Molina Clinical Policy
Skin and Soft Tissue Substitutes: Medicare
Policy No. 357b

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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of the Federal government or CMS for Medicare. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Normal healthy skin provides a protective barrier for the body, aids in thermoregulation, and provides tactile sensations. Wounds, acute or chronic, are disruptions of the skin's structural and functional integrity and normally transition through distinct phases until the skin's structure and function are restored. Usual care for wounds can involve removing necrotic tissue, applying dressings that maintain a moist wound environment, treating wound infections, and restoring blood flow to the wound site. If these procedures fail to restore the healing process additional therapies, such as the application of skin substitutes to promote wound healing, may be considered (Snyder et al. 2020; Shahrohki 2023).

Skin or soft tissue substitutes are proposed as a treatment to cover open wounds and promote healing by preventing dehydration, reducing risk of infection, and providing a scaffold to support newly generated cells. The three most common uses for skin substitutes are to treat venous leg ulcers, diabetic foot ulcers, and burns. Skin substitutes, also known as bioengineered, tissue-engineered, or artificial skin, are a heterogeneous group of products and can generally be classified into 3 main types: cellular (comprised of living cells), acellular (composed of synthetic materials or tissue from which living cells have been removed), or a combination of cellular and acellular components. Due to the unique characteristics of each skin substitute product, there is no simple, universally accepted classification system that allows for categorization of all the products that are commercially available. Selection of a skin substitute should consider the type of wound, which layers of the skin are to be replaced, and the need for temporary versus permanent placement (Shahrohki 2023).

For this policy, the following definitions will be utilized:

- *Acellular Products*: A product composed of synthetic materials or tissue from which living cells have been removed. These are the most common commercially available skin substitute products.
- *Allografts/Allogenic*: A product derived from a human source other than the patient, such as a cadaver
- *Autograft/Autologous*: A product derived from the patient's own body
- *Bioengineered*: Products synthetic in nature, or composite products derived from processed or cultured cells
- *Human Cells, Tissues, or Cellular or Tissue-based Products (HCT/Ps)*: Products containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.
- *Xenograft/Xenographic*: A product derived from non-human (e.g., animal tissue) sources

Regulatory Status

Skin substitutes are developed from different materials and therefore are evaluated by different Food and Drug Administration (FDA) pathways. Some products are regulated and sold in the United States through the Premarket Approval (PMA) process, the 510(k) Premarket clearance process, the Humanitarian Device Exemption (HDE) process, or the Biologics License Application (BLA) process. Others are regulated as human cells, tissues, and cellular and tissue-based products (HCT/Ps) derived from human cadaver skin and human placental membranes per the Public Health Service Act 361 and 21 Code of Federal Regulations (CFR) 1270 & 1271. Any list of commercially available skin substitutes should not be considered comprehensive due to the expanding nature of the industry and ongoing FDA approvals, including skin substitute products currently in development or in the clinical trial phase.

COVERAGE POLICY

Medically Necessary

Use of a skin or soft tissue substitute may be **considered medically necessary** when ALL the following indications are met:

1. Documentation of wound characteristics and treatment plan are present prior to skin or soft tissue substitute application

2. The skin or soft tissue substitute product is FDA approved OR meets all applicable regulations and standards established by the American Association of Tissue Banks for procuring and processing human cells, tissues, and cellular or tissue-based products (HCT/Ps)

3. Absence of ALL the following absolute contraindications:
   a. Active infection or vasculitis in wound to be treated
   b. Involvement of tendon, muscle, joint capsule, or exposed bone or sinus tracts
   c. Active tobacco smoking
      i. Documentation of Member smoking cessation or in current smoking cessation program required
   d. Hypersensitivity or allergy to any components of the skin substitute (e.g., allergy to avian, bovine, porcine, equine products)
   e. For *Diabetic Foot Ulcers*:
      i. Uncontrolled blood sugar, as evidence by a HgA1c ≥ 12% in the last 90 days
      ii. Active Charcot deformity or major structural abnormalities of the affected foot

4. The wound to be treated meets ONE of the following indications:
   a. Breast Reconstruction: For wounds resulting from a medically necessary breast reconstruction procedure
      i. AlloDerm
      ii. Cortiva
      iii. DermACELL
      iv. FlexHD

   b. Burn Wounds: For partial or full thickness thermal burns *post wound excision*, when hemostasis has been achieved and sufficient full-thickness allograft is not available or is contraindicated
      i. Artiss
         1. Indicated to adhere to autologous skin grafts to surgically prepared wound beds resulting from burns in patients at least 1 year of age
      ii. Biobrane
         1. Indicated to be used as a temporary covering for clean partial thickness burn wounds
      iii. Epicel
         1. Indicated for use in patients who have deep dermal or full thickness burns comprising a total body surface area ≥ 30%. 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
      iv. Integra Bilayer Matrix Wound Dressing
         1. Indicated for the management of second-degree burns, including partial thickness burns
      v. Integra Dermal Regeneration Template
         1. Indicated for post-excisional treatment of life-threatening, full thickness or deep partial thickness burns, where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient
      vi. Oasis Matrix
         1. Indicated for the management of second-degree burns, including partial thickness burns
      vii. OrCel
         1. Indicated for the treatment of fresh, clean split thickness donor site wounds in burn patients
      viii. StrataGraft

