, except in specific cases like AlloDerm FD. Further high-quality, long-term, double-arm studies are necessary to confirm comparative profile of specific ADM types and to account for potential confounding variables through multivariable regression analysis.

Davison SP et al (2024) conducted a prospective, patient-blind study of patients undergoing bilateral nipple and/or skin-sparing mastectomies with either tissue expander or silicone implant insertion between 2019 and 2022 were selected for this study. The study design used patients as their own controls between two (2) products randomly assigned to the left or right breast. Outcomes between the products included average time for drain removal, infection rate, seroma rate, and incorporation rates. The prospective clinical data of 55 patients (110 breasts) were recorded for 90 days. There were no significant differences between drain removal time, average drain output, or seroma aspiration amount. A higher percentage of seromas was recorded in the breasts with AlloDerm

(30.91%) compared with breasts containing DermACELL (14.55%, P < .05), and a statistically significant difference between the incorporation rates of AlloDerm (93.4%) and DermACELL (99.8%, P < .05) was observed. Irrespective of patient demographic disparities, both products had a 94.55% success rate for reconstruction outcomes. AlloDerm was determined to have a higher incidence of seroma as a postoperative complication and a trend to lower incorporation.

The Breast Reconstruction Evaluation of Acellular Dermal Matrix as a Sling Trial (BREASTrial) is a blinded, randomized trial comparing the outcomes of tissue expander breast reconstruction using AlloDerm or DermaMatrix (Mendenhall 2023). In this final stage of the trial, outcomes 3 months to 2 years after definitive reconstruction are reported along with patient satisfaction data. A randomized trial was conducted to compare complication rates between groups of patients who underwent reconstruction with AlloDerm and DermaMatrix. Regression models were used to analyze the impact of matrix type, age, chemotherapy, radiation therapy, and reconstructive type on complication rates. Premastectomy and postmastectomy questionnaires were used to assess patient satisfaction and were also analyzed using regression models. Of the 128 patients (199 breasts) who were randomized in the trial, 108 patients (167 breasts) were available for analysis in stage III. There was no difference in the overall complication rates between the AlloDerm and DermaMatrix groups (6% versus 13.2%; P = 0.3) or the severity of those complications (P = 0.7). Obesity was a positive predictor for complications, regardless of reconstruction group (P = 0.02). Patient satisfaction was positive overall and did not grossly vary between AlloDerm and DermaMatrix groups. Findings from the BREASTrial conclude that AlloDerm and DermaMatrix exhibit similar histologic and clinical outcomes. Patient satisfaction is also similar between matrices. Obesity is a predictor of complications, and acellular dermal matrices should be used with caution in these patients.

Broyles et al (2021) conducted a Level 1 prospective, randomized, controlled, multicenter clinical trial to assess complications associated with the use of two human acellular dermal matrices in immediate postmastectomy implant-based breast reconstruction across seven clinical sites. Group A patients received FlexHD Pliable (113 patients with 187 breast reconstructions), and group B patients received AlloDerm RTU (117 patients with 197 breast reconstructions). There was no significant difference with respect to patient demographics, indications, comorbidities, and reconstruction approach between groups. Mean follow-up time was 10.7 ± 3.2 months. There was no statistical difference in the overall matrix-related complications between groups A and B (4.3 percent versus 7.1 percent, p = 0.233). Obesity (OR, 1.14; 95 percent CI, 1.05 to 1.24; p = 0.001) and prepectoral placement of matrix (OR, 4.53; 95 percent CI, 1.82 to 11.3; p = 0.001) were independently associated with greater risks of overall matrix-related complications. The authors concluded that the results support the use of human acellular dermal matrices in implant-based breast reconstruction and demonstrates no significant difference in matrix-related complication rates between FlexHD Pliable and AlloDerm RTU.

Berger et al (2024) published a multicenter retrospective comparative study of patients undergoing immediate prosthesis-based breast reconstruction (iPBR) with SurgiMend PRS, AlloDerm, or DermACELL between January 2014 to July 2022. Primary outcomes included rates of unplanned explantation and total reconstructive failure. Secondary outcomes included 90-day postoperative complications and long-term rates of capsular contracture development. A total of 738 patients (1228 breasts) underwent iPBR during the study period; 405 patients received DermACELL (54.9%), 231

received AlloDerm (31.3%), and 102 received SurgiMend PRS (13.8%). Rates of short-term complications, total reconstruction failure, reoperation within 90 days, capsular contracture, and unplanned explantation were comparable. These findings remained true upon multivariate analysis accounting for baseline differences between cohorts, whereby ADM type was not an independent predictor of any outcome of interest. Conversely, factors such as body mass index, diabetes mellitus, smoking history, neoadjuvant and adjuvant chemotherapy, adjuvant radiation, skin-sparing mastectomy, Wise pattern and peri-areolar incisions, use of tissue expanders, and a subpectoral plane of insertion were significant predictors of postoperative complications. The authors concluded that low rates of complications support the equivalency of fetal bovine and human-derived ADMs in iPBR. Patient characteristics and operative approach are likely more predictive of postoperative outcomes than ADM derivative alone.

Asaad et al (2023) performed a retrospective review of consecutive patients who underwent immediate prepectoral IBR from January of 2018 through December of 2019. Surgical outcomes and PROs (using the BREAST-Q) were compared among the AlloDerm, SurgiMend, and Dermacell ADMs. Overall, 557 breasts (383 patients) were included (78.6% AlloDerm, 14% SurgiMend, 7.4%Dermacell). Patients in the Dermacell group were older (P = 0.001) and more likely to have diabetes (P = 0.001) compared with AlloDerm and SurgiMend patients. Other patient characteristics were similar among the three groups. The overall complication rate was equivalent among the three ADM groups (AlloDerm 27% vs SurgiMend 33% vs Dermacell 39%; P = 0.209). Multivariable frailty models demonstrated that the type of ADM was not significantly associated with overall complications, infection, major complications, or device explantation. BREAST-Q satisfaction with breasts, psychosocial well-being, and sexual well-being were also similar among the three ADM groups (P =0.109, P = 0.439, P = 0.152, respectively). The authors concluded this study shows three (3) of the most commonly used ADMs in the United States have similar surgical outcomes and PROs when used for prepectoral IBR. No significant differences in infection, overall complications, or device removal rates were identified among AlloDerm, SurgiMend, and Dermacell.

A retrospective review compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts) (Liu 2014). A total of 81% of the patients underwent immediate reconstruction; 165 used AlloDerm, and 97 used FlexHD. Mean follow-up was 6.4 months. Compared with breast reconstruction without use of AlloDerm or FlexHD, ADM had a higher rate of delayed healing (20.2% versus 10.3%), although this finding might be related to differences in fill volumes. In univariate analysis, there were no significant differences in complications (return to the operating room, surgical site infection, seroma, hematoma, delayed healing, or implant loss) between AlloDerm and FlexHD. In multivariate analysis, there were no significant differences between AlloDerm and FlexHD for the return to the operating room, surgical site infection, seroma, or delayed healing. Independent risk factors for implant loss included the use of FlexHD, single-stage reconstruction, and smoking.

