Bio-Engineered Skin and Soft Tissue Substitutes

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DESCRIPTION

Note: *For Amniotic Membrane and Amniotic Fluid Grafts see Medical Policy 02.01.60*

Bioengineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman tissue (xenographic), synthetic materials, or a composite of these materials. Bioengineered skin and soft tissue substitutes are being evaluated for a variety of conditions, including breast reconstruction and healing lower-extremity ulcers and severe burns. Acellular dermal matrix (ADM) products are also being evaluated for soft tissue repair.

Skin and Soft Tissue Substitutes

Bioengineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (e.g., dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. Acellular dermal matrix (ADM) products can differ in a number of ways, including by species source (human, bovine, porcine), tissue source (e.g. dermis,

pericardium, intestinal mucosa), additives (e.g., antibiotics, surfactants), hydration (wet, freeze-dried), and required preparation (multiple rinses, rehydration).
Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species (e.g., bovine, porcine). Skin substitutes may also be composed of dermal cells, epidermal cells, or a combination of dermal and epidermal cells, and may provide growth factors to stimulate healing. Bioengineered skin substitutes can be used as either temporary or permanent wound coverings.

Applications
There are a large number of potential applications for artificial skin and soft tissue products. One large category is nonhealing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, nonhealing lower-extremity wounds represent an ongoing risk for infection, sepsis, limb amputation, and death. Bioengineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.
Other situations in which bioengineered skin products might substitute for living skin grafts include certain postsurgical states (e.g., breast reconstruction) in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Second- and third-degree burns are another indication in which artificial skin products may substitute for auto- or allografts. Certain primary dermatologic conditions that involve large areas of skin breakdown (e.g., bullous diseases) may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. ADM products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and other conditions.

Breast Reconstruction

Clinical Context and Therapy Purpose
A variety of breast reconstruction techniques are used postmastectomy, including implant-based (immediate or delayed following use of a tissue expander) and those using autologous tissue flaps. Some of these techniques have been used with acellular dermal matrix (ADM) to provide additional support or tissue coverage. The purpose of bioengineered soft tissue substitutes in patients who are undergoing breast reconstruction is to provide a treatment option that is an alternative to or an improvement on breast reconstruction without use of a biological or biosynthetic matrix.

Populations
The relevant population of interest is patients who are undergoing breast reconstruction, typically following mastectomy.

Interventions
The therapy being considered is bioengineered soft tissue substitutes as a biological matrix that is used to facilitate one-stage tissue expander reconstruction. As noted in the regulatory status section, the U.S. Food and Drug Administration (FDA) has not cleared or approved any surgical mesh device (synthetic, animal collagen-derived, or human collagen-derived) for use in breast surgery. In October 2021, an FDA advisory panel on general and plastic surgery voted against recommending FDA approval of the SurgiMend mesh for the specific indication of breast reconstruction. The advisory panel concluded that the benefits of using the device did not outweigh the risks.

Comparators
The following therapies are currently being used to make decisions about soft tissue substitutes or biological matrices: 2-stage tissue expander reconstruction without a biological matrix.

Outcomes
The general outcomes of interest are symptoms, morbid events, functional outcomes, quality of life (QOL), and treatment-related morbidity. Specific outcomes are the time to permanent implant, pain during and after the procedure, and adverse events including seroma, infection, and necrosis rates, rates of capsular contracture, and malposition of implants. Short-term outcomes would be measured within 3 months with longer-term outcomes apparent by 2 years.

Review of Evidence
The literature on acellular dermal matrix (ADM) for breast reconstruction consists primarily of retrospective, uncontrolled series and systematic reviews of these studies.

A 2013 study used data from the American College of Surgeon's National Surgical Quality Improvement Program to compare ADM-assisted tissue expander breast reconstruction (n=1717) to submuscular tissue expander breast reconstruction (n=7442) after mastectomy. Complication rates did not differ significantly between the ADM-assisted (5.5%) and the submuscular tissue expander groups (5.3%; p=.68). Rates of reconstruction-related complications, major complications, and 30-day reoperation did not differ significantly between cohorts.

Systematic Reviews
A meta-analysis by Lee and Mun (2016) included 23 studies (total N=6199 cases) on implant-based breast reconstruction that were published between February 2011 and December 2014. The analysis included a randomized controlled trial (RCT) and 3 prospective comparative cohort studies; the remainder was retrospective comparative cohort studies. Use of acellular dermal matrix (ADM) did not affect the total complication rate. ADM significantly increased the risk of major infection, seroma, and flap necrosis, but reduced risks of capsular contracture and implant malposition. Use of ADM allowed for significantly greater intraoperative expansion (mean difference, 79.63; 95% confidence interval [CI], 41.99 to 117.26; p<.001) and percentage of intraoperative

filling (mean difference, 13.30; 95% CI, 9.95 to 16.65; p<.001), and reduced the frequency of injections to complete expansion (mean difference, -1.56; 95% CI, -2.77 to -0.35; p=.01).

AlloDerm

Randomized Controlled Trials

McCarthy et al (2012) reported on a multicenter, blinded randomized controlled trial (RCT) of AlloDerm in 2-stage expander/implant reconstruction. Seventy patients were randomized to AlloDerm ADM-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. The trial was adequately powered to detect clinically significant differences in immediate postoperative pain but underpowered to detect the secondary endpoint of pain during tissue expansion. There were no significant differences between the groups in the primary outcomes of immediate postoperative pain (54.6 AlloDerm vs. 42.8 controls on a 100-point visual analog scale) or pain during the expansion phase (17.0 AlloDerm vs. 4.6 controls) or in the secondary outcome of rate of tissue expansion (91 days AlloDerm vs. 108 days controls) and patient-reported physical well-being. There was no significant difference in adverse events, although the total number of adverse events was small.

Comparison Between Products

AlloDerm Versus DermaMatrix

Hinchcliff et al (2017) conducted a randomized controlled trial (RCT) that compared AlloDerm with AlloMax (n=15 each) for implant-based breast reconstruction. Complications were assessed 7,14, and 30 days postoperatively and biopsies of the ADMs were taken during implant exchange. Vessel density in the AlloMax biopsies was higher than in the AlloDerm biopsies. Complications were reported in 26.1% of AlloMax cases and 8.0% of AlloDerm cases; these complication rates did not differ statistically with the 30 patients in this trial.

AlloDerm Versus DermaMatrix

Mendenhall et al (2017) conducted an randomized controlled trial (RCT) that compared AlloDerm with DermaMatrix in 111 patients (173 breasts). There were no significant differences in overall rates of complications (AlloDerm, 15.4%; DermaMatrix, 18.3%; p=.8) or implant loss (AlloDerm, 2.2%; DermaMatrix, 3.7%; p=.5) between the 2 ADMs

AlloDerm Versus FlexHD

A retrospective review by Liu et al (2014) compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts). Eighty-one percent of the sample was immediate reconstruction: 165 used AlloDerm and 97 used FlexHD. Mean follow-up was 6.4 months. Compared with breast reconstruction without the use of AlloDerm or FlexHD, ADM had a higher rate of delayed healing (20.2% vs. 10.3%), although this finding might have been related to differences in fill volumes. In univariate analysis, there were no significant differences in

complications (return to operating room, surgical site infection, seroma, hematoma, delayed healing, implant loss) between AlloDerm and FlexHD. In multivariate analysis, there were no significant differences between AlloDerm and FlexHD for the return to the operating room, surgical site infection, seroma, or delayed healing. Independent risk factors for implant loss included the use of FlexHD, single-stage reconstruction, and smoking.

AlloDerm Versus FlexHD Pliable and DermACELL

Chang and Liu (2017) reported on a prospective comparison of FlexHD Pliable (32 breasts), AlloDerm (22 breasts), and DermACELL (20 breasts) in breast reconstruction. The choice of ADM was based on different years when each ADM was available for use at the investigators' institution; patient demographics were comparable between groups. The pieces of ADM used were all the same size (8 × 16 cm) to eliminate an effect of size on outcomes. The time to drain removal was longer with AlloDerm (26 days) than with FlexHD (20 days) or DermACELL (15 days; p=.001). Complications were low (4 in the Flex Pliable group, 2 in the AlloDerm group, 1 in the DermACELL group), with no significant differences between groups. At the time of exchange for a permanent implant or free flap reconstruction, all grafts had completely incorporated into the mastectomy skin flaps. No patients developed complications requiring removal of the ADM.

Pittman et al (2017) reported a retrospective pilot study of the use of AlloDerm (50 breasts) and DermACELL (50 breasts). The choice of ADM was based on products available during different years and patient demographics were similar between the 2 groups. Patients in the DermACELL group had a significantly lower incidence of "red breast syndrome" (0% vs. 26%, p=.001) and fewer days until drain removal (15.8 days vs. 20.6 days, p=.017). There were no significant differences in the rates of other complications.

Strattice

Dikmans et al (2017) reported on early safety outcomes from an open-label multicenter randomized controlled trial (RCT) that compared porcine ADM-assisted 1-stage expansion with 2-stage implant-based breast reconstruction (see Table 2).[13,] One-stage breast reconstruction with porcine ADM was associated with a higher risk of surgical complications, reoperation, and with removal of implant, ADM, or both (see Table 3). The trial was stopped early due to safety concerns, but it cannot be determined from this study design whether the increase in complications was due to the use of the xenogeneic ADM or to the comparison between 1-stage and 2-stage reconstruction.