1. Indicated for **adult** patients with debrided thermal burns that contain intact dermal elements, and for which surgical intervention is clinically indicated (deep partial thickness burns)

ix. Suprathel Wound and Burn Dressing
1. Indicated for temporary coverage of first- or second-degree burns, including partial thickness burns

x. TransCyte
1. Indicated for temporary wound covering of surgically excised full thickness or deep partial thickness thermal burn wounds in patients who require such a covering prior to autograft placement

c. Diabetic Foot Ulcers (DFU): For partial or full-thickness DFUs between 1cm^2 to 25cm^2 with documented adequate circulation that has not responded to at least 6 weeks of standard wound care, including cleansing, debridement, dressing, infection control, and offloading. *Skin substitute treatment must be used in conjunction with standard DFU therapy for Member with a Type 1 or Type 2 DM diagnosis*

i. AlloPatch Pliable
1. Indicated for replacement of damaged or inadequate integumental tissue, or for the repair, reinforcement, or supplemental support of soft tissue defects. Initial treatment is up to 5 applications, additional applications may be applied if there is evidence of wound healing and are limited to a maximum of 8 applications in twelve weeks

ii. AmnioBand
1. Indicated to serve as a wound scaffold replacement for damaged integumental tissue. Initial treatment is up to 5 applications, additional applications may be applied if there is evidence of wound healing and are limited to a maximum of 8 applications in twelve weeks

iii. Apligraf
1. Indicated for full thickness DFUs which extend through the dermis but without tendon, muscle, capsule, or bone exposure. Additional applications may be applied after initial application once a week if there is evidence of wound healing and are limited to a maximum of 4 applications in twelve weeks

iv. DermACELL AWM
1. Indicated for chronic wounds such as DFUs with a maximum of 2 applications

v. Dermagraft
1. Indicated for full thickness DFUs which extend through the dermis but without tendon, muscle, joint capsule, or bone exposure. Initial treatment is up to 5 applications, additional applications may be applied if there is evidence of wound healing and are limited to a maximum of 8 applications in twelve weeks

vi. EpiFix
1. Indicated for use in the treatment of acute and chronic wounds. Additional applications may be applied after initial application once a week if there is evidence of wound healing and are limited to a maximum of 4 applications in twelve weeks

vii. Geistlich Derma-Gide
1. Indicated for the managements of wounds, including partial and full thickness wounds and DFUs. Initial treatment is up to 5 applications, additional applications may be applied if there is evidence of wound healing and are limited to a maximum of 8 applications in twelve weeks

viii. Grafix
1. Indicated for acute and chronic wounds. Initial treatment is up to 5 applications, additional applications may be applied if there is evidence of wound healing and are limited to a maximum of 8 applications in twelve weeks

ix. GraftJacket NOW
1. Indicated to provide supplemental support, protection, and reinforcement of tendon and ligamentous tissues or other homologous use. For only 1 application

x. Integra Omnigraft Dermal Regeneration Matrix or Integra Dermal Regeneration Template
1. Indicated for partial and full thickness neuropathic DFUs. Additional applications may be applied after initial application once a week if there is evidence of wound healing and are limited to a maximum of 4 applications in twelve weeks

xi. Oasis Matrix

1. the management of wounds including partial and full-thickness wounds and DFUs. Additional applications may be applied after initial application once a week if there is evidence of wound healing and are limited to a maximum of 4 applications in twelve weeks

xii. PriMatrix
1. Indicated for the management of wounds, including partial and full thickness wounds and DFUs. Additional applications may be applied after initial application once a week if there is evidence of wound healing and are limited to a maximum of 3 applications in twelve weeks

xiii. TheraSkin
1. Indicated for the treatment of DFUs. Additional applications may be applied after initial application once a week if there is evidence of wound healing and are limited to a maximum of 4 applications in twelve weeks

d. Venous Stasis Ulcers (VSU): For VSUs of at least 1 cm^2 with documented adequate circulation unresponsive to at least 4 weeks of standard wound care, including cleansing, debridement, dressing, infection control, offloading, and compression therapy. *Skin substitute treatment must be used in conjunction with standard VSU therapy*

i. AmnioBand
1. Indicated to serve as a wound scaffold replacement for damaged integumental tissue. Initial treatment is limited to 1 application, additional applications may be applied once a week if there is evidence of wound healing and are limited to a maximum of 12 applications in twelve weeks

ii. Apligraf
1. Indicated for partial or full thickness VSUs. Initial treatment is limited to 1 application, additional applications may be applied once a week if there is evidence of wound healing and are limited to a maximum of 4 applications in twelve weeks

iii. DermACELL AWM
1. Indicated for chronic wounds such as VSUs with a maximum of 2 applications

iv. EpiFix
1. Indicated for acute and chronic wounds. Initial treatment is limited to 1 application, additional applications may be applied once a week if there is evidence of wound healing and are limited to a maximum of 4 applications in twelve weeks

v. Grafix
1. Indicated for acute and chronic wounds. Initial treatment is limited to 1 application, additional applications may be applied once a week if there is evidence of wound healing and are limited to a maximum of 6 applications in twelve weeks

vi. Oasis Matrix
1. Indicated for the management of wounds including partial and full-thickness wounds and VSUs. Initial treatment is limited to 1 application, additional applications may be applied once a week if there is evidence of wound healing and are limited to a maximum of 4 applications in twelve weeks

vii. PriMatrix
1. Indicated for the management of wounds, including partial and full thickness wounds and VSUs. . Initial treatment is limited to 1 application, additional applications may be applied once a week if there is evidence of wound healing and are limited to a maximum of 3 applications in twelve weeks

viii. TheraSkin
1. Indicated for the treatment of VSUs. Initial treatment is limited to 1 application, additional applications may be applied once a week if there is evidence of wound healing and are limited to a maximum of 4 applications in twelve weeks

e. Dystrophic Epidermolysis Bullosa

i. OrCel
1. Indicated for use in patients at least 1 year of age with mitten hand deformities due to recessive dystrophic epidermolysis bullosa as an adjunct to standard autograft procedures for covering wounds and donor sites created after surgical release of hand contractures

