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AHC Skin Substitutes

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Clinical Indications for Procedure

- Tissue-engineered skin substitute may be indicated for **1 or more** of the following(1)(2)(3)(4)(5)(6)
 - Diabetic ulcers, and Allopatch, Apligraf, Dermagraft, Epifix, Graftax, GraftJacket, Integra Omnigraft Dermal Regeneration Matrix (also known as Omnigraft), Integra™ Flowable Wound Matrix, Oasis Ultra Tri-Layer Matrix, Oasis Wound Matrix, Primatrix or Primatrix® Dermal Repair Scaffold needed, as indicated by **ALL** of the following [A] [B] (10)(11)(12)(13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)(26)(27)(28)(29) [C] :
 - Adequate perfusion of involved limb
 - Conventional wound care and glycemic management to continue during treatment(30)(31)(32)
 - Diabetes mellitus (type 1 or type 2)
 - Full-thickness foot ulcer with location on plantar, medial, or lateral area, and no exposure of tendon, muscle, capsule, or bone
 - Ulcer history, as indicated by **1 or more** of the following:
 - Duration greater than 3 weeks (prior to Apligraf)
 - Duration greater than 6 weeks (prior to Dermagraft)
 - No allergy to bovine products
 - No response to conventional therapy, including **ALL** of the following(33)(32)(34)(35)(36):
 - Dressings to maintain moist environment (eg, saline-moistened dressings)(37)
 - No weight-bearing
 - Optimal glycemic management (eg, HbA1c of 7% (53 mmol/mol) or less)(38)
 - Sharp debridement(39)
 - No wound infection
 - If not listed above, product to be applied has FDA clearance/approval or designated 361 HCT/P exemption for this use. [D] [E] [F]
 - Venous insufficiency ulcers, and Apligraf, Oasis Ultra Tri-Layer Matrix or Oasis Wound Matrix needed, as indicated by **ALL** of the following [G] (40)(41)(42)(43) :
 - Adequate perfusion of involved limb
 - Concurrent conventional wound care

- Concurrent glycemic management, if patient is also diabetic(30)(32)
 - Duration greater than 1 month
 - Partial-thickness or full-thickness ulcer due to venous insufficiency
 - No allergy to bovine products
 - No response to conventional therapy, including **ALL** of the following(44)(45):
 - Compression therapy
 - Dressings to maintain moist wound environment (eg, saline-moistened dressings)
 - Sharp debridement
 - No wound infection
 - If not listed above, product to be applied has FDA clearance/approval or designated 361 HCT/P exemption for this use.
- All other bio-engineered skin substitutes, soft tissue substitutes, amniotic membranes and amniotic fluids are considered experimental or investigational.

Alternatives to Procedure

- Alternatives include:
 - For diabetic ulcers: topical wound treatment (eg, alginate dressings, foam dressings), hyperbaric oxygen therapy, negative pressure wound therapy, or pressure-relieving and offloading devices.(31)(46) See Hyperbaric Oxygen, Negative Pressure Wound Therapy (Vacuum-Assisted Wound Closure), and Pressure-Relieving and Offloading Devices (Total Contact Cast and Removable Cast Walker) for further information.
 - For venous stasis ulcers: graduated compression therapy, saphenous vein radiofrequency ablation, or saphenous vein stripping.(47)(48) See Graduated Compression Stockings, Saphenous Vein Ablation, Radiofrequency, and Saphenous Vein Stripping for further information.

Evidence Summary

Background

Skin substitutes are used when managing deep dermal and full-thickness wounds of various etiologies. These can be biologic or synthetic products.(49) **(EG 2)** Tissue-engineered skin is commercially available as cellular allogeneic, autologous, or xenogeneic products that include single-layer (ie, cultured dermal or epidermal cells) or bilayer (ie, combination of cultured dermal and epidermal cells) options; their primary goal is to replace or reconstruct dermal and/or epidermal skin. These products may be available in suspensions and/or sheets of cells. Cells may originate from bovine, human (eg, amnion, cadaveric skin, chorion, neonatal foreskin), or porcine sources. Synthetic skin substitutes are composed of acellular materials that are natural (eg, bovine collagen, acellular human lyophilized dermis) or nonbiologic (eg, nylon, polyurethane, silicone). These acellular dermal matrices provide a barrier to fluid loss and microbial invasion; no consensus exists on their use.(49)(50)(51)(52) **(EG 2)** Skin substitutes also include minimally processed products derived from human donors (eg, TheraSkin cryopreserved allograft).(49)(53) **(EG 2)** High-level evidence or direct comparisons on many skin substitute products are sparse. Differences in the active components of various skin substitutes limit extrapolation from clinical trials that evaluated other products.(49) **(EG 2)**