Another retrospective review compared complication rates following use of AlloDerm (n=136) or FlexHD (n=233) in a consecutive series of 255 patients (369 breasts) (Seth 2013). Total complication rates for the two products were similar (19.1% for AlloDerm and 19.3% for FlexHD). Analysis by type of complication showed no significant difference between the products, and regression analysis controlling for differences in baseline measures found that the type of ADM was not a risk factor for

any complication.

A retrospective review of complication rates when AlloDerm (n=49), DermaMatrix (n=110), or FlexHD (n=62) was used for tissue expander breast reconstruction (Brooke 2012). Clinically significant complications were defined as cellulitis, abscess, seroma, expander leak or puncture, skin necrosis, wound dehiscence, or hematoma. The total clinically significant complication rate was 22% with AlloDerm, 15% with DermaMatrix, and 16% with FlexHD (not significantly different). Infectious complication rates for the three products were the same at 10%. When compared with breast reconstruction without an ADM (n=64), there was no significant difference in the total complication rate (17% vs 11%), but there was a trend toward a higher incidence of infectious complications (10% vs 2%, p=0.09).

Nasal Repairs, Hernia Repair, and Parotidectomy (Alloderm)

There is limited scientific evidence in the form of retrospective case series (Kissane 2012) to support the use of AlloDerm in rare cases of non-primary hernia repair when chronic infection contraindicates the use of mesh or other conventional repair.

Literature regarding the use of AlloDerm in parotidectomy also consists of small case series; however, the studies support that AlloDerm is beneficial in preventing Frey's syndrome after parotidectomy. A network meta-analysis sought to determine the best method for prevention of Frey syndrome after parotidectomy (Mashrah 2021). Thirty-four studies (n = 2987 patients) with five interventions, namely Alloderm (ADM), temporoparietal fascia (TPF), sternocleidomastoid muscle (SCM), superficial musculoaponeurotic system (SMAS), and free fat graft (FFG), were compared together and with no interposition barrier (NB). The results of NMA showed a statistically significant reduction in both subjective Frey syndrome (SFS) and objective Frey syndrome (OFS) when ADM, TPF, SMAS, FFG, and SCM were compared with NB. No statistical differences were observed when comparing ADM, SCM, SMAS, FFG, and TPF. TPF ranked the best of all treatments (59.4%) and was associated with the least incidence of SFS; whereas ADM ranked the best of all treatments (61.1%) and was associated with the least incidence of OFS.

A sponsored, retrospective study of real-world use of AlloDerm acellular dermal matrix in head and neck procedures in the U.S. was conducted for the period of October 2015 to March 2022 (Dominguez 2024). Descriptive statistics were used to describe surgery types and 30-day follow-up reoperations, graft complications, and all-cause healthcare resource utilization (HCRU). Among 431 patients (51.7% women), mean (SD) age was 52.2 (15.8) years. AlloDerm was most used with oral cavity reconstruction (35.3%), septal perforation repair/rhinoplasty (16.5%), and parotidectomy (13.0%). Most procedures were performed in outpatient settings (hospital, 90.0%; ambulatory surgical center, 8.6%). Over 30 days, less than 1% of patients (4 of 431) required reoperation with AlloDerm; 0.5% (2 of 431) had graft-related complications. Most (75.6%) patients had outpatient visits; few had an emergency room visit (7.9%) or inpatient claim (3.0%). The authors concluded real-world evidence indicates that AlloDerm is used in head- and neck-related procedures in US adults. Post-procedure complications and reoperations were uncommon during the follow-up period.

Burns (Integra Dermal Regeneration Matrix (Omnigraft), Biobrane, Epicel)

Carsin et al (2000) reported 5-year experience in a large, single center series of severely burned and otherwise traumatized patients given cultured epithelial autografts (CEA) (Epicel) from a single

commercial laboratory. From 1991 to 1996, CEA were applied to a mean 37+/-17% of total body surface area (TBSA) of 30 patients. These patients had 78+/-10% average burn size, 65+/-16% average third-degree burn size, 90% prevalence of endoscopically confirmed inhalation injury and 37% prevalence of other serious conditions. CEA achieved permanent coverage of a mean 26+/-15% of TBSA, an area greater than that covered by conventional autografts (a mean 25+/-10% of TBSA). Survival was 90% of these severely burned and otherwise traumatized patients. Final CEA take was a mean 69+/-23%. In subset analyses, only younger age was significantly associated with better CEA take ($p = 0.0001$ in univariate analysis, $p<0.04$ in multivariate analysis, Student's t-test). Epicel CEA successfully provided extensive, permanent burn coverage in severely traumatized patients, proving an important adjunct to achievement of a high survival rate in a patient population whose prognosis previously had been poor. The authors concluded that CEA appeared to have a very high beneficial value in the management of burns >60% TBSA and in some cases it was very likely that CEA was a life-saving treatment.

Biobrane (Dow Hickman/Bertek Pharmaceuticals, Sugar Land, TX), a semi-permeable silicone device embedded with a nylon mesh and a porcine-derived collagen matrix, offers a promising alternative with advantages such as improved wound healing, reduced pain, and fewer dressing changes. A systematic review and meta-analysis (Jabarkhyl 2025) assessed the efficacy of Biobrane. Primary outcomes included burn wound healing time, hospital length of stay and infection rate, while secondary outcomes assessed the need for split-thickness skin grafts (STSGs), pain, and the number of dressing changes. Their data encompassed 781 burn wounds across 12 studies. The results showed that Biobrane significantly shortened wound healing time (mean difference, MD: 5.168 days, $p = 0.001$) and hospital length of stay (MD: 2.009 days, $p < 0.001$) compared to standard dressings. The infection rate was comparable (odds ratio, OR: 2.457, $p = 0.132$), and there was no difference in the requirement for STSGs (OR: 0.965, $p = 0.956$). This systematic review and meta-analysis demonstrate that Biobrane is an effective treatment for superficial pediatric burn injuries, offering faster wound healing, reduced pain and shorter hospital stays compared to traditional dressings.

A systematic review and meta-analysis were conducted to evaluate the role of various dermal regeneration templates (DRTs) in comparison with split-thickness skin grafting in managing acute burn injuries after excision and debridement (Alkhonizy 2024). A total of 28 randomized clinical trials were assessed, encompassing a wide array of DRTs. The most frequently evaluated DRT, Integra Dermal Regeneration Template, not only showed potential for peripheral nerve reinnervation but also indicated a potential for a longer initial healing time, aligning with previous studies highlighting its efficacy in reducing scar formation and wound contracture. TransCyte displayed impressive rates of re-epithelialization and was found suitable for acute partial-thickness burns. Moreover, its low infection rate substantiates its antimicrobial properties and aligns with prior research.

The ReCell device has been evaluated in 2 manufacturer (AVITA Medical) sponsored RCTs (Holmes 2018, 2019). One RCT evaluated ReCell as an adjunct to meshed autologous skin grafting and the other compared ReCell head-to-head with skin grafting. Although the ReCell device was comparable to standard care on outcomes such as complete wound closure, confidence in the strength of the overall body of evidence is limited by individual study limitations and heterogeneity of populations, interventions, and outcome measures across studies. Additional RCT evidence regarding the intended use population is needed. The evidence is insufficient to determine that the technology results in an

improvement in the net health outcome.