Section Summary: Breast Reconstruction

Results of a systematic review found no difference in overall complication rates between ADM allograft and standard procedures for breast reconstruction. Although reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM, rates of capsular contracture and malposition of implants may be reduced. Thus, in cases where there is limited tissue

coverage, the available studies may be considered sufficient to permit informed decision-making about risks and benefits of using allogeneic ADM for breast reconstruction.

Tendon Repair

Clinical Context and Therapy Purpose
The purpose of bioengineered soft tissue substitutes in patients who are undergoing tendon repair is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is patients undergoing tendon repair.

Interventions
The therapy being considered is bioengineered soft tissue substitutes.

Comparators
The following therapies are currently being used to make decisions about tendon repair: tendon repair without bioengineered soft tissue substitutes.

Outcomes
The general outcomes of interest are symptoms, morbid events, functional outcomes, quality of life (QOL), and treatment-related morbidity. Short-term outcomes would be measured within 3 months with longer-term outcomes apparent by 2 years.

Review of Evidence

GraftJacket
Rashid et al (2020) reported disruption of the native extracellular matrix with either GraftJacket or Permacol (porcine acellular dermis) as a patch overlay for rotator cuff repair in a small, controlled study with 13 patients. The disruption was greater in the Permacol group and there was an immune response in 1 of 3 patients following use of the xenograft.

Barber et al (2012) reported an industry sponsored multicenter RCT of augmentation with GraftJacket human ADM for arthroscopic repair of large (>3 cm) rotator cuff tears involving 2 tendons. Twenty-two patients were randomized to GraftJacket augmentation and 20 patients to no augmentation. At a mean follow-up of 24 months (range, 12-38 months), the American Shoulder and Elbow Surgeons score improved from 48.5 to 98.9 in the GraftJacket group and from 46.0 to 94.8 in the control group (p=.035). The Constant score improved from 41 to 91.9 in the GraftJacket group and from 45.8 to 85.3 in the control group (p=.008). The University of California, Los Angeles score did not differ significantly between groups. Gadolinium-enhanced magnetic resonance imaging (MRI) scans showed intact cuffs in 85% of repairs in the GraftJacket group and 40% of repairs in the control group. However, no correlation was found between MRI findings

and clinical outcomes. Rotator cuff retears occurred in 3 (14%) patients in the GraftJacket group and 9 (45%) patients in the control group.

Section Summary: Tendon Repair
One small randomized controlled trial (RCT) was identified that found improved outcomes with GraftJacket ADM allograft for rotator cuff repair. Although results of this trial were promising, additional study with a larger number of patients is needed to corroborate these findings and determine the effects of this technology with greater certainty.

Complex Abdominal Wall Wounds

Clinical Context and Therapy Purpose
The purpose of bioengineered soft tissue substitutes in patients who are undergoing complex abdominal wall reconstruction is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is patients undergoing complex abdominal wall reconstruction.

Interventions
The therapy being considered is bioengineered soft tissue substitutes.

Comparators
The following therapies are currently being used to make decisions about complex abdominal wall reconstruction: complex abdominal wall reconstruction without bioengineered soft tissue substitutes.

Outcomes
The general outcomes of interest are symptoms, morbid events, functional outcomes, quality of life (QOL), and treatment-related morbidity. Short-term outcomes would be measured within 3 months with longer-term outcomes apparent by 2 years.

Review of Evidence

AlloDerm
The treatment of infected or contaminated abdominal wall wounds and defects is difficult. Standard fascial prostheses such as polypropylene and polyester mesh, which are routinely used for non-complex cases, may exacerbate wound infection, fistula and adhesion formation, and erosion, leaving few real options for such individuals. The use of AlloDerm RTM for the treatment of complex abdominal wall wounds has been reported in over 30 peer-reviewed journal articles. These studies demonstrate a high rate of successful wound healing with relatively low numbers of complications. As with the use of AlloDerm RTM for breast reconstruction, AlloDerm RTM for complex abdominal

wall wounds has been widely used and is an accepted treatment method, although data is limited regarding the long-term benefits and outcomes of this use. Expert opinion of surgeons who routinely treat these types of wounds supports the use of AlloDerm RTM for this indication.

Cortiva
The use of Cortiva for abdominal wall reconstruction was reported by Lindsey in 2020. This retrospective chart review involved 82 subjects who underwent abdominal wall reconstruction with either AlloDerm (n=53) or Cortiva (n=29). The overall complication rate was found to be not significantly different between groups (51.92% in the AlloDerm group vs. 72.41% in the Cortiva group, p=0.09921). No explanations were reported. This was the first description of Cortiva used for the treatment of abdominal wall reconstruction procedures. Additional data is needed to fully evaluate the clinical utility of this technique.

Fortiva
Fortiva is a product composed of porcine acellular dermal matrix and has been cleared through the FDA's 510K process. The only currently available published peer-reviewed study addressing its use in a clinical setting was published by Maxwell in 2019, who reported on the results of a retrospective non-randomized controlled study investigating the use of Fortiva (n=72) compared to Strattice (n=98) and Alloderm (n=59) in 229 subjects undergoing abdominal wall reconstruction. The incidence of recurrence of abdominal wall defect was significantly higher in the Alloderm group (20.3%) compared with the Fortiva (10.2%) and Strattice groups (6.9%) (p=0.040). The 1-, 3-, and 5-year survival rates for the repair with Fortiva were 1.4% and 6.9%, and 0%. For Strattice, the results were 5.1%, 9.2%, and 10.2%, and for Alloderm, 6.8%, 18.5%, and 20.3%. Although subjects in the Alloderm group had the longest median hernia-free interval, 26.8 months (2-60 months), this was not found to be significantly different from Fortiva and Strattice (data not provided). The most common complication was surgical site infection (26.2%), followed by delayed healing (24.0%). Seroma formation was reported to have been significantly lower in the Fortiva group vs. the Strattice and Alloderm groups (1.4% vs 13.3% vs 11.9%; p=0.021). This study indicates promising results; however, this data is limited and not methodologically robust. Additional investigation into the safety and efficacy of Fortiva is needed.

Strattice
Strattice is an acellular dermal collagen product of porcine origin and has been cleared under the FDA's 510k process. In 2012, three studies evaluating the use of Strattice were published. The largest was a retrospective, controlled study looking at the use of Strattice (n=96) vs. AlloDerm RTM (n=90) for tissue expander breast reconstruction (Glasberg, 2012). The authors reported a significantly higher complication rate in the AlloDerm RTM group (21.4% vs. 6.3%; p=0.0003), caused by the incidence of seromas (12.7% vs. 1.4%; p=0.0003). No other significant differences were reported, including capsule formation (2.4% for AlloDerm RTM and 2.8% for Strattice). This study was not prospective, randomized, or blinded.

The second trial involved the use of Strattice for complex abdominal reconstruction (Itani, 2012). This case series study involved 80 subjects undergoing contaminated ventral hernia repair that were prospectively enrolled and treated with Strattice. Sixty subjects continued through the final 24-month follow-up (25% loss to follow-up). The authors reported that midline restoration was achieved with primary closure in 64 subjects with defects bridged in 16 subjects. At 24 months, 53 subjects (66%) experienced 95 wound events including seroma (n=23, 29%), infection (n=28, 35%), dehiscence (n=14, 18%), hematoma (n=7, 9%), and abscess (n=7, 9%). No grafts required complete excision. Hernia recurrence was reported in 22 subjects (28%) by month 24. There was no correlation between infection-related events and hernia recurrence.

The third study, by Patel and colleagues, was a retrospective case study also evaluating the use of Strattice for complex abdominal reconstruction (2012). This study involved 41 subjects with complex ventral hernias undergoing component separation with Strattice underlayment. Concomitant panniculectomy was conducted in 9 subjects (22%). The complication rate was 24.4% (10/41), with the majority of early complications being skin necrosis (n=9), but also included Strattice exposure (n=5). These subjects required intervention in the operating room (OR). Wound dehiscence and seroma were noted in 3 subjects respectively. One subject required skin grafting for wound closure.

Rosen (2013) published a study investigating the use of acellular matrix for the reconstruction of infected and contaminated abdominal wall defects. The study involved 128 subjects who received treatment with Strattice (n=102), AlloDerm RTM (n=16), Biodesign (n=4), Xenmatrix (n=4), and BioA (n=4). Postoperative wound complications were identified in 61 (47.7%) subjects. The report indicated that predictors of wound complications included American Society of Anesthesiologists (ASA) score, diabetes, smoking, number of previous abdominal surgeries or hernia repairs, hernia defect size, and operative time. Hernia recurrence was identified in 40 (31.3%) subjects at a mean follow-up time of 21.7 months. The majority of recurrent hernias were asymptomatic, and 7 subjects underwent repair.

Use of Strattice was reported in a study of 41 subjects with complex abdominal wall defects at increased risk for perioperative complications (Patel, 2013). Reported comorbidities included coronary artery disease (63.4%), diabetes mellitus (36.6%), and chronic obstructive pulmonary disease (17.1%). The authors reported that fascial closure was achieved in 40 subjects (97.6%). Recurrent/complex hernia was present in 78% subjects. The overall complication rate was 22.0%, and included seroma (7.3%), wound dehiscence with Strattice exposure (4.9%), cellulitis (2.4%), and hematoma (2.4%). All subjects achieved abdominal wall closure with no recurrent hernias or need for Strattice removal.

Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with Strattice, an acceptable level of safety

and efficacy has been established for the use of this product for the surgical repair of complex abdominal wall wounds.

Surgical Repair of Hernia or Parastomal Reinforcement

Clinical Context and Therapy Purpose
The purpose of bioengineered soft tissue substitutes in patients who are undergoing surgical repair of hernias or require parastomal reinforcement is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is patients undergoing surgical repair of hernias or requiring parastomal reinforcement.

Interventions
The therapy being considered is bioengineered matrix support.

Comparators
The following therapies are currently being used for surgical repair of hernias or parastomal reinforcement: synthetic mesh.

Outcomes
The general outcomes of interest are symptoms, morbid events, functional outcomes, quality of life (QOL), and treatment-related morbidity. Specific outcomes are surgical site occurrence of postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, or mechanical failure. Short-term outcomes would be measured within 3 months with longer-term outcomes apparent by 2 years.

Review of Evidence
A 2013 systematic review evaluated the clinical effectiveness of acellular collagen-based scaffolds for the repair of incisional hernias. The bioprosthetic materials could be harvested from bovine pericardium, human cadaveric dermis, porcine small intestine mucosa, porcine dermal collagen, or bovine dermal collagen. Products included in the search were Surgisis, Tutomesh, Veritas, AlloDerm, FlexHD, AlloMax, CollaMend, Permacol, Strattice, FortaGen, ACell, DermaMatrix, XenMatrix, and SurgiMend. Sixty publications with 1212 repairs were identified and included in the review, although meta-analysis could not be performed. There were 4 level III studies (2 AlloDerm, 2 Permacol); the remainder were level IV or V. The largest number of publications were on AlloDerm (n=27) and Permacol (n=18). No publications on incisional hernia repair were identified for AlloMax, FortaGen, DermaMatrix, or ACell. The overall incidence of a surgical site occurrence (eg, postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, mechanical failure) was 82.6% for porcine small intestine mucosa, 50.7% for xenogeneic dermis, 48.3% for human dermis, and 6.3% for xenogeneic pericardium. No comparative data were identified that could establish superiority to permanent synthetic meshes.

Comparison Between Products

AlloDerm Versus Surgisis Gold

Gupta et al (2006) compared the efficacy and complications associated with use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair. The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine submucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7 to 10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in 8 (24%) hernia recurrences. Fifteen (45%) of the AlloDerm patients developed a diastasis or bulging at the repair site. Seroma formation was only a problem in 2 patients

AlloDerm Versus FlexHD

A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery. From 2005 to 2007, AlloDerm was used to repair large (>200 cm^2) symptomatic complicated ventral hernias that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD was used to repair large, complicated ventral hernias in patients meeting the same criteria (n=40). The 2 groups were comparable at baseline. At 1 year follow-up, all AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, true recurrence) requiring a second repair. Eleven (31%) patients in the FlexHD group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

FlexHD Versus Strattice

Roth et al (2017) reported on a prospective study assessing clinical and QOL outcomes following complex hernia repair with a human (FlexHD) or porcine (Strattice) ADM. The study was funded by the Musculoskeletal Transplant Foundation, which prepares and supplies FlexHD. Patients were enrolled if they had a hernia at least 6 cm in the transverse dimension, active or prior infection of the abdominal wall, and/or enterocutaneous fistula requiring mesh removal. Eighteen (51%) of the 35 patients had undergone a previous hernia repair. After abdominal wall repair with the ADM, 20 (57%) patients had a surgical site occurrence, and nearly one-third had hospital readmission. The type of biologic material did not impact hernia outcomes. There was no comparison with synthetic mesh in this study, limiting interpretation.

Strattice Versus Synthetic Mesh

Bellows et al (2014) reported early results of an industry-sponsored multicenter RCT that compared Strattice (non-cross-linked porcine ADM, n=84) with a standard synthetic mesh (n=88) for the repair of inguinal hernias.[21,] The trial was designed by the surgeons and was patient- and assessor-blinded to reduce risk of bias. Blinding continued through 2 years of follow-up. The primary outcome was resumption of activities of daily living at 1 year. Secondary outcomes included complications, recurrences, or chronic pain (ie,

pain that did not disappear by 3 months postsurgery). At 3-month follow-up, there were no significant differences in either the occurrence or type of wound events (relative risk, 0.98; 95% CI, 0.52 to 1.86). Pain was reduced from 1 to 3 days postoperative in the group treated with Strattice, but at 3-month follow-up pain scores did not differ significantly between groups.

Strattice Versus No Reinforcement
Also in 2014, the Parastomal Reinforcement with Strattice (PRISM) Study Group reported a multicenter, double-blinded, randomized trial of Strattice for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies. Patients were randomized to standard stoma construction with no reinforcement (n=58) or stoma construction with Strattice as parastomal reinforcement (n=55). At 24-month follow-up (n=75), the incidence of parastomal hernias was similar for the 2 groups (13.2% of controls, 12.2% of study group).

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

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

Diabetic Lower-Extremity Ulcers

Clinical Context and Therapy Purpose
The purpose of bioengineered soft tissue substitutes in patients who have diabetic lower extremity ulcers is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is patients with diabetic lower extremity ulcers.

Interventions
The therapy being considered is bioengineered skin substitutes.

Comparators
The following therapies are currently being used: standard wound care which involves regular debridement and moist wound covering.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, and QOL.

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

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

Time to wound closure can be measured at 6 months with longer-term outcomes apparent by 1 year. More complex wounds may require more than 6 months to heal.

Review of Evidence

Agency for Healthcare Research and Quality (AHRQ)
Skin Substitutes for Treating Chronic Wounds (2020)

Key Points

- Variation in study design reduces the ability to compare outcomes across studies.
- Comparisons across studies may be enhanced by standardizing approaches for inclusion criteria (wound size, wound duration before study inclusion, wound severity) by using a 2- to 4-week run-in period before study enrollment and a 12-week study period, by reporting wound recurrence up to 6 months as well as wounds healed during the study, and by blinded wound assessment.
- KIs suggested that patient inclusion criteria could be expanded to include patients more representative of clinical practice and of poorer health than typical patients included in RCTs. This would allow subanalysis of gender, race, ethnicity, age, and comorbidities that may help direct specific product use for different wound conditions.
- KIs suggested that failure to heal after 6 weeks of treatment with a skin substitute may be an appropriate criterion for discontinuing use of a skin substitute and switching to another advanced therapy option.
- KIs suggested that 40 percent to 50 percent wound closure in 4 weeks was a good predictor of successful wound closure.

Guo et al (2017) reported a systematic review of ADM for the treatment of diabetic foot ulcers. Most data were from an RCT of Integra Dermal Regeneration Template, which is a bilayer product with the outer layer composed of a thin silicone film and not a pure ADM.

A 2016 Cochrane review evaluated skin substitutes for the treatment of diabetic foot ulcers. Seventeen trials (N=1655) were included in the meta-analysis. Most trials

identified were industry-sponsored, and an asymmetric funnel plot indicated publication bias. Pooled results of published trials found that skin substitutes increased the likelihood of achieving complete ulcer closure compared with standard of care (SOC) alone (relative risk, 1.55; 95% CI, 1.30 to 1.85). Use of skin substitutes also led to a statistically significant reduction in amputations (relative risk, 0.43; 95% CI, 0.23 to 0.81), although the absolute risk difference was small. Analysis by individual products found a statistically significant benefit on ulcer closure for Apligraf, EpiFix, and Hyalograft-3D. The products that did not show a statistically significant benefit for ulcer closure were Dermagraft, GraftJacket, Kaloderm, and OrCel.

Martinson and Martinson (2016) conducted an industry-sponsored analysis of Medicare claims data (13193 treatment episodes) to compare efficacy and cost of skin substitutes for the management of diabetic foot ulcers. Included in the analysis were treatment episodes with Apligraf (37%), Dermagraft (42%), Oasis (19%), and Cytal (MatriStem, 2%). The mean number of applications was 3.24 for Apligraf, 4.48 for Oasis, 5.53 for Cytal, and 5.96 for Dermagraft. All comparisons were statistically significant. Healing at 90 days was modestly but statistically higher for Oasis (63%) and Cytal (62%) than for Apligraf (58%) or Dermagraft (58%). Amputation rates were similar after treatment with the 4 products, ranging from 1.3% for Oasis to 2.1% for Cytal.

Apligraf, Dermagraft, AlloPatch, Integra Dermal Regeneration Template, or Integra Flowable Wound Matrix

Apligraf

Veves et al (2001) reported on a randomized prospective trial on the effectiveness of Apligraf (previously called Graftskin), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers. The trial involved 24 centers in the United States; 208 patients were randomized to ulcer treatment with Apligraf (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical débridement and adequate foot off-loading, was provided in both groups. Apligraf was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of 5 applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Apligraf-treated patients achieved complete wound healing compared with 36 (38%) in the control group (p=.004). The Kaplan-Meier method median time to complete closure was 65 days for Apligraf, which was significantly lower than the 90 days observed in the control group (p=.003). The rates of adverse reactions were similar between groups, except osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf group. Trialists concluded that application of Apligraf for a maximum of 4 weeks resulted in higher healing rates than state-of-the-art treatment and was not associated with any significant adverse events. This trial was reviewed in a 2001 TEC Assessment, which concluded that Apligraf, in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.