Apligraf (previously known as Graftskin) is a tissue-engineered, living, bilayered skin substitute made from allogeneic human keratinocytes (epidermal layer) and fibroblasts in a bovine collagen lattice (dermal layer).(7)(50) **(EG 2)**

Dermagraft is a cryopreserved, living, single-layer skin substitute derived from human allogeneic fibroblasts.(8)(50)(9) **(EG 2)**

AlloPatch® Pliable is an acellular allogeneic human dermal graft derived from the reticular layer of the dermis designed to support host tissue remodeling. (54)

EpiFix Amniotic Membrane Allograft is a placental tissue allograft composed of dehydrated human amnion/chorion membrane (DHACM).(55)

Grafix Core is an allograft containing endogenous mesenchymal stem cells indicated for the treatment of deep chronic wounds, limb salvage procedures, tendon repair and burns. Grafix Prime is an allograft containing endogenous mesenchymal stem cells indicated for upper epithelial layer chronic wounds and burns(56)

Graftjacket tissue matrix (Wright Medical Technology, Inc, Arlington, TN) is an acellular regenerative tissue matrix that is designed to provide a scaffold for wound repair(57)

Integra is a bilayered matrix wound dressing composed of a porous layer of cross-linked bovine tendon collagen and glycosaminoglycan and a semipermeable polysiloxane (silicone) layer. (58)

Oasis Wound Matrix is a naturally derived, extracellular matrix (ECM) created from the submucosal layer of porcine small intestine(59)

PriMatrix Acellular Dermal Tissue Matrix is an acellular collagen dermal tissue matrix derived from fetal bovine skin. Primatrix creates a scaffold capable of being integrated, remodeled and eventually replaced by functional host tissue. (60)

Other situations in which bioengineered skin products might substitute for living skin grafts include certain postsurgical states (eg, 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 (eg, 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. For situations not described in this policy, the plan will review on a case-by-case basis.

Criteria

For diabetic ulcers, Systematic reviews and a health technology assessment concluded that add-on therapy with skin substitutes, including Apligraf and Dermagraft, may be an alternative to standard wound care for the treatment of diabetic ulcers of the lower extremity, leading to a higher proportion of patients with complete wound closure and shorter time to complete wound healing.(61)(62)(63) **(EG 1)** A systematic review and meta-analysis evaluating biologic skin substitutes for healing of diabetic foot ulcers included 5 studies of Apligraf and 7 studies of Dermagraft and found that both agents were associated with improved healing at 12 weeks compared with standard of care alone. However, the authors noted that the analysis was limited by the number of different skin substitutes and protocols included, the number of unblinded trials, and the lack of information on adverse events; they stated that more prospective comparative trials are needed to generate evidence-based decisions on which substitute and corresponding application protocol to use.(64) **(EG 1)** A randomized controlled trial of patients with diabetic foot ulcers found that the 35 patients who received standard wound care healed in a mean time of 57.4 days, while the 33 patients who received Apligraf healed in a mean time of 47.9 days.(65) **(EG 1)**

In a meta-analysis to compare human-derived acellular dermal matrices (H-ADMs) with standard of care (SOC) which included 6 studies and 3 subtypes of H-ADM: AlloPatch Pliable, DermACELL, and GRAFTJACKET; found that H-ADMs are more effective in healing patients within a 12-week and 16-week period in comparison with SOC. Further, the mean time to complete healing was shorter in the H-ADM group in comparison with SOC. The authors noted that the analysis was limited by few available studies and the total number of DFUs from the studies covered is relatively low and often industry-associated, thus, the results are likely somewhat confounded by publication bias and, further research is needed to better characterize the effects of H-ADM on DFUs at increased lengths of follow-up.(66)

In a multicentered Randomized control trial which included 110 patients with Diabetic foot ulcer (DFU) was undertaken to determine whether EpiFix led to improved wound healing compared to SOC. The study found both intent-to-treat and per-protocol participants receiving weekly EpiFix were significantly more likely to completely heal than those not receiving EpiFix. The authors noted that the limitations included the short term follow-up and lack of blinding(67)