Manning et al (2022) conducted a randomized, open-label trial with one of the investigators of the study being the developer of ReCell and the products were donated from their foundation. Forty-nine eligible foot wounds in 45 participants were randomized to receive an application of non-cultured autologous skin cells ("spray-on" skin; ReCell) or standard care interventions for large (>6 cm2), adequately vascularized wounds. A total of 32 (65.3%) index wounds were completely healed at 6 months, including 16 of 24 (66.7%) in the spray-on skin group and 16 of 25 (64.0%) in the standard care group (unadjusted OR [95% CI]: 1.13 (0.35-3.65), P = .845). Lower body mass index (P = .002) and non-plantar wounds (P = .009) were the only patient- or wound-related factors associated with complete healing at 6 months. The authors concluded that spray-on skin resulted in high rates of complete healing at 6 months in patients with large diabetes-related foot wounds but was not significantly better than standard care.

PROFESSIONAL GUIDELINE(S)

In February 2020, the Agency for Health Research and Quality (AHRQ) completed a technology assessment addressing Skin Substitutes for Treating Chronic Wounds. The assessment addresses 76 products commercially available in the U.S. that are used to manage or treat chronic wounds and are regulated by FDA. Based on FDA regulations, skin substitutes can be organized into four groups:

- human-derived products regulated as HCT/Ps (human cells, tissues, and tissue-based products)
- human- and human/animal-derived products regulated through PMA or humanitarian device exemption (HDE)
- animal-derived products regulated under the 510(k) process
- synthetic products regulated under the 510(k) process

Of those included in the tech assessment, 68 (89%) were categorized as acellular dermal substitutes, mostly replacements from human placental membranes and animal tissue sources. Three systematic reviews and 22 RCTs examined use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Twenty-one ongoing clinical trials (all RCTs) examined an additional nine skin substitutes with similar classifications. Studies rarely reported clinical outcomes, such as amputation, wound recurrence at least two weeks after treatment ended, or patient related outcomes, such as return to function, pain, exudate, and odor. The large majority of skin substitute products listed in the report did not have efficacy data from RCTs. Industry funds most published studies and funded 20 of 22 RCTs included in this report, which raises significant concerns about possible publication bias or selective outcome reporting. The clearest implications of this Technical Brief 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.

The National Institute for Health and Care Excellence (NICE 2019) guidelines for diabetic foot problems: prevention and management recommend the following:

- Consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service.

NICE guidance on the ReCell system for treating skin loss, scarring, and depigmentation after burn injury (2020) recommended that there is insufficient evidence on its use in clinical practice, particularly in relation to which patients might benefit most from its use, to support the case for its routine adoption in the NHS.

The Association of Breast Surgery and the British Association of Plastic, Reconstructive and Aesthetic Surgeons published joint practice guidelines (Whisker 2021) regarding biological and synthetic mesh assisted breast reconstruction procedures. They make the following recommendations:

- Biological or synthetic mesh may be used in the following settings:
    - Implant-based total breast reconstruction after mastectomy; both for breast cancer patients and in women undergoing risk-reducing surgery
        - Immediate reconstruction
        - Total pre-pectoral or partially sub-pectoral reconstruction
    - Revision of cosmetic concerns following breast surgery
        - In the clinical setting of revising implant-based reconstructions e.g., correction of “bottoming out,” symmastia and implant rippling
        - Revision of cosmetic concerns following oncoplastic breast conserving surgery e.g., correction of “bottoming out” after mammoplasty or mastopexy
    - Congenital asymmetry/deformity surgery
- There are a large number of products available, and the product range is rapidly evolving. There is no clear consensus on the ideal biological or synthetic mesh or evidence to inform mesh selection. The guideline group recommends consideration of the following when selecting a product:
    - Biological versus synthetic
        - Biological products (e.g., ADMs) are usually animal derived. Ensure the patient is informed and comfortable with the mesh origin.
        - Synthetic mesh may be composed from absorbable and/or non-absorbable materials.

The International Society for Burn Injury (ISBI) published practice guidelines for burn care (2016) which make the following recommendations:

- Modern dressings and biologic membranes are the preferred dressing choices as they ensure the best means against infection as well as scar quality outcome.
- Raw area, similar to the superficial partial thickness burn and graft donor site, is an area of the body that lacks epithelial covering. Raw areas should be dressed with a closed technique. Biologic dressings seem to be superior to nonbiologic dressings. Type (temporary or semi-

permanent) and frequency of dressing are decided according to the wound condition and availability of these products.

- Amniotic membrane—whether it was used as fresh, lyophilized, and/or irradiated—showed superiority in most of the studies compared to conventional dressing, particularly in chronic burn wounds. Amniotic membrane was very effective, even with resistant strains like Pseudomonas, in areas with scarce blood supply, such as the cornea.
- After excision or debridement of the deep burn wound, it is essential that the wound is covered with autograft skin or an appropriate skin substitute. A wound too large to be safely repaired with autograft should be repaired with allograft or skin substitute. Failure to achieve adequate wound coverage after excision commonly results in invasive infection, or at best, desiccation of the exposed wound surface.
- Five substitute alternatives can be used to replace autograft following excision or debridement of deep burn wounds. These alternatives are described below.
    - Human allograft skin
        - Cryopreserved allograft is widely used and can provide good quality temporary skin cover for excised wounds for several weeks, until rejection occurs. Cryopreservation allows full donor-virus testing to be carried out so as to avoid risk of transmission of illness. Fresh allograft is the most effective skin replacement, and takes for many weeks, but fresh cadaveric allograft is seldom readily available. Fresh donor-related allograft (typically from a parent) may be suitable for small children but is not widely used. Glycerol-preserved or lyophilized skin is nonviable, and functions as a very good biologic dressing rather than a vascularized graft. It can be very effective as a short-term cover (up to approximately 2 weeks) for excised wounds.
    - Dermal regeneration matrices (or templates)
        - Following the successful introduction of a bovine collagen–based dermal regeneration template, a number of dermal regeneration products have been used. These biosynthetic products have been derived from bovine collagen, human allograft dermis, and porcine dermis, and also from synthetic substances. These acellular products are commonly based on collagen and produce a matrix on which a ‘‘neodermis’’ may regenerate. Broadly, these acellular products can be divided into those for either two- or one-stage use. The two-stage products are most suitable for acute major burns, as they provide temporary wound closure, prior to secondary autografting later with thin autograft or cultured cells (for instance: with Integra short-term wound closure is achieved with a surface silicone layer, which is removed prior to autografting at approximately 3 weeks, when ideally the patient is more stable). The one-stage use products offer the advantage of enhanced dermal reconstruction with very thin autograft harvest, but if used immediately after burn injury, they require a donor site of the full extent of the wound. Of techniques evolved to date for major burn injuries, the dermal regeneration matrices are probably the closest to producing a widely

available, reliable "synthetic skin. However, they do require full coverage with autograft epithelium. Disadvantages of the dermal regeneration matrices include a higher risk of problems with infection than with autograft or allograft, and relatively high cost which precludes anything but the most occasional use in an RLS.