Continuation of Therapy

1. Skin or soft tissue substitute use in the treatment of chronic wounds will last no more than 12 weeks
2. Skin substitute applications must comply with FDA guidelines for the specific product and shall not exceed 10 applications or treatments per 12-week period of care
3. Only one skin or soft tissue substitute may be used per wound at a time. Product change within the wound episode is allowed, not to exceed the application limit per wound per 12-week period of care

NOT Medically Necessary

The following indications and/or skin or soft tissue substitutes are considered **experimental, investigational, and unproven** due to insufficient evidence in the peer-reviewed medical literature to establish long-term safety, efficacy, and effect on net health outcomes:

1. Skin substitutes are **not medically necessary** for ANY of the following indications:
   a. Any indications other than those noted in the clinical criteria section above
   b. Decubitus ulcer treatment
   c. Continued treatment when the ulcer fails to heal by ≥ 50% within the first 6 weeks of treatment
   d. Treatment beyond 12 weeks regardless of wound status
   e. Continued skin substitute use after treatment failure, defined as the repeat or alternative application course (of up to 12 weeks) of skin substitute grafts within one year of any given course of skin substitute treatment for a venous stasis ulcer or diabetic foot ulcer
   f. Retreatment of healed ulcers (those showing greater than 75% size reduction and smaller than 1cm^2)

2. All other skin or soft tissue substitutes products not included in the clinical criteria section above are considered **experimental, investigational, and unproven** due to insufficient evidence in the peer reviewed medical literature and include, but are not limited to**, ALL the following:

Acesso DL or Acesso TL
Actigraft
Activate Matrix
Affinity Human Amniotic Allograft
AlloGen
AlloSkin or AlloSkin RT
AltiPly
AmniCore Pro
AmniCore Pro+
Amnio Quad-Core
Amnio Tri-Core Amniotic
Amnio Wound
Amnio Wrap2
AmnioAMP-MP
AmnioArmor
AmnioBand
AmnioBind or DermaBind TL
AmnioCore
AmnioCyte Plus
AMNIOEXCEL products (AMNIOEXCEL Amniotic Allograft Membrane)
AmnioHeal Plus
AMNIOMATRIX
Amnio-Maxx or Amnio-Maxx
AMNIOREPAIR
AmnioText or AmnioText patch
Amnio Wound
AMNIPLY
Artacent products (Artacent Flex, Artacent Wound)
Arthroflex
Ascent
AxoBioMembrane
Axolotl Ambient or Axolotl Cryo
Axolotl Graft or Axolotl DualGraft
InteguPly
Interfyl
Kerecis Omega3
Keroxx (including Keroxx Flowable Wound Matrix)
Marigen Omega3
Matrion
MatriStem (MatriStem Burn Matrix, MatriStem Micromatrix, and MatriStem Wound Matrix)
Mediskin
Memoderm
MIRODERM Biologic Wound Matrix
Mirragen Advanced Wound Matrix
MyOwn Skin
NeoMatriX
NeoPatch
NeoStim Membrane, NeoStim TL
Membrane, NeoStimDL
NEOX
NEOX FLO
Novachor
Novafix
Novafix DL
NovoSorb SynPath
NuDYN
NuShield
Omeza Collagen Matrix
ORION
PalinGen (PalinGen Membrane, PalinGen XPlus Membrane, PalinGen XPlus Hydromembrane, PalinGen Flow, PalinGen SportFlow, ProMatrX ACF)
Phoenix Wound Matrix
Polycyte
PriMatrix
Procenta

Barrera SL or Barrera DL
BellaCell HD
bio-ConneKt
BioDfence or BioDFence DryFlex
BioNextPATCH
carePATCH
Cellesta products (Cellesta Amniotic Membrane, Cellesta Flowable Amnion)
Clarix Regenerative Matrix
Cogenex Amniotic Membrane or Cogenex Flowable Amnion
Coll-e-Derm
Conexa
Corecyte
Coretext or Protext
CorMatrix
Corplex or Corplex P
CoreText
Cryo-Cord
Cymetra
Cygnus products (Cygnus MATRIX, Cygnus MAX, and Cygnus SOLO)
Cytal products (Cytal Wound Matrix, MatriStem Wound Matrix, Multilayer Wound Matrix)
Dermacyte Amniotic Membrane Allograft
Dermacyte Amniotic Wound Care Liquid
Derma-Gide
Derm-Maxx
EpiCord products (EpiCord Dehydrated Human Umbilical Cord Allograft)
E-Z Derm
GammaGraft
Genesis Amniotic Membrane
hMatrix
Human Health Factor 10 Amniotic Patch
Hyalomatrix
InnovaBurn
InnovaMatrix products (InnovaMatrix XL, InnovaMatrix AC, InnovaMatrix FS, InnovaMatrix PD)
ProText
PuraPly products (PuraPly Antimicrobial Wound Matrix, PuraPly AM, PuraPly AM XT, PuraPly XT)
REGUaRD
Relese
Repriza
Restorigin Amnion Patch or AFT
Restrata or Restrata Minimatrix
Revita
SkinTE
STRATTICE
Stravix or StravixPL
Supra SDRM
Suprathel
Surederm
Surfactor
surgiGRAFT
SurgiMend
Talymed
TenSIX
TheraGenesis
TheraSkin
Therion
TissueMend
Transcyte (except for indication specified in this policy)
TruSkin
Unite Biomatrix
Vendaje
Vim
WoundEx or WoundEx Flow
WoundFix products (WoundFix Membrane, WoundFix Plus Membrane, WoundFix XPlus Membrane)
WoundPlus Membrane or E-graft
XCelliStem
XCellerate
XCM BIOLOGIC Tissue Matrix
XWRAP/XWRAP ECM
Zenith Amniotic Membrane

** Any other skin substitute not specified in this policy as medically necessary (according to criteria section) are considered experimental, investigational, and/or unproven.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Benefits for other conditions other than those listed in the coverage criteria using skin substitutes for wound healing have not been clearly demonstrated in robust clinical studies published in the peer reviewed medical literature. Evidence directly comparing different skin substitute products or types is extremely limited and insufficient to inform whether any one product or product type is superior to another. Safety data were generally limited but do not suggest skin substitutes are associated with serious harms or greater safety risks than standard wound care alone.