In a Randomized control trial performed to contrast the effectiveness of a human viable wound matrix (hVWM) (i.e., Grafix) to Standard of Care (SOC) for ulcer closure in chronic Diabetic foot ulcer (DFU) found that the percentage of patients who attained complete ulcer closure was substantially higher in the active treatment group compared with the control group. The authors concluded that treatment with Grafix substantially improved DFU healing in comparison to SOC therapy. Limitations of the study included lack of blinding, short-term follow-up, and high risk of bias.(68)

In a multicentered Randomized control trial compared subjects with Diabetic foot ulcer (DFU) receiving acellular matrix (GraftJacket Regenerative Tissue Matrix) compared to standard of care noted a complete healing time of 69.6% at 5.7 weeks for the treatment group compared to 46.2% at 6.8 weeks for the control group. Strengths of the study included randomization and defined control group with certain limitations noted such as a short-term follow-up and high risk of bias(69)

In a Randomized control trial which compared 153 patients in the control arm who received standard of care treatment and 154 patients who received Integra Dermal Regeneration Matrix for DFUs found that complete closure of the ulcer

at 16 weeks was significantly greater in the active group in comparison to the control group. (70)

In a multicenter Randomized control trial to evaluate the safety and efficacy of a fetal bovine acellular dermal matrix (PriMatrix) plus standard of care (SOC) versus SOC alone for treating hard-to-heal Diabetic foot ulcers found the wound closer was higher in the PriMatrix group with less median time to close. The authors noted study limitations such as short term follow up, inability to blind investigators or subjects to treatment type, patient selection bias towards healthier patients, and an overall high risk of bias(71)

In a multicenter Randomized control trial to compare clinical outcomes of patients treated with tri-layer Oasis vs. standard of care (SOC) , the Oasis group achieved a significantly greater number of complete closures compared to the SOC group Limitations included unblinded design, short duration of follow up, and high risk of bias due to missing outcome, but intention to treat analysis was performed to reduce this potential risk. (72)

For venous insufficiency ulcers, Systematic reviews and a comparative effectiveness study found randomized controlled trials that indicate greater effectiveness of bilayer artificial skin, including Apligraf, in treating lower extremity ulcers associated with venous insufficiency compared with standard compression and a simple dressing.(63)(73)(47) **(EG 1)** Systematic reviews either did not evaluate single-layer products in venous insufficiency ulcers or found no difference when they were compared with standard care.(63)(73) **(EG 1)** In a randomized controlled trial using standard care with or without the addition of Dermagraft for the treatment of venous insufficiency ulcers, healing rate after 12 weeks was statistically similar in both groups.(74) **(EG 1)** A comparative effectiveness review found limited evidence of the effectiveness of cryopreserved, living, single-layer skin substitutes derived from human allogeneic fibroblasts due to few studies and small sample sizes.(47) **(EG 1)**

In a multicenter Randomized control trial comprised of 120 patients with venous leg ulcers to compare the Oasis Wound Matrix plus Standard of care) to SOC alone showed that at 12 weeks, the treatment group achieved 55% healing as compared to 34% in the SOC group. Ulcer recurrence did not occur in any of the healed patients in the treatment group over a 6-month period. The limitations noted include lack of blinding, small sample size, short duration of follow-up, limited number of wounds evaluated at 6 months, and high risk of bias.(75)

Committee Approval

- 01/09/2024, 02/20/2025

Application

- This policy applies to the following states: Arizona, California, Nevada, and North Carolina.
- This policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:
 - Texas -- please refer to Local Coverage Determination L35041
- Please refer to the CMS website for the most current applicable National Coverage Determination (NCD)/ Local Coverage Determination (LCD)/Local Coverage Article (LCA)/CMS Online Manual System/Transmittals.

Policy Revision History

- 10/10/2022: Creation date
- 10/31/2023, 12/11/2023: Revision
- 11/17/2024: Annual review, FL removed as applicable state, criteria updated

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Footnotes

[A] For diabetic foot ulcers, Apligraf is applied with meticulous sterile technique and covered with a nonadherent sterile primary dressing, followed by a secondary absorbent dressing. Routine wound care should be continued. Additional applications may be required, but safety and effectiveness have not been established for greater than 5 applications. (7) [A in Context Link 1]

[B] For diabetic foot ulcers, Dermagraft is applied with meticulous sterile technique and covered with a sterile dressing, remaining undisturbed for 72 hours. After this time, dressing changes and routine wound care may be continued. Safety and effectiveness have not been established for greater than 8 applications.(8)(9) [B in Context Link 1]

[C] All other bio-engineered skin substitutes, soft tissue substitutes, amniotic membranes and amniotic fluids are considered experimental or investigational. [C in Context Link 1]