- Xenograft-derived temporary wound coverage
    - The most common source of xenograft material for use in burns has been porcine-derived materials. These include untreated pigskin; cryopreserved pigskin; lyophilized porcine dermis; and popular biosynthetic products composed of porcine collagen with nylon and silicone. Considerable evidence supports the value of many of these materials when used as dressings in treatment of partial thickness wounds. For excised deep burn wounds, these xenograft products produce only short-term reliable wound cover (a few days). This can be useful in getting a patient safely through a major burn excision, before later application of definitive wound cover; but if used for more prolonged periods on excised wounds, the risks of invasive infection are higher.
- Amniotic membrane
    - Amniotic membrane is potentially universally available as good short-term coverage for excised wounds, and as a biologic dressing. In some RLS, its availability has been restricted by the cost of virus testing and by resultant practical barriers to its use. Amniotic membrane can be stored as cryopreserved, irradiated, or glycerol-preserved and in many parts of the world this has proved a useful technique for short-term coverage of excised wounds.
- Cell-based therapies
    - Cultured epithelial cells have been widely used in burn treatment, both as autograft and allograft. Autograft takes time to grow, so it is not available as an immediate skin substitute for early major burn excision. Although cultured epithelium has gained acceptance for many indications in burn-wound management, problems with failure of adhesion of cultured epithelium to full thickness wound beds and poor durability of cover mean that cultured cells have not achieved a consistently effective role as the sole skin replacement for full thickness wounds. Cultured epithelium serves best where a native or regenerated dermis is present in the wound bed. Similarly, autologous epithelial cells in suspension, or stem cells of a variety of origins, have been shown to have significant potential for enhanced healing of a variety of burn wounds: partial thickness wounds, wounds covered with meshed skin grafts, or wounds where dermis (native or regenerated) is present. These techniques have huge potential for skin replacement therapies in future.

The Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine published joint clinical practice guidelines for the management of the diabetic foot (Hingorani 2016). Their recommendations are as follows:

- "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 (platelet-derived growth factor [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)."
- "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."
- "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. A bovine collagen lattice is used as a base to support the organization of dermal fibroblasts and epithelial cells seeded after expansion of the separated neonatal cells. A layer of allogeneic keratinocytes is cultured over the fibroblast layer to form a stratified epidermis. The bilayer has a structure similar to human skin, with the absence of hair follicles or sweat glands. The growth factors and cytokines secreted by the cellular components of Apligraf include fibroblast growth factor, VEGF, PDGF, transforming growth factor b, and multiple interleukins, paralleling those secreted by healthy human skin. The product requires a well-granulated wound bed in which exudate and bacterial levels have been controlled to yield positive results."
- "Dermagraft (Organogenesis) is an allogeneic dermal fibroblast culture derived from human neonatal foreskin samples and grown on a biodegradable scaffold. The resulting three-dimensional matrix can be implanted into chronic nonhealing wounds to supply functional fibroblasts and their corresponding expressed proteins. The scaffold biodegrades during a 1- to 2-week period, leaving behind only cellular components and proteins. Several in vitro studies have evaluated the ability of Dermagraft to express clinically significant quantities of growth factors after cryopreservation and thawing. VEGF, PDGF-A, and insulin-like growth factor I were all found to recover to significant levels as measured by enzyme-linked immunosorbent assay in wounds to which Dermagraft was applied."
- "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."

- "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."
- "We recommend that patients with DFU have pedal perfusion assessed by ABI, ankle and pedal Doppler arterial waveforms, and either toe systolic pressure or transcutaneous oxygen pressure (TcPO2) annually (Grade 1B)."

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) does not refer to any single product or class of products as "skin substitutes". Products in this review cover products that do not require FDA approval or clearance as well as a number of products cleared through the 510(k) pathway with a variety of FDA product codes. A large number of artificial skin and soft-tissue products are commercially available or in development. Commercial availability is not a reflection of a product's regulatory status.

Human Amniotic Membrane and Acellular Dermal Matrix Products

Allograft ADM products derived from donated cadaveric human skin tissue are supplied by tissue banks compliant with standards of the American Association of Tissue Banks and FDA guidelines. The processing removes the cellular components (i.e., epidermis, all viable dermal cells) that can lead to rejection and infection. ADM products from human skin tissue are regarded as minimally processed and not significantly changed in structure from the natural material; FDA classifies ADM products as banked human tissue and, therefore, not requiring FDA approval for homologous use.

Human amniotic membrane is classified by the FDA as banked human tissue and, therefore, does not require FDA approval.

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

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

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

DermACELL (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL and PRESERVON.

DermaMatrix (Synthes) is a freeze-dried ADM derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation.

Epicord Dehydrated Human Umbilical Cord (DHUC) Allograft (MIMEDX Group, Inc.) is a placental-based tissue product that acts as a barrier and provides a protective environment to help support the healing process. It is comprised of an extracellular matrix of hyaluronic acid (HA) and collagen. Epicord is regulated as a human cell, tissue, or cellular or tissue-based product.

EpiFix (MIMEDX Group, Inc.) is a placental tissue allograft composed of dehydrated human amnion/chorion membrane (DHACM). EpiFix is regulated as a human cell, tissue, or cellular or tissue-based product.

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

GRAFIX (Smith and Nephew) lyopreserved and cryopreserved placental membrane products and surgical applications retain all components of placental tissue, including native placental cells.

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

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

Although frequently used by surgeons for breast reconstruction, FDA does not consider this homologous use and has not cleared or approved any surgical mesh device (synthetic, animal collagen-derived, or human collagen-derived) for use in breast surgery. The indication of surgical mesh for general use in “Plastic and reconstructive surgery” was cleared by the FDA before surgical mesh was described for breast reconstruction in 2005. FDA states that the specific use of surgical mesh in breast procedures represents a new intended use and that a substantial equivalence evaluation via 510(k) review is not appropriate and a pre-market approval evaluation is required.

The FDA issued a statement on March 31, 2021, stating while used for other types of reconstruction, the FDA has not cleared or approved ADM for use in breast reconstruction. The statement informed patients, caregivers, and health care providers that certain ADM products used in implant-based breast reconstruction may have a higher chance for complications or problems. The FDA requests prompt reporting of adverse events to help evaluate the risks.

FDA product codes: FTM, OXF.

<u>Xenogeneic Products</u>

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

ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds.

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

The FDA issued a class II recall for PriMatrix on September 30, 2024, for possible out of specification endotoxin test results due to issues with in-process and finished goods endotoxin testing.

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

FDA Product codes: KGN, FTL, FTM.

Living Cell Therapy

Apligraf (Organogenesis) is a bilayered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. Apligraf is supplied as needed, in 1 size, with a shelf-life of 10 days. In 1998, it was approved by the FDA for use in conjunction with compression therapy for the treatment of noninfected, partial- and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower-extremity ulcers nonresponsive to standard wound therapy.