Steinberg et al (2010) reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of noninfected diabetic foot ulcers. The s tudy design and patient population were similar to the 208-subject U.S. study (previously described), which led to FDA approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with noninfected neuropathic diabetic foot ulcers present for at least 2 weeks were enrolled in prospective, multicenter, open-label RCTs that compared Apligraf use plus standard therapy (sharp debridement, standard wound care, off-loading) with standard therapy alone. Pooling of data was performed because of the similarity and consistency of the 2 studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration, which was significantly longer in the European study (21 months vs.10 months in the U.S. study). Reported adverse events by 12 weeks were comparable across treatment groups in the 2 studies. Efficacy measures demonstrated superiority of Apligraf treatment over control-treated groups in both studies. Combining the data from both studies, 55.2% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared with 34.3% (46/134) of control subjects ($p<.001$), and Apligraf subjects had a significantly shorter time to complete wound closure ($p<.001$). The authors concluded that both the EU and U.S. studies exhibited superior efficacy and comparable safety for subjects treated with Apligraf compared with control subjects and that the studies provided evidence of the benefit of Apligraf in treating diabetic foot ulcers.

Kirsner et al (2010) analyzed 2517 patients with diabetic neuropathic foot ulcers treated between 2001 and 2004. This retrospective analysis used a wound care database; the patients received advanced biologic therapy, specifically, Apligraf (446 patients), Regranex, or Procuren. The analysis found that advanced biologic therapy was used, on average, within 28 days from the first wound clinic visit and was associated with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biologic therapy were 31% more likely to heal than wounds first treated with topical recombinant growth factor ($p<.001$) and 40% more likely to heal than those first treated with platelet releasate ($p=.01$). Wound size, wound grade, duration of wound, and time to initiation of advanced biologic therapy affected the time to healing.

Dermagraft

A 2003 pivotal multicenter FDA regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft (human-derived fibroblasts cultured on mesh) or control. Over the 12-week study, patients received up to 8 applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91% compared with 78% for the control group. Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious adverse events were attributed to Dermagraft. Ulcer infections developed in 10.4% of the Dermagraft patients compared with 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group (19% vs. 32.5%). A 2015 retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft (5.5% vs. 12.6%,

p=.031).[32,] Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

AlloPatch

AlloPatch Pliable human reticular acellular dermis was compared with SOC in an industry-sponsored multicenter trial by Zelen et al (2017, 2018). The initial trial with 20 patients per group was extended to determine the percent healing at 6 weeks with 40 patients per group. Healing was evaluated by the site investigator and confirmed by an independent panel. At 6 weeks, 68% (27/40) of wounds treated using AlloPatch had healed compared with 15% (6/40) in the SOC-alone group (p<.001). At 12 weeks, 80% (32/40) of patients in the AlloPatch group had healed compared to 30% (12/40) in the control group. Mean time to heal within 12 weeks was 38 days (95% CI: 29-47 days) for the HR-ADM group and 72 days (95% CI: 66-78 days) for the SOC group (p<.001).
Integra Omnigraft Dermal Regeneration Template or Integra Flowable Wound Matrix
Integra Dermal Regeneration Template is a biosynthetic skin substitute that is FDA approved for life-threatening thermal injury. The FOUNDER (Foot Ulcer New Dermal Replacement) multicenter study (32 sites) assessed Integra Dermal Regeneration Template (marketed as Omnigraft) for chronic nonhealing diabetic foot ulcers under an FDA regulated investigational device exemption. A total of 307 patients with at least 1 chronic diabetic foot ulcer were randomized to treatment with the Integra Template or a control condition (sodium chloride gel 0.9%). Treatment was given for 16 weeks or until wound closure. There was a modest increase in wound closure with the Integra Template (51% vs. 32%, p=.001) and a shorter median time to closure (43 days vs. 78 days, p=.001). 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. Trial strengths included adequate power to detect an increase in wound healing of 18%, which was considered to be clinically significant, secondary outcomes of wound closure and time to wound closure by computerized planimetry, and intention-to-treat (ITT) analysis.

Integra Flowable Wound Matrix is composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. It is supplied as a granular product that is mixed with saline. Campitiello et al (2017) published an RCT that compared the flowable matrix with wet dressing in 46 patients who had Wagner grade 3 diabetic foot ulcers. The ulcers had developed over 39 weeks. Complete healing at 6 weeks was achieved in significantly more patients in the Integra Flowable Wound Matrix group than in the control group, while the risk of rehospitalization and major amputation was reduced with Integra Flowable Wound Matrix.

Section Summary: Apligraf, Dermagraft, AlloPatch, or Integra for Diabetic Lower-Extremity Ulcers

RCTs have demonstrated the efficacy of Apligraf, Dermagraft, AlloPatch, Integra Dermal Regeneration Template, and Integra Flowable Wound Matrix over SOC for the treatment of diabetic lower-extremity ulcers.

Bioengineered Skin Substitutes Other Than Apligraf, Dermagraft, AlloPatch, or Integra GraftJacket Regenerative Tissue Matrix Brigido et al (2004) reported a small (N=40) randomized pilot study comparing GraftJacket with conventional treatment for chronic nonhealing diabetic foot ulcers. Control patients received conventional therapy with debridement, wound gel with gauze dressing, and off-loading. GraftJacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the GraftJacket group. Preliminary 1-month results showed that, after a single treatment, ulcers treated with GraftJacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs. 15%), width (50% vs. 23%), area (73% vs. 34%), and depth (89% vs. 25%), respectively. With follow-up to 4 weeks, no data were reported on the proportion with complete closure or the mean time to heal. All grafts were incorporated into the host tissue.

Reyzelman et al (2009) reported an industry-sponsored multicenter randomized study that compared a single application of GraftJacket with SOC in 86 patients with diabetic foot ulcers. Eight patients, 6 in the study group and 2 in the control group, did not complete the trial. At 12 weeks, complete healing was observed in 69.6% of the GraftJacket group and 46.2% of controls. After adjusting for ulcer size at presentation, a statistically significant difference in nonhealing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks for the GraftJacket group versus 6.8 weeks for the control group. The authors did not report whether this difference was statistically significant. Median time to healing was 4.5 weeks for GraftJacket (range, 1-12 weeks) and 7.0 weeks for control (range, 2-12 weeks). Kaplan-Meier method survivorship analysis for time to complete healing at 12 weeks showed a significantly lower nonhealing rate for the study group (30.4%) than for the control group (53.9%). The authors commented that a single application of GraftJacket, as used in this study, was often sufficient for complete healing. Conclusions drawn from this study are limited by the small study population and differences in ulcer size at baseline. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant.

Reyzelman and Bazarov (2015) reported an industry-sponsored meta-analysis of GraftJacket for diabetic foot ulcers that included the 2 studies described above and a third RCT by Brigido (2006)[40,] with 28 patients (N=154). The time to heal was estimated for the Brigido (2004) study, based on the average wound reduction per week. The estimated difference in time to heal was considerably larger for Brigido's (2004) study (-4.30 weeks) than for the other 2 studies that measured the difference in time to heal (-1.58 weeks and -1.10 weeks). Analysis of the proportion of wounds that healed included Brigido (2006) and Reyzelman et al (2009). The odds ratio in the smaller study by Brigido (2006) was considerably larger, with a lack of precision in the estimate (odds ratio, 15.0; 95% CI, 2.26 to 99.64), and the combined odds (3.75; 95% CI, 1.72 to 8.19) was not significant when analyzed using a random-effects model. Potential sources of bias, noted by Reyzelman and Bazarov (2015), included publication and reporting biases,

study selection biases, incomplete data selection, post hoc manipulation of data, and subjective choice of analytic methods. Overall, results of these studies do not provide convincing evidence that GraftJacket is more effective than SOC for healing diabetic foot ulcers.

DermACELL Versus GraftJacket Regenerative Tissue Matrix or Standard of Care
DermACELL and GraftJacket are both composed of human ADM. Walters et al (2016) reported on a multicenter randomized comparison of DermACELL, GraftJacket, or SOC (2:1:2 ratio) in 168 patients with diabetic foot ulcers. The study was sponsored by LifeNet Health, a nonprofit organ procurement association and processor for DermACELL. At 16 weeks, the proportion of completely healed ulcers was 67.9% for DermACELL, 47.8% for GraftJacket, and 48.1% for SOC. The 20% difference in completely healed ulcers was statistically significant for DermACELL versus SOC (p=.039). The mean time to complete wound closure did not differ significantly for DermACELL (8.6 weeks), GraftJacket (8.6 weeks), and SOC (8.7 weeks).

A second report from this study was published in 2017. This analysis compared DermACELL with SOC and did not include the GraftJacket arm. The authors reported that either 1 or 2 applications of DermACELL led to a greater proportion of wounds healed compared with SOC in per-protocol analysis (see Table 5), but there was no significant difference between DermACELL (1 or 2 applications) and SOC when analyzed by ITT. For the group of patients who received only a single application, the percentage of patients who achieved complete wound healing was significantly higher than SOC at 16 and 24 weeks, but not at 12 weeks. Although reported as an ITT analysis, results were analyzed only for the group who received a single application of DermACELL. This would not typically be considered ITT unless the number of DermACELL applications was prespecified.