[D] Evaluation of the clinical literature indicates that studies comparing the efficacy of bioengineered skin substitute to alternative wound care approaches with patients' autologous skin are limited in number, apply mainly to generally healthy patients, and examine only a small portion of the skin substitute products available in the United States. Therefore, all products with US Food and Drug Administration (FDA) clearance/approval or designated 361 HCT/P exemption used in accordance with that product's individualized application guidelines will be equally considered for the purpose and may be considered reasonable and necessary. [D in Context Link 1]

[E] The US Food and Drug Administration (FDA) does not refer to any product or class of products as "skin substitutes." However, products commonly described as "skin substitutes" are regulated by FDA under one of the 4 categories described below depending on the origin and composition of the product and listed as a "Skin Substitute" with a HCPCS code Q41XX. **Human Cells, Tissues, and Cellular and Tissue-Based Products:** Cells and tissues taken from human donors and transplanted to a recipient are regulated under PHS 361 (21 CFR 1270 and 1271). This regulation describes the rules concerning the use of HCT/Ps for human medical purposes. The final rule, 21 CFR Part 1271, became effective on April 4, 2001, for human tissues intended for transplantation that are regulated under section 361 of the PHS Act and 21 CFR Part 1270. HCT/Ps are regulated by the Center for Biologics Evaluation and Research (CBER). CBER is responsible for regulating biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies. Establishments producing HCT/Ps must register with the FDA and list their HCT/Ps. HCT/Ps establishments are not required to demonstrate the safety or effectiveness of their products and FDA does not evaluate the safety or effectiveness of these products. **Premarket Approval:** Premarket approval (PMA) by the FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices. Before Class III devices can be marketed, they must have an approved PMA application. Therefore, wound care products regulated under the PMA process will require evidence that they promote wound healing before they are approved for marketing. **510(k) Submissions:** According to FDA documents a "510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent (SE), to a legally marketed device (21 CFR 807.92(a)(3)) that is not subject to PMA." Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims. Unlike PMA, 510(k) confers reasonable assurance of safety and effectiveness via demonstration of substantial equivalence to a legally marketed device that does not require premarket approval. Therefore, wound care products regulated under the 510(k) process will not typically require clinical evidence to establish effectiveness in wound healing, as compared with products regulated under the PMA process in which substantial clinical evidence is always required. **Humanitarian Device Exemption (HDE):** An HDE is similar in both form and content to a PMA application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market. HDE approval is based on evidence of probable benefit in a disease population occurring at a frequency of less than 4000 patients per year in the United States. [E in Context Link 1]

[F] Expanded classification criteria and explanation are included in the HHS/AHRQ Final Report, December 18, 2012 entitled *Skin Substitutes for Treating Chronic Wounds*. Per the American Medical Association and the CPT® Manual, "Skin Replacement Surgery" or "Skin Substitute Grafting" is a conceptual model focusing on the work and services provided regardless of the product used. This removes the requirement for maintenance and education on the use of supply codes that have little impact on the "typical patient" or the provider effort for application of the product. The application of skin substitute (or CTP) is distinguished according to the wound characteristics and surface area rather than by product description. Currently, no product has demonstrated individual superiority for the treatment of diabetic foot ulcers (DFU) and venous leg ulcers (VLU) of the lower extremity, and frequently such products are utilized inappropriately. **Definitions per CPT®:** Autografts/tissue cultured autografts: Include the harvest or application of an autologous skin graft. Skin substitute grafts: Include non-autologous human cellular and tissue products (eg, dermal or epidermal, cellular and acellular, homograft or allograft), non-human cellular or tissue products (ie, xenograft), and biological products (synthetic or xenogeneic) that are applied in a sheet over an open wound to augment wound closure or skin growth. [F in Context Link 1]

[G] For venous leg ulcers, Apligraf is applied to the venous ulcer, covered by a nonadherent dressing, then covered by a nonocclusive dressing, and finally by a self-adherent elastic wrap. The dressing should be changed at least weekly, and more often in highly exudative wounds. Additional applications may be required, but safety and effectiveness have not been established for greater than 5 applications.(7) [G in Context Link 1]

Codes

CPT® : 15271, 15272, 15273, 15274, 15275, 15276, 15277, 15278

HCPCS: C5271, C5272, C5273, C5274, C5275, C5276, C5277, C5278, Q4100, Q4101, Q4102, Q4104, Q4105, Q4106, Q4107, Q4110, Q4114, Q4116, Q4122, Q4124, Q4128, Q4132, Q4182, Q4186

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