Breast Reconstruction

According to the United States Food and Drug Administration (FDA) (2021), the agency has not cleared or approved any acellular dermal matrix (ADM) products or surgical mesh for breast reconstruction. Despite this, ADM is commonly

used off-label in implant-based breast reconstruction. In a safety communication, the FDA highlighted concerns about higher complication rates associated with certain ADM products in implant-based breast reconstruction. Specifically, FlexHD and AlloMax were found to have significantly higher rates of explantation, reoperation, and infection two years following surgery compared to SurgiMend, AlloDerm, or no ADM. The FDA strongly encourages patients to discuss the risks and benefits of ADM use with their surgeon and to report any adverse events though its MedWatch program. They also emphasized the importance of monitoring ongoing scientific literature and adverse event reports to better understand the risks associated with ADM use. In 2022, The Plastic Surgery Foundation received investigational device exemption (IDE) approval for the use of ADM in pre-pectoral breast reconstruction, the study is ongoing ([1]ClinicalTrials.gov 2024). In 2023, RTI Surgical received IDE approval for Cortiva in breast reconstruction, the study is ongoing ([2]ClinicalTrials.gov 2024). In 2023, MTF Biologics received IDE approval for FlexHD in breast reconstruction, the study has not begun (MTF Biologics 2023).

Randomized Controlled Trials

Arnaout et al. (2021) conducted a RCT comparing Alloderm-RTU to DermACELL in immediate subpectoral implant-based breast reconstruction. The primary outcome of the study was the duration of postoperative drain placement, as a surrogate endpoint for the extent of seroma formation, with secondary outcomes including episodes of seroma aspiration following drain removal, removal of the implant, unplanned revisional surgery/return to the operating room, wound infection requiring antibiotics, wound dehiscence or need for debridement, capsular contracture, and red breast syndrome. A total of 62 patients were randomized 1:1; however, only 59 patients were included in final analysis for a spread of Alloderm-RTU (n=38 breasts) and DermACELL (n=40 breasts). The mean duration of drain placement was 10.8 days (standard deviation, SD, 5.5) with Alloderm-RTU and 9.2 days (SD 4.5) with DermACELL. Complications within the first 6 months post-op were reported as follows: wound infections requiring antibiotics occurred in 3 breasts (7.9%) in the Alloderm-RTU group and 1 (2.5%) in the DermACELL group (p = 0.35). Unplanned reoperation due to complications was necessary for 6 breasts (15.8%) in the Alloderm-RTU group and 3 breasts (7.5%) in the DermACELL (p = 0.30) group. Minor complications, including seroma requiring aspiration, red breast syndrome, wound dehiscence, wound infection, hematoma, skin necrosis, and capsular contracture, were observed in 36.8% of the Alloderm-RTU group and in 32.5% of the DermACELL group. The authors concluded that there were minimal differences between the two products and that further studies into a cost analysis of each should be explored.

McCarthy et al. (2012) conducted a double blind RCT on the use of ADMs in two stage implant-based breast reconstruction. Following their mastectomy 70 patients were randomized 1:1 into the ADM group (n= 36) versus the tissue expander (TE) group (n=34). The primary outcome evaluated was patient pain report, which was evaluated pre-operatively and five times post-operatively using the Visual Analog Scale (VAS) and the BREAST-Q© Physical Well-Being: Chest and Upper Body Scale. The results revealed there were no differences in patient pain via both VAS scores and immediate post-op narcotic use between the two groups at any time point in the assessments. Similarly, there were no differences in physical well-being in the immediate post-operative period, during the expansion phase, or prior to the exchange period (p= 0.52, p=0.77, p=0.82, respectively) via the BREAST-Q scale. In congruence with the lack of differentiation between the two groups, both cohorts had similar complication rates. The authors concluded that the use of ADMs neither hinders nor enhances post-operative outcomes in implant-based breast reconstruction.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Wu et al. (2013) conducted an open label prospective case series on the dimensional changes and stretching of ADMs in tissue expander implant-based breast reconstruction. The primary outcome of the study was to measure the construct size on post op day 1 and post op month 3 to assess stretching. Thirty-one patients were included in the study and resulted in a mean perimeter increase from 38 (6) cm on postoperative day 1-42 (7) cm at month 3 (+11%; P=0.002), and a surface area increased from 73 (22) to 88 (28) cm2 (+21%; range, 4-35%; P=0.002). The secondary outcome of the study was patient satisfaction, which was comparable to those who did not receive an ADM in their reconstruction. Safety outcomes revealed complications in the ADM group were late seroma, red breast syndrome and urinary tract infection versus cellulitis, expander explantation, delayed wound healing and skin necrosis in those that did not receive an ADM. The authors concluded that the use of ADMs was a viable treatment modality with moderate stretching and comparable patient satisfaction in implant-based breast reconstruction.