TheraSkin Versus Standard of Care
An industry-funded retrospective study by Gurtner et al (2020) was a matched comparison of TheraSkin to standard of care alone in 3994 lower extremity wounds of multiple etiologies. Data were collected from electronic medical records from 644 wound care centers that were managed by a single large wound management company. Patients were matched for 8 characteristics including wound size, severity, duration, comorbidities and body mass index. Diabetic wounds comprised 42% of the total cases and venous ulcers 29%. The next most frequent etiologies were pressure ulcers (~8%), surgical wounds (~9%), and trauma (~8%). Patients were excluded from analysis if they had greater than 50% wound closure during a 4-week run-in period. The overall healing rate was 68.3% in the allograft group and 60.3% for standard of care (p<.001). Diabetic wounds were treated with an average of 2.8 allografts prior to closure with a difference in closure rates of approximately 12% (67.5% vs 55.1%). A limitation of this retrospective analysis is that although the groups were well-matched on a number of variables, the application of the TheraSkin allograft was at the investigators discretion and not standardized.

TheraSkin Versus Dermagraft

Sanders et al (2014) reported on a small (N=23) industry-funded randomized comparison of TheraSkin (cryopreserved human skin allograft with living fibroblasts and keratinocytes) and Dermagraft for diabetic foot ulcers. 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 2 groups (p=.51). Grafts were applied according to manufacturers' instructions over the first 12 weeks of the study until healing, with an average of 4.4 TheraSkin grafts (every 2 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<.049). At 20 weeks, complete wound healing was observed in 90.9% of the TheraSkin-treated ulcers compared with 66.7% of the Dermagraft group (p=.428).

TheraSkin Versus Apligraf

DiDomenico et al (2011) compared TheraSkin with Apligraf for the treatment of diabetic foot ulcers in a small (N=29) RCT. The risk of bias in this study is uncertain because reporting did not include a description of power analysis, statistical analysis, method of randomization, or blinding. The percentage of wounds closed at 12 weeks was 41.3% in the Apligraf group and 66.7% in the TheraSkin group. Results at 20 weeks were not substantially changed from those at 12 weeks, with 47.1% of wounds closed in the Apligraf group and 66.7% closed in the TheraSkin group. The percentage healed in the Apligraf group was lower than expected based on prior studies. The average number of grafts applied was similar for both groups (1.53 for Apligraf, 1.38 for TheraSkin). The low number of dressing changes may have influenced results, with little change in the percentage of wounds closed between 12 and 20 weeks. An adequately powered trial with blinded evaluation of wound healing and a standard treatment regimen would permit greater certainty on the efficacy of this product.

Cytal (MatriStem) Versus Dermagraft

Frykberg et al (2017) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cytal (a porcine urinary bladder-derived extracellular matrix) versus Dermagraft in 56 patients with diabetic foot ulcers. The mean duration of ulcers before treatment was 263 days (range, 30-1095 days). The primary outcome was the percent wound closure with up to 8 weeks of treatment using blinded evaluation of photographs. ITT analysis found complete wound closure in 5 (18.5%) wounds treated with Cytal compared with 2 (6.9%) wounds treated with Dermagraft (p=not significant [*NS*]). QOL, measured by the Diabetic Foot Ulcer Scale, improved from 181.56 to 151.11 in the Cytal group and from 184.46 to 195.73 in the Dermagraft group (p=.074). It should be noted that this scale is a subjective measure and patients were not blinded to treatment. Power analysis indicated that 92 patients would be required; further recruitment is ongoing for completion of the study.

PriMatrix

Randomized Controlled Trial
Lantis et al (2021) reported on a multicenter RCT comparing PriMatrix plus standard of care to PriMatrix alone in 226 patients with diabetic foot ulcers.

Study subjects underwent a 2-week run-in period of SOC treatment and were excluded if they had a wound reduction of 30% or more. Patients randomized to the SOC group received weekly treatment at the study site identical to the SOC treatment applied during the screening period. In addition, control group patients performed daily dressing changes, which consisted of wound cleaning, application of saline gel and secondary dressings. The primary endpoint was the percentage of subjects with complete wound closure, defined as 100% re-epithelialization without drainage during the 12-week treatment phase.

Significantly more patients in the PriMatrix group experienced complete wound closure at 12 weeks (45.6% vs 27.9%; p=.008). It is unclear if this difference (17.7%) is clinically significant; the study was powered to detect a 20% difference between groups. The time to complete healing did not differ between groups for the wounds that healed. Major study limitations include lack of blinding, limited generalizability, and insufficient duration of follow-up to assess wound recurrence.

Nonrandomized Studies
Kavros et al (2014) reported a prospective multicenter study of PriMatrix (a xenograft fetal bovine dermal collagen matrix) for the treatment of chronic diabetic foot ulcers in 55 patients. The average duration of ulcers before treatment was 286 days, and the average wound area was 4.34 cm^2. Of the 46 patients who completed the study, 76% healed by 12 weeks with an average of 2 applications of PriMatrix. For the ITT population, 64% of wounds healed by 12 weeks.

Karr (2011) published a retrospective comparison of PriMatrix and Apligraf in 40 diabetic foot ulcers. The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. The criteria were: diabetic foot ulcers of 4 weeks in duration; ulcer of at least 1 cm^2 in diameter and to the depth of subcutaneous tissue; healthy tissue at the ulcer; adequate arterial perfusion to heal; and ability to off-load the diabetic ulcer. The time to complete healing for PriMatrix was 38 days with 1.5 applications compared with 87 days with 2 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to compare the efficacy of PriMatrix with current SOC or advanced wound therapies.

Section Summary: Bioengineered Skin Substitutes Other Than Apligraf, Dermagraft, AlloPatch, or Integra for Diabetic Lower-Extremity Ulcers
Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients who only required a single application of the ADM. Studies are needed to further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of

GraftJacket, TheraSkin, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies.

Lower-Extremity Ulcers due to Venous Insufficiency

Clinical Context and Therapy Purpose
The purpose of bio-engineered soft tissue substitutes in patients who have lower extremity ulcers due to venous insufficiency is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is patients who have lower extremity ulcers due to venous insufficiency.

Interventions
The therapy being considered is bioengineered skin substitutes.

Comparators
The following therapies are currently being used: SOC which includes debridement of necrotic tissue and compression.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, and QOL.

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

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

Time to wound closure can be measured at 6 months with longer-term outcomes apparent by 1 year. Complex wounds may require more than 6 months to heal.

Review of Evidence
RCTs have demonstrated the efficacy of Apligraf or Oasis Wound Matrix over SOC for lower-extremity ulcers due to venous insufficiency.

In a moderately large RCT, Dermagraft was not shown to be more effective than controls in the primary or secondary endpoints for the entire population and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or wound diameter of 10 cm or less. An initial study with 18 patients found that and DermACELL (ADM) was not more effective than

SOC. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment compared with current SOC.

Deep Thermal Burns

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

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

Interventions
The therapy being considered is bioengineered skin substitutes.

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

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

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

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

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

Review of Evidence

Fresh Frozen Unprocessed Allograft Skin for Burns (including AlloSkin and TheraSkin)
The use of fresh, unfrozen, unprocessed skin allograft has been used as a treatment of serious burn injuries since the First World War and it has become an accepted standard therapy. The current process for the collection and preparation of these allografts involves several steps, starting with the harvesting of the skin sample from carefully selected cadaver donors. Following harvesting, initial serological and microbial testing takes place to screen for communicable diseases, including HIV and hepatitis. Next, the

sample is bathed in a solution of various chemicals, including antibiotics, for several hours to several days to kill or inactivate possible pathogens. The tissue is then packaged aseptically for shipping and clinical use. The shelf life of this type of product is approximately 3 days from the time of harvesting, and it must be used within this time. One complexity in the use of this type of product is that, in urgent clinical situations, the results of final, definitive pathological tests are not usually available until approximately 10-14 days after harvesting. This means that, in urgent clinical situations, the clinician using the product is expected to use it prior to being assured of absolute clearance of pathogens. This concern, as well as other issues such as shelf life, etc., has led to the use of fresh frozen (cryopreserved) skin allograft as an acceptable alternative product for the treatment of burns for over 40 years. This product is processed in a similar manner to the fresh unfrozen products, but it is frozen once the initial screening is completed, and it is not released for use until after the definitive pathology reports have been completed. This additional step of freezing also allows for a shelf life of up to 5 years, which makes it more easily accessible for use in urgent medical situations. However, there is some evidence that indicates that this type of product loses some degree of viability due to the cryopreservation process, which may have an impact on its clinical effectiveness. However, this issue has not been well studied.

There are several brands of fresh, frozen, unprocessed allograft, including AlloSkin and TheraSkin. These products are treated as human tissue for transplantation under the FDA's HCT/P process.

The use of fresh, unfrozen, unprocessed skin allograft products has been a part of standard medical practice for the treatment of burns for almost a century. However, concerns regarding the risk of disease transmission and shelf life continue to be an issue, and other products have been proposed as an alternative. One of the most commonly used alternative products is fresh frozen skin allograft. Unfortunately, the current level of evidence addressing the safety and efficacy of fresh frozen skin allograft is weak. No solid conclusions can be made regarding the superiority, equivalency, or inferiority of these types of products in relation to other treatment options. However, despite this lack of evidence, a decades-long anecdotal track record for these products, easy access and availability, and a higher degree of certainty that the product is free from communicable pathogens has led to their acceptance as the standard of care in the burn treatment community.