Dermagraft (Organogenesis) is composed of cryopreserved human-derived fibroblasts and collagen derived from newborn human foreskin and cultured on a bioabsorbable polyglactin mesh scaffold. Dermagraft has been approved by the FDA for repair of diabetic foot ulcers.

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

FDA product codes: FTM, PFC, OCE, ODS.

Autologous Cell Harvesting Device

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

FDA product code: QCZ.

Biosynthetic Products

Biobrane/Biobrane-L (Smith and Nephew) is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially embedded into the film. The fabric creates a complex 3-dimensional structure of trifilament thread, which chemically binds collagen. Blood/sera clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs. Biobrane was granted pre-market approval by the FDA as a temporary covering of full thickness burns until autografting is clinically appropriate.

Integra Dermal Regeneration Template (also marketed as Omnigraft Dermal Regeneration Matrix; Integra Life Sciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It was approved by the FDA for use in the post excisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable because of the physiologic condition of the patient, for the repair of scar contractures when other therapies have failed.

In January 2016, the FDA approved the Integra Dermal Regeneration Template, marketed as Omnigraft, for use in the treatment of partial- and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon, or bone exposed, when used in conjunction with standard diabetic ulcer care.

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

FDA product codes: FRO, MDD, MGR.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
15011 (E/I)	Harvest of skin for skin cell suspension autograft; first 25 sq cm or less
15012 (E/I)	Harvest of skin for skin cell suspension autograft; each additional 25 sq cm or part thereof (List separately in addition to code for primary procedure)
15013 (E/I)	Preparation of skin cell suspension autograft, requiring enzymatic processing, manual mechanical disaggregation of skin cells, and filtration; first 25 sq cm or less of harvested skin

Code	Description
15014 (E/I)	Preparation of skin cell suspension autograft, requiring enzymatic processing, manual mechanical disaggregation of skin cells, and filtration; each additional 25 sq cm of harvested skin or part thereof (List separately in addition to code for primary procedure)
15015 (E/I)	Application of skin cell suspension autograft to wound and donor sites, including application of primary dressing, trunk, arms, legs; first 480 sq cm or less
15016 (E/I)	Application of skin cell suspension autograft to wound and donor sites, including application of primary dressing, trunk, arms, legs; each additional 480 sq cm or part thereof (List separately in addition to code for primary procedure)
15017 (E/I)	Application of skin cell suspension autograft to wound and donor sites, including application of primary dressing, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 480 sq cm or less
15018 (E/I)	Application of skin cell suspension autograft to wound and donor sites, including application of primary dressing, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 480 sq cm or part thereof (List separately in addition to code for primary procedure)
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	each additional 25 sq cm wound surface area, or part thereof
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	each additional 100 sq cm wound surface area, or part thereof, or each additional 1% body area of infants and children, or part thereof
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	each additional 25 sq cm wound surface area, or part thereof
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	each additional 100 sq cm wound surface area, or part thereof, or each additional 1% body area of infants and children, or part thereof
15777	Implantation of biologic implant (e.g., acellular dermal matrix) for soft tissue reinforcement (i.e., breast, trunk)
15778	Implantation of absorbable mesh or other prosthesis for delayed closure of defect(s) (i.e., external genitalia, perineum, abdominal wall) due to soft tissue infection or trauma

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HCPCS Codes

Code	Description
A2001 (E/I)	Innovamatrix ac, per sq cm
A2002 (E/I)	Mirragen advanced wound matrix, per sq cm
A2004 (E/I)	Xcellistem, 1 mg
A2005 (E/I)	Microlyte matrix, per sq cm
A2007 (E/I)	Restrata, per sq cm
A2008 (E/I)	TheraGenesis, per sq cm
A2009 (E/I)	Symphony, per sq cm
A2010 (E/I)	Apis, per sq cm
A2011 (E/I)	Supra SDRM, per sq cm
A2012 (E/I)	SUPRATHEL, per sq cm
A2013 (E/I)	Innovamatrix FS, per sq cm
A2014 (E/I)	Omeza collagen matrix, per 100 mg
A2015 (E/I)	Phoenix wound matrix, per sq cm
A2016 (E/I)	PermeaDerm B, per sq cm
A2017 (E/I)	PermeaDerm glove, each
A2018 (E/I)	PermeaDerm C, per sq cm
A2019 (E/I)	Kerecis Omega3 MariGen shield, per sq cm
A2020 (E/I)	AC5 Advanced Wound System (AC5)
A2021 (E/I)	NeoMatrix, per sq cm
A2026 (E/I)	Restrata MiniMatrix, 5 mg
A2027 (E/I)	MatriDerm, per sq cm
A2028 (E/I)	MicroMatrix Flex, per mg
A2029 (E/I)	MiroTract Wound Matrix sheet, per cc
A2030 (E/I)	Miro3d fibers, per milligram
A2031 (E/I)	Mirodry wound matrix, per square centimeter
A2032 (E/I)	Myriad matrix, per square centimeter
A2033 (E/I)	Myriad morcells, 4 milligrams
A2034 (E/I)	Foundation drs solo, per square centimeter
A2035 (E/I)	Corplex p or theracor p or allacor p, per milligram
A2036 (E/I)	Cohealyx Collagen Dermal Matrix, per sq cm
A2037 (E/I)	G4Derm Plus, per ml
A2038 (E/I)	MariGen Pacto, per sq cm
A2039 (E/I)	InnovaMatrix FD, per sq cm
A4100	Skin substitute, FDA-cleared as a device, not otherwise specified
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
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 (list separately in addition to code for primary procedure)

Code	Description
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
C5274	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
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
C5276	each additional 25 sq cm or less wound surface area, or part thereof
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
C5278	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
C9354 (E/I)	Acellular pericardial tissue matrix of non-human origin (Veritas), per sq cm
C9356 (E/I)	Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per sq cm
C9358	Dermal substitute, native, nondenatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm
C9360	Dermal substitute, native, nondenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm
C9363 (E/I)	Skin substitute (Integra Meshed Bilayer Wound Matrix), per sq cm
C9364 (E/I)	Porcine implant, Permacol, per sq cm
Q4100	Skin substitute, not otherwise specified
Q4101	Apligraf, per sq cm
Q4102	Oasis wound matrix, per sq cm
Q4103 (E/I)	Oasis burn matrix, per sq cm
Q4104 (E/I)	Integra bilayer matrix wound dressing (BMWD), per square cm
Q4105	Integra dermal regeneration template (DRT) or Integra Omnigraft dermal regeneration matrix, per sq cm
Q4106	Dermagraft, per sq cm
Q4107	GRAFTJACKET, per sq cm
Q4108	Integra matrix, per sq cm
Q4110 (E/I)	PriMatrix, per sq cm
Q4111 (E/I)	GammaGraft, per sq cm
Q4112 (E/I)	Cymetra, injectable, 1 cc
Q4113 (E/I)	GRAFTJACKET XPRESS, injectable, 1 cc
Q4114 (E/I)	Integra flowable wound matrix, injectable, 1 cc
Q4115 (E/I)	AlloSkin, per sq cm
Q4116	AlloDerm, per sq cm
Q4117 (E/I)	HYALOMATRIX, per sq cm