Burn Wounds

Randomized Controlled Trials

Gibson et al. (2021) conducted a phase 3, open-label RCT to evaluate the safety and efficacy of a bioengineered allogeneic cellularized construct (StrataGraft) as a donor-site sparing alternative to autografting in patients with deep

partial-thickness thermal burns. The study enrolled 71 adult patients (n = 71) who presented with DPT burns involving 3-48% of their total body surface area, with wounds located on the torso or extremities and deemed clinically appropriate for excision and autografting. Each patient received both StrataGraft and autograft treatments on two comparable wound areas to ensure an intrapatient comparison, minimizing variability from individual healing differences. By Month 3, the mean percentage of the StrataGraft treatment area requiring autografting was 4.3%, compared to 102.1% for autograft treatment sites ($p < 0.0001$). Durable wound closure, defined as 100% re-epithelialization without drainage or dressing requirements at consecutive evaluations, was achieved at the StrataGraft site in 92% of patients (95% CI, 85.6-98.8), compared to 95% at the autograft sites. At Month 3, molecular analysis confirmed the absence of StrataGraft DNA at the treatment sites, indicating that healing occurred via the patient's own cells. By Month 12, all wounds that achieved durable closure at Month 3 remained closed. In addition to wound closure efficacy, the study evaluated secondary outcomes related to donor-site morbidity. Patients treated with StrataGraft reported significantly less donor-site pain through Day 14 compared to autograft-treated sites, as measured by the Wong-Baker FACES pain rating scale. Pain intensity scores averaged 0.15 for StrataGraft donor sites versus 2.55 for autograft donor sites ($p < 0.0001$). Cosmesis outcomes, assessed using POSAS, favored StrataGraft at Month 3, with significantly better scar scores (mean score: 6.3 for StrataGraft donor sites vs 16.3 for autograft donor sites, $p < 0.0001$). At Month 12, cosmesis at StrataGraft and autograft treatment sites was clinically similar, with no significant difference in scar scores. Mild to moderate treatment-emergent adverse events (TEAEs) occurred in 84.5% of patients. Pruritus was the most common StrataGraft-related TEAE, reported in 15.5% of patients. Other TEAEs, such as hypertrophic scarring and localized wound complications, were reported in low frequencies and were consistent with those seen in standard burn care. No serious adverse events were attributed StrataGraft, and immunological evaluations revealed no clinically significant immune responses. Anti-bovine serum albumin antibodies were detected in a small proportion of patients, but their clinical relevance remains unclear. The sample size of 71 patients and exclusion of certain anatomical locations and full-thickness burns limits the generalizability of the results. The study concluded that StrataGraft offers a viable alternative to autografting by providing effective wound closure while reducing or eliminating the morbidity associated with donor-site harvesting.

Hundeshagen et al. (2018) conducted a prospective RCT comparing Suprathel versus Mepilex Ag in treating burn wounds. The outcomes assessed were re-epithelialization, wound pain, discomfort during dressing changes, and treatment cost, as well as a Patient and Observer Scar Assessment Scale was performed at 1 month post burn. A total of 62 patients were enrolled with 30 in the Mepilex Ag group and 32 in the Suprathel group. Mean TBSA burned was 5.9 ± 5.8% (range, 1–29%) in the Mepilex Ag group and 5.5 ± 4.6% (range, 1–20%) in the Suprathel group. Subjective patient findings in favor of Suprathel were significantly lower pain ratings in those treated with Suprathel during the first 5 days after burn injury ($P < 0.05$) with ratings converging at a common lower level after this time, and patients rated the overall appearance of their healed wound better after treatment with Suprathel (S: 2; Confidence Interval, 1.4–3.5; M: 4.5; Confidence Interval, 3.8–6.2; $P = 0.002$). Subjective findings that did not show significant differences between groups were patient ratings for pain, itch, color, stiffness, thickness, and irregularity at the 1-month assessment. Objective findings were the median time to complete re-epithelialization was 12 days in both groups ($P = 0.75$) with 20% (6/30) of patients having a re-epithelialization time greater than 21 days in the Mepilex Ag group versus 7% (2/30) in the Suprathel group ($P = 0.25$). At the 1-month assessment observer scores of the healed wound at this time did not show significant differences for vascularity, pigmentation, thickness, relief, pliability, surface, or overall appearance. Observer score for pliability (M: 5; S: 2; $P = 0.08$) and patient score for irregularity (M: 3.5; S: 2; $P = 0.075$) approached significance. The adverse events consisted of infection, of which 2 infections (8%) were confirmed in the Suprathel group versus none observed in the Mepilex Ag group ($P = 0.5$). The cost per square centimeter of Mepilex Ag was $0.08, and on average, each patient required 2 dressing changes. Suprathel cost $0.56 per square centimeter and was applied once per patient, resulting in direct product costs of $0.16/cm2 per patient for Mepilex Ag and $0.56/cm2 per patient for Suprathel. The authors concluded that both dressings were viable treatments for burn wounds.

Systematic Reviews and Meta-Analyses

Press et al. (2023) performed a systematic review and meta-analysis to assess the efficacy and safety of acellular dermal substitutes (ADS) for treating acute burns. They assessed 16 studies, including nine RCTs (n = 346) and seven observational studies (n = 745). Primary outcomes were graft take and infection rates, while secondary outcomes included scar quality, graft loss, and length of hospital stay. ADS products included Integra Dermal Regeneration Template, Matriderm, and NovoSorb Biodegradable Temporizing Matrix. Patient populations consisted of adults and pediatrics with deep partial and full-thickness burns requiring excision and grafting. Sample sizes ranged from 10 to 270 participants, which included adults, pediatrics, or both. Meta-analysis revealed no statistically significant difference

(mean difference of 5.15%, p = 0.37) in graft take rates, with ADS slightly lower compared to standard split-thickness skin grafts. Infection rates were also comparable between ADS and conventional treatments (odds ratio 1.06, p = 0.87). Scar quality showed mixed results, measured using the Vancouver Scare Scale (VSS) and the Patient and Observer Scar Assessment Scale (POSAS). Four RCTs reported significantly improved scar quality with ADS, while others found no difference compared to conventional grafting methods. Improvements in scar elasticity were also observed in some studies, particularly with Matriderm. Adverse events included delayed wound healing and infection. While infection rates varied, they were generally consistent with those seen in conventional burn treatments, with some studies noting higher rates in patients with larger burns or in centers with less experience using ADS. Graft loss was infrequently reported, though one study cited a high rate of loss due to infection. Length of hospital stay showed no consistent trends, as results were influenced by variations in burn severity and treatment protocols. The review highlights several limitations, including a high risk of bias in many trials due to small sample sizes, lack of blinding, and heterogeneity in methodologies. Observational studies were also prone to confounding factors and inconsistent reporting. Despite these limitations, the review concludes that ADS provide a viable alternative to conventional burn treatments, offering comparable efficacy in graft take and infection rates and potential improvements in scar quality.