Epicel

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

Integra Dermal Regeneration Template

Hicks et al (2019) conducted a systematic review of Integra dermal regeneration template for the treatment of acute full thickness burns and burn reconstruction.[64,] A total of 72 studies with 1084 patients (4 RCTs, 4 comparative studies, 5 cohort studies, 2 case control studies, 24 case series, and 33 case reports) were included in the review. The majority of patients (74%) were treated with Integra for acute burns, and the remainder (26%) for burn reconstruction. The take of the skin substitute was 86% (range 0–100%) for acute burn injuries and 95% (range 0–100%) for reconstruction. The take of the split-thickness skin graft over the template was 90% for acute burn injuries and 93% for reconstruction. There was high variability in reporting of outcomes, but studies generally supported satisfactory cosmetic results in patients who have insufficient autograft and improvement in range of motion in patients who were treated with Integra for burn reconstruction. There was an overall complication rate of 13%, primarily due to infection, graft loss, hematoma formation, and contracture.

An infection rate of 18% was noted in a systematic review of complication rates in 10 studies that used Integra dermal regeneration template for burns.

A 2013 study compared Integra with split-thickness skin graft and with viscose cellulose sponge (Cellonex), using 3, 10´5 cm test sites on each of 10 burn patients.[61,] The surrounding burn area was covered with meshed autograft. Biopsies were taken from each site on days 3, 7, 14, and 21, and at months 3 and 12. The tissue samples were stained and examined for markers of inflammation and proliferation. The Vancouver Scar Scale was used to assess scars. At 12-month follow-up, the 3 methods resulted in similar clinical appearance, along with similar histologic and immunohistochemical findings.

Branski et al (2007) reported on a randomized trial that compared Integra with a standard autograft-allograft technique in 20 children with an average burn size of 73% TBSA (71% full-thickness burns).[62,] Once vascularized (about 14-21 days), the Silastic epidermis was stripped and replaced with thin (0.05-0.13 mm) epidermal autograft. There were no significant differences between the Integra group and controls in burn size (70% vs. 74% TBSA), mortality (40% vs. 30%), and hospital length of stay (41 vs. 39 days), all respectively. Long-term follow-up revealed a significant increase in bone mineral content and density (24 months) and improved scarring in terms of height, thickness, vascularity, and pigmentation (at 12 months and 18-24 months) in the Integra group. No differences were observed between groups in the time to first reconstructive procedure, cumulative reconstructive procedures required during 2 years, and cumulative operating room time required for these procedures. The authors concluded that Integra can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

Section Summary: Deep Dermal Burns

Epicel is FDA-approved under a humanitarian device exemption (HDE) for the treatment of deep dermal or full-thickness burns comprising a TBSA of 30% or more, with patient survival of 90%. Integra Dermal Regeneration Template has been compared with

autograft in a within-subject study and with autograft-allograft in a small RCT with 10 patients per group. Outcomes are at least as good as with autograft or allograft, with a reduction in scarring and without risks associated with cadaver skin. This product has also been studied in a large series with over 222 burn patients, showing a take rate of 76% and with a take rate of epidermal autograft placed over Integra of 87.7%.

Other Indications

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

Section Summary: Dystrophic Epidermolysis Bullosa
Dystrophic epidermolysis bullosa is a rare disorder. Because this is a rare disorder, it is unlikely that RCTs will be conducted to evaluate whether OrCel improves health outcomes for this condition. Therefore, the HDE for OrCel is considered sufficient.

Punch Biopsy Wounds
Baldursson et al (2015) reported a double blinded RCT with 81 patients (162 punch biopsy wounds) that compared Kerecis Omega3 Wound (derived from fish skin) with Oasis SIS ECM (porcine small intestinal submucosa extracellular matrix).[69,] The primary outcome (the percentage of wounds healed at 28 days) was similar for the fish skin ADM (95%) and the porcine SIS ECM (96.3%). The rate of healing was faster with Kerecis Omega3 (p=.041). At 21 days, 72.5% of the fish skin ADM group had healed compared with 56% of the porcine SIS ECM group. Interpretation of this study is limited because it did not include an accepted control condition for this indication.

Pressure Ulcers
Brown-Etris et al (2019) reported an RCT of 130 patients with stage 3 or stage 4 pressure ulcers who were treated with Oasis Wound Matrix (extracellular collagen matrix derived from porcine small intestinal submucosa) plus SOC or SOC alone.[71,] At 12 weeks, the proportion of wounds healed in the collagen matrix group was 40% compared to 29% in the SOC group. This was not statistically significant (p=.111). There was a statistical difference in the proportion of patients who achieved 90% wound healing (55% vs. 38% p=.037), but complete wound healing is the preferred and most reliable measure. It is possible that longer follow-up may have identified a significant improvement in the percent of wounds healed. The study did include 6-month follow-up, but there was high loss to follow-up and an insufficient number of patients at this time point for statistical comparison.

Miscellaneous
In addition to indications previously reviewed, off-label uses of bioengineered skin substitutes have included inflammatory ulcers (e.g., pyoderma gangrenosum, vasculitis),

scleroderma digital ulcers, post keloid removal wounds, genetic conditions, and variety of other conditions. Products that have been FDA-approved or -cleared for one indication (e.g., lower-extremity ulcers) have also been used off-label in place of other FDA-approved or -cleared products (eg, for burns). No controlled trials were identified for these indications.

Summary of Evidence

Breast Reconstruction

For individuals who are undergoing breast reconstruction who receive allogeneic acellular dermal matrix (ADM) products, the evidence includes RCTs and systematic reviews. A systematic review found no difference in overall complication rates with ADM allograft compared with standard procedures for breast reconstruction.

Reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM. However, capsular contracture and malposition of implants may be reduced. Thus, in cases where there is limited tissue coverage, the available evidence may inform patient decision making about reconstruction options. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Tendon Repair

For individuals who are undergoing tendon repair who receive GraftJacket, the evidence includes an RCT. The RCT identified found improved outcomes with the GraftJacket ADM allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of patients is needed to evaluate the consistency of the effect. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Surgical Repair of Hernias or Parastomal Reinforcement

For individuals who are undergoing surgical repair of hernias or parastomal reinforcement who receive acellular collagen-based scaffolds, the evidence includes RCTs. Several comparative studies including RCTs have shown no difference in outcomes between tissue-engineered skin substitutes and either standard synthetic mesh or no reinforcement. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Complex Abdominal Wall Wounds

AlloDerm RTM for complex abdominal wall wounds has been widely used and is an accepted treatment method, although data is limited regarding the long-term benefits and outcomes of this use. Expert opinion of surgeons who routinely treat these types of wounds supports the use of AlloDerm RTM for this indication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Based on clinical practice standards, relevant expert opinions, the above-mentioned studies, and the overall clinical experience with Strattice, an acceptable level of safety and efficacy has been established for the use of this product for the surgical repair of complex abdominal wall wounds. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Diabetic Lower-Extremity Ulcers
For individuals who have diabetic lower-extremity ulcers who receive AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. RCTs have demonstrated the efficacy of AlloPatch (reticular ADM), Apligraf and Dermagraft (living cell therapy), and Integra (biosynthetic) over the SOC. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have diabetic lower-extremity ulcers who receive ADM products other than AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients who only required a single application of the ADM. Studies are needed to further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of GraftJacket, TheraSkin, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

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

Dystrophic Epidermolysis Bullosa
For individuals who have dystrophic epidermolysis bullosa who receive OrCel, the evidence includes case series. OrCel was approved under a humanitarian drug exemption for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction

surgery, to close and heal wounds created by the surgery, including those at donor sites. Outcomes have been reported in small series (e.g., 5 patients).

Dystrophic epidermolysis bullosa is a rare disorder. Because this is a rare disorder, it is unlikely that RCTs will be conducted to evaluate whether OrCel improves health outcomes for this condition. Therefore, the HDE for OrCel is considered sufficient.

Deep Dermal Burns
For individuals who have deep dermal burns who receive bioengineered skin substitutes (i.e., Epicel, Integra Dermal Regeneration Template), the evidence includes RCTs. Overall, few skin substitutes have been approved, and the evidence is limited for each product. Epicel (living cell therapy) has received FDA approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a TBSA of 30% or more. Comparative studies have demonstrated improved outcomes for biosynthetic skin substitute Integra Dermal Regeneration Template for the treatment of burns. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Fresh frozen unprocessed allograft skin for burns (including AlloSkin and TheraSkin), has been a part of standard medical practice for the treatment of burns for almost a century. However, concerns regarding the risk of disease transmission and shelf life continue to be an issue, and other products have been proposed as an alternative. One of the most commonly used alternative products is fresh frozen skin allograft.

Unfortunately, the current level of evidence addressing the safety and efficacy of fresh frozen skin allograft is weak. No solid conclusions can be made regarding the superiority, equivalency, or inferiority of these types of products in relation to other treatment options. However, despite this lack of evidence, a decades-long anecdotal track record for these products, easy access and availability, and a higher degree of certainty that the product is free from communicable pathogens has led to their acceptance as the standard of care in the burn treatment community.