Code	Description
Q4118 (E/I)	MatriStem micromatrix, 1 mg
Q4121	TheraSkin, per sq cm
Q4122	DermACELL, DermACELL AWM or DermACELL AWM Porous, per sq cm
Q4123 (E/I)	AlloSkin RT, per sq cm
Q4124 (E/I)	OASIS ultra tri-layer wound matrix, per sq cm
Q4125 (E/I)	ArthroFlex, per sq cm
Q4126 (E/I)	MemoDerm, DermaSpan, TranZgraft or IntéguPly, per sq cm
Q4127 (E/I)	Talymed, per sq cm
Q4128	FlexHD, AllopatchHD, per sq cm
Q4130 (E/I)	Strattice TM, per sq cm
Q4132	Grafix Core and GrafixPL Core, per sq cm
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq cm
Q4134 (E/I)	HMatrix, per sq cm
Q4135 (E/I)	Mediskin, per sq cm
Q4136 (E/I)	E-Z Derm, per sq cm
Q4137 (E/I)	AmnioExcel, AmnioExcel Plus or BioDExcel, per sq cm
Q4138 (E/I)	BioDFence DryFlex, per sq cm
Q4139 (E/I)	AmnioMatrix or BioDMatrix, injectable, 1 cc
Q4140 (E/I)	BioDFence, per sq cm
Q4141 (E/I)	AlloSkin AC, per sq cm
Q4142 (E/I)	XCM biologic tissue matrix, per sq cm
Q4143 (E/I)	Repriza, per sq cm
Q4145 (E/I)	EpiFix, injectable, 1 mg
Q4146 (E/I)	Tensix, per sq cm
Q4147 (E/I)	Architect, Architect PX, or Architect FX, extracellular matrix, per sq cm
Q4148 (E/I)	Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per sq cm
Q4149 (E/I)	Excellagen, 0.1 cc
Q4150 (E/I)	AlloWrap DS or dry, per sq cm
Q4151	AmnioBand or Guardian, per sq cm
Q4152 (E/I)	DermaPure, per sq cm
Q4153 (E/I)	Dermavest and Plurivest, per sq cm
Q4154	Biovance, per sq cm
Q4155 (E/I)	Neox Flo or Clarix Flo, 1 mg
Q4156 (E/I)	Neox 100 or Clarix 100, per sq cm
Q4157 (E/I)	Revitalon, per sq cm
Q4158 (E/I)	Kerecis Omega3, per sq cm
Q4159 (E/I)	Affinity, per sq cm
Q4160 (E/I)	NuShield, per sq cm
Q4161 (E/I)	Bio-ConneKt wound matrix, per sq cm
Q4162 (E/I)	WoundEx Flow, BioSkin Flow, 0.5 cc
Q4163 (E/I)	WoundEx, BioSkin, per sq cm

Code	Description
Q4164 (E/I)	Helicoll, per sq cm
Q4165 (E/I)	Keramatrix or Kerasorb, per sq cm
Q4166 (E/I)	Cytal, per sq cm
Q4167 (E/I)	Truskin, per sq cm
Q4168 (E/I)	AmnioBand, 1 mg
Q4169 (E/I)	Artacent wound, per sq cm
Q4170 (E/I)	Cygnus, per sq cm
Q4171 (E/I)	Interfyl, 1 mg
Q4173 (E/I)	PalinGen or PalinGen Xplus, per sq cm
Q4174 (E/I)	PalinGen or ProMatrX, 0.36 mg per 0.25 cc
Q4175 (E/I)	Miroderm, per sq cm
Q4176 (E/I)	Neopatch or therion, per square centimeter
Q4177 (E/I)	FlowerAmnioFlo, 0.1 cc
Q4178 (E/I)	FlowerAmnioPatch, per sq cm
Q4179 (E/I)	FlowerDerm, per sq cm
Q4180 (E/I)	Revita, per sq cm
Q4181 (E/I)	Amnio Wound, per sq cm
Q4182	Transcyte, per sq cm
Q4183 (E/I)	Surgigraft, per sq cm
Q4184 (E/I)	Cellesta or Cellesta Duo, per sq cm
Q4185 (E/I)	Cellesta Flowable Amnion (25 mg per cc); per 0.5 cc
Q4186	Epifix, per sq cm
Q4187	Epicord, per sq cm
Q4188 (E/I)	AmnioArmor, per sq cm
Q4189 (E/I)	Artacent AC, 1 mg
Q4190 (E/I)	Artacent AC, per sq cm
Q4191 (E/I)	Restorigin, per sq cm
Q4192 (E/I)	Restorigin, 1 cc
Q4193 (E/I)	Coll-e-Derm, per sq cm
Q4194 (E/I)	Novachor, per sq cm
Q4195 (E/I)	PuraPly, per sq cm
Q4196 (E/I)	PuraPly AM, per sq cm
Q4197 (E/I)	PuraPly XT, per sq cm
Q4198 (E/I)	Genesis Amniotic Membrane, per sq cm
Q4199 (E/I)	Cygnus matrix, per sq cm
Q4200 (E/I)	SkinTE, per sq cm
Q4201 (E/I)	Matrion, per sq cm
Q4202 (E/I)	Keroxx (2.5 g/cc), 1cc
Q4203 (E/I)	Derma-Gide, per sq cm
Q4204 (E/I)	XWRAP, per sq cm
Q4205 (E/I)	Membrane Graft or Membrane Wrap, per sq cm

Code	Description
Q4206 (E/I)	Fluid Flow or Fluid GF, 1 cc
Q4208 (E/I)	Novafix, per sq cm
Q4209 (E/I)	SurGraft, per sq cm
Q4211 (E/I)	Amnion Bio or axoBioMembrane, per sq cm
Q4212 (E/I)	AlloGen, per cc
Q4213 (E/I)	Ascent, 0.5 mg
Q4214 (E/I)	Cellesta Cord per sq cm
Q4215 (E/I)	Axolotl Ambient or Axolotl Cryo, 0.1 mg
Q4216 (E/I)	Artacent Cord, per sq cm
Q4217 (E/I)	WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm
Q4218 (E/I)	SurgiCORD, per sq cm
Q4219 (E/I)	SurgiGRAFT-DUAL, per sq cm
Q4220 (E/I)	BellaCell HD or Surederm, per sq cm
Q4221 (E/I)	Amnio Wrap2, per sq cm
Q4222 (E/I)	ProgenaMatrix, per sq cm
Q4224 (E/I)	Human Health Factor 10 Amniotic Patch (HHF10-P), per sq cm
Q4225 (E/I)	AmnioBind, per sq cm
Q4226 (E/I)	MyOwn Skin, includes harvesting and preparation procedures, per sq cm
Q4227 (E/I)	AmnioCore TM, per sq cm
Q4229 (E/I)	Cogenex Amniotic Membrane, per sq cm
Q4230 (E/I)	Cogenex Flowable Amnion, per 0.5 cc
Q4232 (E/I)	Corplex, per sq cm
Q4233 (E/I)	SurFactor or NuDyn, per 0.5 cc
Q4234 (E/I)	XCellerate, per sq cm
Q4235 (E/I)	AMNIOREPAIR or AltiPly, per sq cm
Q4236 (E/I)	CarePATCH, per sq cm
Q4237 (E/I)	Cryo-Cord, per sq cm
Q4238 (E/I)	Derm-Maxx, per sq cm
Q4239 (E/I)	Amnio-Maxx or Amnio-Maxx Lite, per sq cm
Q4240 (E/I)	CoreCyte, for topical use only, per 0.5 cc.
Q4241 (E/I)	PolyCyte, for topical use only, per 0.5 cc
Q4242 (E/I)	AmnioCyte Plus, per 0.5 cc
Q4245 (E/I)	AmnioText, per cc
Q4246 (E/I)	CoreText or ProText, per cc
Q4247 (E/I)	Amniotext patch, per sq cm
Q4248 (E/I)	Dermacyte Amniotic Membrane Allograft, per sq cm
Q4249 (E/I)	AMNIPLY, for topical use only, per sq cm
Q4250 (E/I)	AmnioAmp-MP, per sq cm
Q4251 (E/I)	VIM per sq cm
Q4252 (E/I)	Vendaje, per sq cm