Wardhana and Valeria (2022) conducted a systematic review and analyzed the effectiveness of skin substitutes in the treatment of acute burns. Thirteen articles were included in the review and six types of skin substitutes were evaluated including Biobrane, TransCyte, Integra, Glyaderm, Suprathel, and Apligraft. Burns ranged from superficial to full-thickness depth with TBSA from 2-97%. Across four studies, Biobrane showed significantly shortened wound healing time and reduced pain scores compared to treatment with silver sulfadiazine. Two studies reported a shorter length of hospitalization, and a decreased frequency of dressing changes compared to the silver sulfadiazine group. When compared to modern dressings (e.g., Duoderm and Duoderm + Intrasite + Acticoat) Biobrane demonstrated comparable outcomes in wound healing time, pain, dressing change frequency and Vancouver Scar Scale (VSS) scores. Transcyte was significantly more effective in decreasing wound healing time, pain alleviation, reducing dressing change frequency, and managing scar formation compared to silver sulfadiazine. Integra presented better scar outcomes compared to allograft based on the Hamilton burn-scar scoring system. Suprathel was compared to split-thickness skin grafts (STSG) for full thickness burns. VSS parameters including pigmentation, pliability, and height had similar results between the two groups. On the patient and observer scar assessment scale (POSAS) elasticity, relief, and pliability were significantly superior in the Suprathel group compared to the STSG group. Apligraf when combined with autograft produced superior results in scar evaluation compared to the STSG group. All skin substitutes included in the review demonstrated, at minimum, non-inferior to superior performance when compared to conventional treatment modalities in treating various burn wounds.

Lower Limb Ulcers

Randomized Controlled Trials

Armstrong et al. (2024) conducted an RCT to compare the efficacy and safety of a purified reconstituted bilayer membrane (Geistlich Derma-Gide) with standard of care (SOC) for non-healing diabetic foot ulcers (DFUs). 105 patients were randomized into two groups for intent to treat: Geistlich Derma-Gide (n = 54) and SOC (n = 51). 80 patients completed the study per protocol: Geistlich Derma-Gide (n = 47) and SOC (n = 33). The primary outcome was the proportion of wounds fully healed after 12 weeks. In the intent to treat analysis, 83% of the Geistlich Derma-Gide group achieved complete healing compared to 45% in the SOC group (p = 0.00004). In the per-protocol analysis, the healing rates were 92% for the Geistlich Derma-Gide and 67% for SOC (p = 0.005). Secondary outcomes included time to healing, percentage area reduction, quality of life measures, and cost to closure. Geistlich Derma-Gide treated wounds healed significantly faster, with a mean time to closure of 42 days compared to 62 days for SOC (p = 0.00074). The Geistlich Derma-Gide group achieved a mean wound area reduction of 94% at 12 weeks versus 51% for the SOC group (p = 0.0023). No treatment-related adverse events or serious adverse events were reported in either group. Limitations included small sample size, inclusion of only Wagner Grade 1 non-infected DFUs, and lack of long-term follow-up to assess wound recurrence or additional outcomes. The authors concluded that purified reconstituted bilayer membrane is a safe and effective option for treating non-healing DFUs.

Serena et al. (2022) conducted an RCT to evaluate the safety and efficacy of weekly and biweekly applications of dehydrated human amnion and chorion allograft (AmnioBand) combined with SOC compared to SOC alone for chronic venous leg ulcers (VLUs). The study included 60 participants (n = 60) randomized into three equal groups: SOC alone, weekly AmnioBand plus SOC, and biweekly AmnioBand plus SOC. Patients were eligible if they had chronic VLUs that failed to heal with prior treatments and were of specific wound size (2-20 cm^2). The primary outcome was the proportion of ulcers achieving complete closure at 12 weeks, measured with a Silhouette three-dimensional laser

camera system. Secondary outcomes included the proportion of ulcers achieving ≥ 40% area reduction at 4 weeks and the incidence of adverse events. At 12 weeks, significantly more VLUs healed in the AmnioBand-treated groups (75%) compared to the SOC group (30%) (p = 0.001). At 4 weeks, there were no significant differences in wounds achieving ≥ 40% closure among the groups. At 12 weeks, the median percentage area reduction was significantly higher in the AmnioBand groups (100%) compared to the SOC group (75%, p = 0.012). 38 adverse events were reported, an incidence rate of 63.5%, with the most common being wound infections and the development of new ulcers. 9 serious adverse events were reported, including infections requiring hospitalization, but none were related to graft or procedure. All adverse events resolved with appropriate treatment. The authors concluded that dehydrated human amnion and chorion allograft significantly improved healing rates in chronic VLUs compared to SOC alone and offered a safe and effective adjunctive treatment option. The study was registered at ClinicalTrials.gov as NCT02609594.