Professional Guidelines and Position Statements

National Institute for Health and Care Excellence
In 2019, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems. The guideline included 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.

Regulatory Status
A large number of artificial skin and soft-tissue products are commercially available or in development. The following section summarizes commercially available skin and soft

tissue substitutes that have substantial relevant evidence on efficacy. Information on additional products is available in a 2020 Technical Brief on skin substitutes for treating chronic wounds that was commissioned by the Agency for Healthcare Research and Quality.

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 U.S. Food and Drug Administration (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.

In 2017, FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps) [2,] HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

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

- 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.

- Cortiva® (previously marketed as AlloMax™ Surgical Graft and before that NeoForm™) is an acellular non-cross-linked human dermis allograft.
- 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 postmastectomy breast reconstruction.
- FlexHD® and the newer formulation FlexHD® Pliable™ (Musculoskeletal Transplant Foundation) are acellular hydrated reticular dermis allograft derived from donated human skin.
- 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.
- DermaPure™ (Tissue Regenix Wound Care) is a single-layer decellularized human dermal allograft for the treatment of acute and chronic wounds.
- 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.

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.

In March 2019, the FDA held an Advisory Committee meeting on breast implants, at which time the panel noted that while there is data about ADM for breast reconstruction, the FDA has not yet determined the safety and effectiveness of ADM use for breast reconstruction. The panel recommended that patients are informed and also recommended studies to assess the benefit and risk of ADM use in breast reconstruction.

In March 2021, FDA issued a Safety Communication to inform 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. An FDA analysis of patient-level data from real-world use of ADMs for implant-based breast reconstruction suggested that 2 ADMs—FlexHD and Allomax—may have a higher risk profile than others.

In October 2021, an FDA advisory panel on general and plastic surgery voted against recommending FDA approval of the SurgiMend mesh for the specific indication of breast reconstruction. The advisory panel concluded that the benefits of using the device did not outweigh the risks. FDA product codes: FTM, OXF.

Xenogeneic Products

Cytal™ (previously called MatriStem®) Wound Matrix, Multilayer Wound Matrix, Pelvic Floor Matrix, MicroMatrix, and Burn Matrix (all manufactured by ACell) are composed of porcine-derived urinary bladder matrix.

Helicoll (Encol) is an acellular collagen matrix derived from bovine dermis. In 2004, it was cleared for marketing by the FDA through the 510(k) process for topical wound management that includes partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (eg, abrasions, lacerations, second-degree bums, skin tears), and surgical wounds including donor sites/grafts.

Keramatrix® (Keraplast Research) is an open-cell foam comprised of freeze-dried keratin that is derived from acellular animal protein. In 2009, it was cleared for marketing by the FDA through the 510(k) process under the name of Keratec. The wound dressings are indicated in the management of the following types of dry, light, and moderately exudating partial and full-thickness wounds: pressure (stage I-IV) and venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, donor sites, and grafts.

Kerecis™ Omega3 Wound (Kerecis) is an ADM derived from fish skin. It has a high content of omega 3 fatty acids and is intended for use in burn wounds, chronic wounds, and other applications.

Permacol™ (Covidien) is xenogeneic and composed of cross-linked porcine dermal collagen. Cross-linking improves tensile strength and long-term durability but decreases pliability.

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. FDA product code: KGN.

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

Strattice™ Reconstructive Tissue Matrix (LifeCell Corp.) is a xenogeneic non-cross-linked porcine-derived ADM. There are pliable and firm versions, which are stored at room temperature and come fully hydrated.

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. FDA Product code: KGN.

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. FDA product code: FTM.

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. FDA product code: PFC.

TheraSkin® (Soluble Systems) 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.

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 code: OCE.

OrCel™ (Forticell Bioscience; formerly Composite Cultured Skin) is an absorbable allogeneic bilayered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. It was approved by FDA premarket approval for healing donor site wounds in burn victims and under a humanitarian device exemption for use in patients with recessive dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites. FDA product code: ODS.

Biosynthetic Products
Biobrane®/Biobrane-L (Smith & 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. FDA product code: FRO.

Integra® Dermal Regeneration Template (also marketed as Omnigraft Dermal Regeneration Matrix; Integra LifeSciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It was approved by the FDA for use in the postexcisional 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, and for certain diabetic foot ulcers. Integra® Matrix Wound Dressing and Integra® Meshed Bilayer Wound Matrix are substantially equivalent skin substitutes and were cleared for marketing by the FDA through the 510(k) process for other indications. Integra® Bilayer Matrix Wound Dressing (Integra LifeSciences) is designed to be used in conjunction with negative pressure wound therapy. The meshed bilayer provides a flexible wound covering and allows drainage of wound exudate. FDA product code: MDD.

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.

Synthetic Products
Suprathel® (PolyMedics Innovations) is a synthetic copolymer membrane fabricated from a tripolymer of polylactide, trimethylene carbonate, and s-caprolactone. It is used to provide temporary coverage of superficial dermal burns and wounds. Suprathel® is covered with gauze and a dressing that is left in place until the wound has healed.

PRIOR APPROVAL

Not applicable.

POLICY

Note: *For Amniotic Membrane and Amniotic Fluid Grafts see Medical Policy 02.01.60*

Breast Reconstruction Surgery
The following products may be considered **medically necessary** when used for breast reconstruction surgery:

- AlloDerm RTM and AlloDerm RTU (Q4116); or
- Allomend (A4100 or Q4100); or
- Cortiva (AlloMax) (A4100 or Q4100); or
- DermACELL (Q4122); or
- DermaMatrix (A4100 or Q4100); or
- FlexHD, FlexHD Pliable (Q4128); or
- Graftjacket (Q4107); or
- Strattice (Q4130)

Burns
The following products may be considered **medically necessary** when used for the treatment of full-thickness or deep partial-thickness burns:

- Biobrane (A4100, Q4100 or C1849); or
- Ez Derm (Q4136); or
- Epicel (A4100, Q4100 or C1849); or
- Fresh frozen unprocessed allograft skin products (for example AlloSkin (Q4121), TheraSkin Q4123); or
- Integra Bilayer Matrix Wound Dressing (Q4104)
- Integra Dermal Regeneration Template (Q4105)
- Transcyte (Q4182)

Treatment of fresh, clean, split-thickness donor site wounds in burn victims using the following tissue-engineered skin substitute may be considered **medically necessary**:

- OrCel (A4100, Q4100 or C1849)

Complex Abdominal Wall Wounds
The following products may be considered **medically necessary** for the surgical repair of complex abdominal wounds:

- AlloDerm RTM and AlloDerm RTU (Q4116); or
- Strattice (Q4130)

Diabetic Lower Extremity Ulcer(s)
The following products may be considered **medically necessary** for the treatment of chronic, non-infected full thickness diabetic lower extremity ulcer(s) that have not healed with standard conservative therapy (such as surgical debridement, complete off loading, and standard dressing changes) attempted for at least 2 to 4 weeks (past start of therapy) with the following supporting documentation: the ulcer(s) has failed to decrease in size and depth, or there is no change in baseline size or depth with no sign of improvement, or no indication that improvement is likely:

- AlloPatch (Q4128)
- Apligraft (Q4101)
- Dermagraft (Q4106)

- Integra Omnigraft Dermal Regeneration Matrix (also known as Omnigraft) and Integra Flowable Wound Matrix (Q4114)

Dystrophic Epidermolysis Bullosa
The following product may be considered **medically necessary** for the treatment of dystrophic epidermolysis bullosa:

- OraCel (A4100, Q4100 or C1849) (for the treatment of mitten-hand deformity when standard wound therapy has failed and when provided in accordance with the humanitarian device exemption [HDE] specifications of the U.S. Food and Drug Administration [FDA])

Venous Stasis Ulcers
The following products may be considered **medically necessary** for the treatment of chronic, non-infected partial or full-thickness lower extremity skin ulcers due to venous insufficiency which have not adequately responded following a 1-month period of conventional ulcer therapy:

- Apligraf (Q4101)
- Oasis Wound Matrix (Q4102, Q4103, Q4124)

The following products are considered **investigational**, when the above criteria are not met and for any use not listed above, including, but not limited to the following due to a lack of clinical evidence demonstrating an impact on improved health outcomes:

- ACell UBM Hydrated/Lyophilized Wound Dressing
- Aongen™ Collagen Matrix
- Apis
- Architect extracellular matrix (ECM), PX, FX
- ArthroFlex™ (FlexGraft)
- Avaulta Plus™Belladerm®
- AxoGuard®Nerve Protector (AxoGen)
- Bio-ConneKt®
- CollaCare®
- CollaCare® Dental
- Collagen Wound Dressing (Oasis Research)
- CollaGUARD®
- CollaMend™
- CollaWound™
- Coll-e-derm,
- Collexa®
- Collieva®
- Conexa™
- Coreleader Colla-Pad
- CorMatrix®
- Cymetra® (Micronized AlloDerm)™
- Cytal® (previously MatriStem®)