Code	Description
Q4253 (E/I)	Zenith Amniotic Membrane, per sq cm
Q4254 (E/I)	Novafix DL, per sq cm
Q4255 (E/I)	REGUaRD, for topical use only, per sq cm
Q4256 (E/I)	MLG-Complete, per sq cm
Q4257 (E/I)	Relese, per sq cm
Q4258 (E/I)	Enverse, per sq cm
Q4259 (E/I)	Celera Dual Layer or Celera Dual Membrane, per sq cm
Q4260 (E/I)	Signature APatch, per sq cm
Q4261 (E/I)	TAG, per sq cm
Q4262 (E/I)	Dual Layer Impax Membrane, per sq cm
Q4263 (E/I)	SurGraft TL, per sq cm
Q4264 (E/I)	Cocoon Membrane, per sq cm
Q4265 (E/I)	NeoStim TL, per sq cm
Q4266 (E/I)	NeoStim Membrane, per sq cm
Q4267 (E/I)	NeoStim DL, per sq cm
Q4268 (E/I)	SurGraft FT, per sq cm
Q4269 (E/I)	SurGraft XT, per sq cm
Q4270 (E/I)	Complete SL, per sq cm
Q4271 (E/I)	Complete FT, per sq cm
Q4272 (E/I)	Esano A, per sq cm
Q4273 (E/I)	Esano AAA, per sq cm
Q4274 (E/I)	Esano AC, per sq cm
Q4275 (E/I)	Esano ACA, per sq cm
Q4276 (E/I)	ORION, per sq cm
Q4278 (E/I)	EPEFFEICT, per sq cm
Q4279 (E/I)	Vendaje AC, per sq cm
Q4280 (E/I)	Xcell Amnio Matrix, per sq cm
Q4281 (E/I)	Barrera SL or Barrera DL, per sq cm
Q4282 (E/I)	Cygnus Dual, per sq cm
Q4283 (E/I)	Biovance Tri-Layer or Biovance 3L, per sq cm
Q4284 (E/I)	DermaBind SL, per sq cm
Q4285 (E/I)	NuDYN DL or NuDYN DL MESH, per sq cm
Q4286 (E/I)	NuDYN SL or NuDYN SLW, per sq cm
Q4287 (E/I)	DermaBind DL, per sq cm
Q4288 (E/I)	DermaBind CH, per sq cm
Q4289 (E/I)	RevoShield+ Amniotic Barrier, per sq cm
Q4290 (E/I)	Membrane Wrap-Hydro, per sq cm
Q4291 (E/I)	Lamellas XT, per sq cm
Q4292 (E/I)	Lamellas, per sq cm
Q4293 (E/I)	Acesso DL, per sq cm
Q4294 (E/I)	Amnio Quad-Core, per sq cm

Code	Description
Q4295 (E/I)	Amnio Tri-Core Amniotic, per sq cm
Q4296 (E/I)	Rebound Matrix, per sq cm
Q4297 (E/I)	Emerge Matrix, per sq cm
Q4298 (E/I)	AmniCore Pro, per sq cm
Q4299 (E/I)	AmniCore Pro+, per sq cm
Q4300 (E/I)	Acesso TL, per sq cm
Q4301 (E/I)	Activate Matrix, per sq cm
Q4302 (E/I)	Complete ACA, per sq cm
Q4303 (E/I)	Complete AA, per sq cm
Q4304 (E/I)	GRAFIX PLUS, per sq cm
Q4305 (E/I)	American Amnion AC Tri-Layer, per sq cm
Q4306 (E/I)	American Amnion AC, per sq cm
Q4307 (E/I)	American Amnion, per sq cm
Q4308 (E/I)	Sanopellis, per sq cm
Q4309 (E/I)	VIA Matrix, per sq cm
Q4310 (E/I)	Procenta, per 100 mg
Q4311 (E/I)	Acesso, per sq cm
Q4312 (E/I)	Acesso AC, per sq cm
Q4313 (E/I)	DermaBind FM, per sq cm
Q4314 (E/I)	Reeva FT, per sq cm
Q4315 (E/I)	RegeneLink Amniotic Membrane Allograft, per sq cm
Q4316 (E/I)	AmchoPlast, per sq cm
Q4317 (E/I)	VitoGraft, per sq cm
Q4318 (E/I)	E-Graft, per sq cm
Q4319 (E/I)	SanoGraft, per sq cm
Q4320 (E/I)	PelloGraft, per sq cm
Q4321 (E/I)	RenoGraft, per sq cm
Q4322 (E/I)	CaregraFT, per sq cm
Q4323 (E/I)	alloPLY, per sq cm
Q4324 (E/I)	AmnioTX, per sq cm
Q4325 (E/I)	ACApatch, per sq cm
Q4326 (E/I)	WoundPlus, per sq cm
Q4327 (E/I)	DuoAmnion, per sq cm
Q4328 (E/I)	MOST, per sq cm
Q4329 (E/I)	Singlay, per sq cm
Q4330 (E/I)	TOTAL, per sq cm
Q4331 (E/I)	Axolotl Graft, per sq cm
Q4332 (E/I)	Axolotl DualGraft, per sq cm
Q4333 (E/I)	ArdeoGraft, per sq cm
Q4334 (E/I)	AmnioPlast 1, per sq cm
Q4335 (E/I)	AmnioPlast 2, per sq cm