Lantis et al. (2021) conducted an RCT evaluating the safety and efficacy of using a fetal bovine acellular dermal matrix (FBADM) in conjunction with SOC to treat DFUs were evaluated. The study included 226 patients, with 110 assigned to the FBADM group and 116 to the SOC group. Eligible patients had confirmed type 1 or 2 diabetes, a hemoglobin A1c ≤ 12%, a foot ulcer lasting at least 2 weeks, an ulcer area between 1–12 cm2 post-debridement, and adequate vascular perfusion. Exclusion criteria included active infection, exposed tendon or bone, or wound reduction ≥ 30% during the 2-week run-in period. Outcome measures included time to closure, weekly closure rate, percentage area reduction at 12 weeks, incidence of closure and ulcer duration, and recurrence. A significantly higher proportion of wounds treated with FBADM (45.6%) achieved complete closure compared to SOC alone (27.9%) (p = 0.008). Median closure time was 43 days for FBADM versus 57 days for SOC. At 12 weeks, FBADM treatment resulted in a 2.2 times greater likelihood of complete closure compared to SOC. No adverse events related to the product or procedure were noted. Limitations included the inability to blind investigators or subjects, a short follow-up of four weeks, and potential patient selection bias favoring healthier individuals with DFUs. Overall, the study suggests FBADM, combined with SOC, as a reasonable therapy for treatment of DFUs.

Systematic Reviews and Meta-Analyses
Alvaro-Afonso et al. (2020) conducted a systematic review of the recent advances in dermo epidermal skin substitutes for the treatment of DFUs. A total of 28 RCTs were reviewed to analyze rates of complete wound closure and time to healing for 17 commonly available dermal skin substitutes. The healing rates after 12 weeks and time to complete closure in DFUs were heterogeneous among the 28 RCTs, with the best 12-week healing rates accomplished with dermal cellular substitutes (Epifix, 100% and Amnioband, 85%). The authors concluded that skin substitutes used in conjunction with standard care appear to improve the healing rates of DFUs compared to standard wound care alone. The authors stated more homogenous studies are needed to confirm these findings, with studies considering wound size and comorbidities.

Cazzell (2019) conducted an open-label RCT to compare the safety and efficacy of a human acellular dermal matrix (DermACELL) with conventional care for treating chronic VLUs. The study included 28 patients (n = 28), with 18 assigned to the DermACELL group and 10 to the conventional care group. Patients were treated and followed weekly for up to 24 weeks or until complete wound closure, defined as 100% re-epithelialization without drainage confirmed at two consecutive visits two weeks apart. Healed ulcers were monitored for an additional 12 weeks post-closure to assess durability. At 24 weeks, the DermACELL group demonstrated a higher wound closure rate (44.4%) compared to conventional care (33.3%), although this difference was not statistically significant due to the small sample size. DermACELL showed significantly greater reduction in wound area, with an average reduction of 59.6% versus 8.1% for conventional care. In the conventional care group, wound area increased by more than 100% for one-third of patients. Healed ulcers in the DermACELL group remained closed at higher rates than conventional care during the follow-up period. AEs were monitored with no events attributed to DermACELL. Bias was minimized by using a blinded, independent adjudicator to confirm wound healing. Limitations included a small sample size and unequal randomization. The author concluded that DermACELL is a promising treatment for chronic VLUs, demonstrating superior wound area reduction and better healing outcomes compared to conventional care. Further larger-scale, RCTS are warranted. The study was registered at ClinicalTrials.gov as NCT01970163.

DiDomenico et al (2018) conducted an RCT to compare the effectiveness of a dehydrated human amnion and chorion allograft (AmnioBand) to SOC in healing chronic DFUs. The study involved 80 participants who were randomized 1:1 to receive either AmnioBand with SOC or SOC alone. The primary outcome was the percentage of wounds healed at 6 weeks, while secondary outcomes included percentage of wounds healed at 12 weeks, time to heal, number of

applications, tissue wastage, and cost of closure. At 6 weeks, 68% of patients in the AmnioBand group achieved complete wound closure compared to 20% in the SOC group ($p = 1.9 \times 10^{-5}$). By 12 weeks, 85% of AmnioBand treated wounds were healed, compared to 33% in the SOC group ($p = 6.0 \times 10^{-6}$). The mean time to heal was significantly faster in the AmnioBand group, with 37 days compared to 67 days for the SOC group ($p = 6.0 \times 10^{-6}$). The number need to treat at 12 weeks was 1.9 (95% CI: 1.4-2.9). The AmnioBand group used a mean of 4.0 grafts per healed wound over 12 weeks, with an average cost to closure of $1,771. The mean tissue wastage was 35.3%, which the authors highlighted as efficient compared to other advanced wound care products. The study demonstrated a hazard ratio of 4.25 (95% CI: 3.02-6.31, $p = 2.5 \times 10^{-5}$) for AmnioBand compared to SOC, indicating that AmnioBand-treated wounds were more than four times as likely to heal within 12 weeks. 11 adverse events occurred, with 3 in the AmnioBand group and 8 in the SOC group, most of which were localized infections. 4 serious adverse events were reported, with in the AmnioBand group and 3 in the SOC group, all of which involved infections requiring hospitalization. There were no graft-related adverse events. The authors concluded that dehydrated human amnion and chorion allograft significantly improves the likelihood and rate of healing in chronic DFUs when combined with SOC, as well as providing cost-efficiency advantages and lower wastage compared to other advanced cellular and tissue-based products. The study was registered at ClinicalTrials.gov as NCT02399826.