- Dermadapt™ Wound Dressing
- Derma-gide
- DermaPure™
- DermaSpan™
- DressSkin™
- Durepair Regeneration Matrix®
- Endoform Dermal Template™
- ENDURAgen™
- Excellagen
- ExpressGraft™
- E-Z Derm™
- Flowerderm
- GammaGraft
- Genesis amniotic membrane, per square centimeter
- GraftJacket® Xpress, injectable
- Helicoll
- hMatrix
- Hyalomatrix®
- Hyalomatrix® PA
- InteguPly™
- Keramatrix®
- Kerecis omega3
- Keroxx™
- MatriDerm®
- MatriStem
- Matrix HD™
- Mediskin®
- MemoDerm™
- MicroMatrix®
- Miroderm®
- Mirragen Advanced Wound Matrix
- Mediskin®
- Microlyte Matrix
- MyOwn skin
- NovoSorb SynPath dermal matrix,
- Oasis® Burn Matrix
- Oasis® Ultra
- Ologen™ Collagen Matrix
- Omega3 Wound (originally Merigen wound dressing)
- Omeza Collagen Matrix
- Permacol™
- Permeaderm b

- Permeaderm glove
- Permeaderm c
- Phoenix Wound Matrix
- PriMatrix
- PriMatrix™ Dermal Repair Scaffold
- Progenamatrix
- Puracol® and Puracol® Plus Collagen Wound Dressings
- PuraPly™ Wound Matrix (previously FortaDerm™)
- PuraPly™ AM (Antimicrobial Wound Matrix)
- Puros® Dermis
- RegenePro™
- Repliform®
- Repriza™
- Restrata
- SkinTE™
- StrataGraft®
- Suprathel®
- SurgiMend®
- Symphony
- Talymed®
- TenoGlide™
- TenSIX Acellular Dermal Matrix
- TissueMend®
- TheraForm™ Standard/Sheet
- TheraGenesis
- TheraSkin®
- TransCyte
- TruSkin™
- Veritas® Collagen Matrix
- Xcm Biologic Tissue Matrix
- XCelliStem
- XenMatrix™ AB

Policy Guidelines

Required Documentation

Diabetic Lower-Extremity Ulcer(s) or Venous Insufficiency
Prior to the application of the skin substitute for diabetic or venous insufficiency ulcers, it is expected that the medical record documentation will contain evidence of the following:

- Documentation that conservative measures have failed, or the medical record supports that the wound is so clinically severe that it requires immediate, aggressive therapy.

- Documentation that the ulcer has failed to decrease in size and depth, or that there has been no change in baseline size or depth with no sign of improvement, or no indication that improvement is likely.
- Documentation of venous insufficiency either by history of deep venous thrombosis in the affected leg, or documentation of valvular reflux by duplex ultrasound, venography, or air/photo plethysmography
- The individual's medical record must reflect the frequency of skin substitute application, and this should be consistent with each individual's history and response to the skin substitute application and product safety criteria. Repeated application to the same wound within the same treatment period without signs of improvement may be denied.
- Documentation that the skin substitute product was appropriately applied and immobilized in accordance with the manufacturer's label instructions.

Grading System for Diabetic Ulcers
The following grading system for diabetic ulcers is frequently utilized:

Wagner Grading System

A. Grade 1: Superficial Diabetic Ulcer
B. Grade 2: Ulcer extension
    1. Involves ligament, tendon, joint capsule or fascia
    2. No abscess or Osteomyelitis
C. Grade 3: Deep ulcer with abscess or Osteomyelitis (infection inferred)
D. Grade 4: Gangrene to portion of forefoot (infection inferred)
E. Grade 5: Extensive gangrene of foot (infection inferred)

Conventional Non-Surgical Therapy for Chronic Venous Insufficiency Ulcers and Chronic Diabetic Foot Ulcers include:

- Control of edema, venous hypertension, or lymphedema
- Control of any nidus of infection or colonization with bacterial or fungal elements
- Elimination of underlying cellulitis, osteomyelitis, foreign body, or malignant process
- Appropriate debridement of necrotic tissue or foreign body (exposed bone or tendon)
- For diabetic foot ulcers, appropriate non-weight bearing or off-loading pressure
- For venous stasis ulcers, compression therapy provided with documented diligent use of multilayer dressings, compression stockings of greater than 20mmHg pressure, or pneumatic compression
- Provision of wound environment to promote healing (protection from trauma and contaminants, elimination of inciting or aggravating processes)
- Management of concomitant and inciting medical issues (e.g., diabetes, tobacco use).

Failed Response - defined as an ulcer or skin deficit that has failed to respond to documented appropriate wound-care measures, has increased in size or depth, or has not

changed in baseline size or depth and has no indication that improvement is likely (i.e., granulation, epithelialization, or progress towards closing)

Re-Application - refers to an additional application of skin substitute to the same ulcer within the same treatment period.

Retreatment - refers to a new treatment period where the same ulcer is being treated again because the initial treatment has failed.

Unsuccessful treatment - defined as increase in size or depth of an ulcer or no change in baseline size or depth and no sign of improvement or indication that improvement is likely (such as granulation, epithelialization, or progress towards closing) for a period of 2-4 weeks past start of therapy.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- A2002 Mirragen Advanced Wound Matrix, per sq cm
- A2003 Bio-connekt wound matrix, per sq cm
- A2004 XCelliStem, 1 mg
- A2005 Microlyte Matrix, per sq cm
- A2006 NovoSorb SynPath dermal matrix, per sq cm
- A2007 Restrata, per sq cm
- A2008 TheraGenesis, per sq cm
- A2009 Symphony, per sq cm
- A2010 Apis, per sq cm
- A0211 Supra sdrm, per sq cm
- A2012 Suprathel, per sq cm
- A2014 Omeza collagen matrix, per 100 mg
- A2015 Phoenix wound matrix, per square centimeter
- A2016 Permeaderm b, per square centimeter
- A2017 Permeaderm glove, each
- A2018 Permeaderm c, per square centimeter
- A4100 Skin substitute, FDA cleared as a device, not otherwise specified
- C9354 Accellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm
- C9356 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 Skin substitute (Integra Meshed Bilatyer Wound Matrix), per square cm
- C9364 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 Oasis burn matrix, per sq cm
- Q4104 Integra bilayer matrix wound dressing (BMWD), per sq cm
- Q4105 Integra dermal regeneration template (DRT), per sq cm
- Q4106 Dermagraft, per sq cm
- Q4107 GRAFTJACKET, per sq cm
- Q4108 Integra matrix, per sq cm
- Q4110 PriMatrix, per sq cm
- Q4111 GammaGraft, per sq cm
- Q4112 Cymetra, injectable, 1 cc
- Q4113 GraftJacket Xpress, injectable, 1 cc
- Q4114 Integra flowable wound matrix, injectable, 1 cc
- Q4115 AlloSkin, per sq cm
- Q4116 AlloDerm, per sq cm
- Q4117 Hyalomatrix, per sq cm
- Q4118 MatriStem micromatrix, 1 mg
- Q4121 TheraSkin, per sq cm
- Q4122 DermACELL, dermacell awm or dermacell awm porous, per sq cm
- Q4123 AlloSkin RT, per sq cm
- Q4124 Oasis ultra tri-layer wound matrix, per sq cm
- Q4125 Arthroflex, per sq cm
- Q4126 MemoDerm, per sq cm
- Q4127 Talymed, per sq cm
- Q4128 FlexHD or AllopatchHD, per sq cm
- Q4130 Strattice TM, per sq cm
- Q4134 Hmatrix, per sq cm
- Q4135 Mediskin, per sq cm
- Q4136 Ez-derm, per sq cm
- Q4141 Alloskin ac, per square cm
- Q4142 Xcm biologic tissue matrix, per square cm
- Q4143 Repriza, per square cm
- Q4146 Tensix, per square cm
- Q4147 Architect extracellular matrix, per square cm
- Q4149 Excellagen, 0.1cc
- Q4152 Dermapure, per sq cm
- Q4158 Kerecis omega 3, per sq cm
- Q4161 Bio-ConneKt wound matrix, per sq cm
- Q4164 Helicoll, per sq cm
- Q4165 Keramatrix or kerasorb, per sq cm

- Q4166 Cytal, per sq cm
- Q4167 Truskin, per sq cm
- Q4175 Miroderm, per sq cm
- Q4179 Flowerderm, per sq cm
- Q4182 Trancyte, per sq cm
- Q4193 Coll-e-derm, per sq cm
- Q4195 Puraply, per sq cm
- Q4196 Puraply am, per sq cm
- Q4197 Puraply xt, per sq cm
- Q4200 Skin TE, per sq cm
- Q4202 Keroxx (2.5 g/cc), 1 cc
- Q4203 Derma-gide, per sq cm
- Q4222 Progenamatrix, per sq cm
- Q4226 MyOwn skin, includes harvesting and preparation procedures, per sq cm
- 15271 Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
- 15272 Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
- 15273 Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
- 15274 Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15275 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
- 15276 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
- 15277 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
- 15278 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

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POLICY HISTORY		
Date	**Reason**	**Action**
March 2022	Annual Review	Policy Revised
March 2021	Annual Review	Policy Revised
March 2020	Annual Review	Policy Revised
March 2019	Annual Review	Policy Revised
March 2018	Annual Review	Policy Revised
March 2017	Annual Review	Policy Revised
November 2016	Interim Review	Policy Revised
September 2016	Interim Review	Policy Revised
March 2016	Annual Review	Policy Revised
April 2015	Annual Review	Policy Revised
June 2014	Annual Review	Policy Revised
July 2013	Annual Review	Policy Revised
May 2013	Interim Review	Policy Renewed
August 2012	Annual Review	Policy Renewed
September 2011	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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