Code	Description
Q4336 (E/I)	Artacent C, per sq cm
Q4337 (E/I)	Artacent Trident, per sq cm
Q4338 (E/I)	Artacent Velos, per sq cm
Q4339 (E/I)	Artacent Vericlen, per sq cm
Q4340 (E/I)	SimpliGraft, per sq cm
Q4341 (E/I)	SimpliMax, per sq cm
Q4342 (E/I)	TheraMend, per sq cm
Q4343 (E/I)	Dermacyte AC Matrix Amniotic Membrane Allograft, per sq cm
Q4344 (E/I)	Tri-Membrane Wrap, per sq cm
Q4345 (E/I)	Matrix HD Allograft Dermis, per sq cm
Q4346 (E/I)	Shelter DM Matrix, per sq cm
Q4347 (E/I)	Rampart DL Matrix, per sq cm
Q4348 (E/I)	Sentry SL Matrix, per sq cm
Q4349 (E/I)	Mantle DL Matrix, per sq cm
Q4350 (E/I)	Palisade DM Matrix, per sq cm
Q4351 (E/I)	Enclose TL Matrix, per sq cm
Q4352 (E/I)	Overlay SL Matrix, per sq cm
Q4353 (E/I)	Xceed TL Matrix, per sq cm
Q4354 (E/I)	Palingen dual-layer membrane, per square centimeter
Q4355 (E/I)	Abiomend xplus membrane and abiomend xplus hydromembrane, per square centimeter
Q4356 (E/I)	Abiomend membrane and abiomend hydromembrane, per square centimeter
Q4357 (E/I)	Xwrap plus, per square centimeter
Q4358 (E/I)	Xwrap dual, per square centimeter
Q4359 (E/I)	Choriply, per square centimeter
Q4360 (E/I)	Amchoplast fd, per square centimeter
Q4361 (E/I)	Epixpress, per square centimeter
Q4362 (E/I)	Cygnus disk, per square centimeter
Q4363 (E/I)	Amnio burgeon membrane and hydromembrane, per square centimeter
Q4364 (E/I)	Amnio burgeon xplus membrane and xplus hydromembrane, per square centimeter
Q4365 (E/I)	Amnio burgeon dual-layer membrane, per square centimeter
Q4366 (E/I)	Dual layer amnio burgeon x-membrane, per square centimeter
Q4367 (E/I)	Amniocore sl, per square centimeter
Q4368 (E/I)	AmchoThick, per sq cm
Q4370 (E/I)	AeroGuard, per sq cm
Q4371 (E/I)	NeoGuard, per sq cm
Q4372 (E/I)	AmchoPlast EXCEL, per sq cm
Q4373 (E/I)	Membrane Wrap-Lite, per sq cm
Q4375 (E/I)	duoGRAFT AC, per sq cm
Q4376 (E/I)	Duograft AA, per sq cm
Q4377 (E/I)	triGRAFT FT, per sq cm

Code	Description
Q4378 (E/I)	Renew FT Matrix, per sq cm
Q4379 (E/I)	AmnioDefend FT Matrix, per sq cm
Q4380 (E/I)	AdvoGraft One, per sq cm
Q4382 (E/I)	AdvoGraft Dual, per sq cm
Q4383 (E/I)	Axolotl Graft Ultra, per sq cm
Q4384 (E/I)	Axolotl DualGraft Ultra, per sq cm
Q4385 (E/I)	Apollo FT, per sq cm
Q4386 (E/I)	Acesso TrifACA, per sq cm
Q4387 (E/I)	NeoThelium FT, per sq cm
Q4388 (E/I)	NeoThelium 4L, per sq cm
Q4389 (E/I)	NeoThelium 4L Plus, per sq cm
Q4390 (E/I)	Ascendion, per sq cm
Q4391 (E/I)	AmnioPlast Double, per sq cm
Q4392 (E/I)	GRAFIX Duo, per sq cm
Q4393 (E/I)	SurGraft AC, per sq cm
Q4394 (E/I)	SurGraft ACA, per sq cm
Q4395 (E/I)	Acelagraft, per sq cm
Q4396 (E/I)	Natalin, per sq cm
Q4397 (E/I)	Summit AAA, per sq cm

ICD10 Codes

Code	Description
C07	Malignant neoplasm of parotid gland
C50.011-C50.019	Malignant neoplasm of nipple and areola, female breast (code range)
C50.111-C50.119	Malignant neoplasm of central portion of female breast (code range)
C50.211-C50.219	Malignant neoplasm of upper-inner quadrant of female breast (code range)
C50.221-C50.229	Malignant neoplasm of upper-inner quadrant of male breast (code range)
C50.311-C50.319	Malignant neoplasm of lower-inner quadrant of female breast (code range)
C50.321-C50.329	Malignant neoplasm of lower-inner quadrant of male breast (code range)
C50.411-C50.419	Malignant neoplasm of upper-outer quadrant of female breast (code range)
C50.421-C50.429	Malignant neoplasm of upper-outer quadrant of male breast (code range)
C50.511-C50.519	Malignant neoplasm of lower-outer quadrant of female breast (code range)

Code	Description
C50.521-C50.529	Malignant neoplasm of lower-outer quadrant of male breast (code range)
C50.611-C50.619	Malignant neoplasm of axillary tail of female breast (code range)
C50.621-C50.629	Malignant neoplasm of axillary tail of male breast (code range)
C50.811-C50.819	Malignant neoplasm of overlapping sites of female breast (code range)
C50.821-C50.829	Malignant neoplasm of overlapping sites of male breast (code range)
C50.911-C50.919	Malignant neoplasm of unspecified site of female breast (code range)
C50.921-C50.929	Malignant neoplasm of unspecified site of male breast (code range)
D05.00-D05.92	Carcinoma in situ of breast (code range)
D11.0-D11.9	Benign neoplasm of major salivary gland (code range)
D37.030-D37.039	Neoplasm of uncertain behavior of the salivary glands (code range)
E08.621	Diabetes mellitus due to underlying condition with foot ulcer
E09.621	Drug or chemical induced diabetes mellitus with foot ulcer
E10.621	Type 1 diabetes mellitus with foot ulcer
E11.621	Type 2 diabetes mellitus with foot ulcer
E13.621	Other specified diabetes mellitus with foot ulcer
I83.001-I83.009	Varicose veins of unspecified lower extremity with ulcer (code range)
I83.011-I83.029	Varicose veins of lower extremity with ulcer (code range)
I83.201-I83.229	Varicose veins of lower extremity with both ulcer and inflammation (code range)
I87.311-I87.319	Chronic venous hypertension (idiopathic) with ulcer (code range)
K11.1-K11.9	Disease of salivary gland (code range)
K43.0-K43.2	Incisional hernia (code range)
L97.101-L97.929	Non-pressure chronic ulcer of lower limb, not elsewhere classified (code range)
T20.00XA-T25.399S	Burns - by site and degree of burn (code range)
T30.0	Burn of unspecified body region, unspecified degree
T30.4	Corrosion of unspecified body region, unspecified degree
T31.0-T31.99	Burns (code range)
T32.0-T32.99	Corrosions (code range)

Code	Description
Z85.3	Personal history of malignant neoplasm of breast
Z90.10-Z90.13	Acquired absence of breast and nipple (code range)

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Skin substitutes are not addressed in National or Regional Medicare coverage determinations or policies.

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.

- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
01/01/27	
Date	**Summary of Changes**
01/01/27	• Original effective date