Zelen et al. (2018) conducted an RCT to assess the efficacy, safety, and cost of a human reticular acellular dermal matrix (AlloPatch Pliable) for treating DFUs, expanding on a prior study of 40 patients adding 40 more to create a total cohort of 80 (n = 80). Participants were adults aged 18 or older with type 1 or type 2 diabetes and a non-infected DFU of at least 4 weeks duration that had not healed after SOC. Participants were randomized 1:1 to receive weekly applications of AlloPatch Pliable with SOC versus SOC alone for up to 12 weeks. Primary outcomes were the proportion of DFUs healed at 6 weeks, and secondary outcomes included the proportion healed at 12 weeks, time to heal, adverse events, and cost metrics. At 6 weeks, 68% (27/40) in the AlloPatch group were completely healed compared to 15% (6/40) in the SOC group ($p = 2.7 \times 10^{-6}$). At 12 weeks, 80% (32/40) of DFUs in the AlloPatch group achieved full closure compared to 30% (12/40) in the SOC group ($p = 8.4 \times 10^{-6}$). Mean time to heal within 12 weeks was significantly shorted in the AlloPatch group (38 days) compared to the SOC group (72 days). The mean number of AlloPatch grafts applied per wound was 4.7, and the mean product cost to achieve closure was $1,200, with a mean wastage of 57%. The AlloPatch group reported 8 adverse events, including 3 diabetic foot infections requiring hospitalization and IV antibiotics, none of which were attributed to the graft. The SOC group also reported 8 adverse events, including 6 being serious, primarily infections leading to hospitalizations. 5 participants were withdrawn from the trial due to severe infections or complications. The authors concluded that human reticular acellular dermal matrix is clinically superior to SOC for DFU management, promoting fast healing and a higher proportion of wound closures, as well as providing cost-efficiency advantages and lower wastage compared to other advanced wound therapies. The study was registered at ClinicalTrials.gov as NCT02331147.

Cazzell et al. (2017) conducted an RCT to compare the safety and efficacy of a human acellular dermal matrix (DermACELL) to conventional care and another acellular dermal matrix (GraftJacket), for chronic DFUs. The clinical trial enrolled 168 (n = 168) participants with Wagner grade 1 or 2 DFUs of at least 30 days duration and adequate circulation. Participants were randomized into three groups: DermACELL (n = 71), conventional care (n = 69), and GraftJacket (n = 28). The primary outcome was complete wound closure at 12 weeks defined as 100% re-epithelialization without drainage or dressing needs, confirmed at two consecutive visits two weeks a part. Secondary outcomes included time to wound closure, percentage wound area reduction, and proportion of wounds that remained healed after treatment. At 12 weeks, 65% of wounds in the DermACELL group achieved closure compared to 41.1% in the conventional care group ($p = 0.0123$). By 24 weeks, healing rates increased to 89.7% for DermACELL and 67.3% for conventional care ($p = 0.0008$). GraftJacket showed no significant improvement over conventional care. DermACELL also achieved greater wound area reduction from Weeks 2 through 24 compared to conventional care, while GraftJacket showed significant reduction during specific weeks. At 4 weeks post-termination, 100% of wounds healed with DermACELL remained closed compared to 86.7% with conventional care ($p = 0.0435$), though no significant differences were observed at later follow-ups (8- and 12-weeks post-termination). AEs rates were 64.8% for DermACELL, 64.7% for conventional care, and 71.4% for GraftJacket. The most common severe AE was osteomyelitis, but no AEs were related to the study products. One death occurred in the DermACELL group during follow-up and was determined to be unrelated to the treatment. Bias potential was minimized by using a laser system for wound measurement and a blinded third-party to confirm wound healing outcomes. The authors concluded that DermACELL is a safe and effective treatment for chronic DFUs, demonstrating superior healing rates, faster wound area reduction, and better long-term wound closure maintenance compared to conventional care. The study was registered at ClinicalTrials.gov as NCT01970163.

Lavery et al. (2014) conducted a single-blinded RCT to evaluate the safety and efficacy of Grafix, a human viable wound matrix, compared to standard wound care for chronic DFUs. The study included 97 patients, randomized to either Grafix (n = 50) or standard wound care (n = 47). Participants were aged 18 to 80 years with chronic DFUs of 4-52 weeks and wound sizes of 1-15 cm^2. The primary outcome was complete wound closure, defined as 100% re-epithelialization with no drainage, confirmed by a blinded wound core laboratory. Secondary outcomes included time to wound closure, reduction in wound area, adverse events, and wound recurrence rates. 62% of patients in the Grafix group achieved complete wound closure by 12 weeks compared to 21% for standard wound care ($p < 0.001$). The median time to wound closure was 42 days for Grafix and 69.5 days for standard care ($p = 0.019$). 62% of Grafix patients achieved at least a 50% reduction in wound area by day 28, compared to 40.4% for standard care ($p = 0.035$). Wound recurrence rates were 17.9% for Grafix and 30% for standard care, but the difference was not statistically significant ($p = 0.42$). Grafix was associated with fewer AEs overall (44% vs. 66%, $p = 0.031$) and significantly fewer wound-related infections (18% vs. 36.2%, $p = 0.044$). No treatment related serious AEs were reported. Patients in the Grafix group required fewer clinic visits to achieve closure, reducing the overall treatment burden. The authors concluded that Grafix significantly improves healing rates and reduces complications associated with chronic DFUs compared to standard wound care. The study was funded by the manufacturer of Grafix, Osiris Therapeutics, Inc.

Harding et al. (2013) conducted an RCT to analyze venous leg ulcer healing when treated with Dermagraft vs compression therapy alone (control group). Three hundred and sixty-six patients were included, 186 in the Dermagraft group vs 180 in the control group. The primary outcome was the proportion of patients with completely healed study ulcers by 12 weeks. In the Dermagraft group 64 (34%) of 186 patients experienced healing by week 12 compared with 56 (31%) of 180 patients in the control group ($P = 0{\cdot}235$). For ulcers ≤ 12 months duration, 49 (52%) of 94 patients in the Dermagraft group versus 36 (37%) of 97 patients in the control group healed at 12 weeks ($P = 0{\cdot}029$). For ulcers ≤ 10 cm^2, complete healing at week 12 was observed in 55 (47%) of 117 patients in the Dermagraft group compared with 47 (39%) of 120 patients in the control group ($P = 0{\cdot}223$). Adverse event rates did not markedly differ between the two groups. The authors concluded that as the efficacy of Dermagraft appeared to improve younger ulcers, the suggestion is made that Dermagraft should be utilized early in wound care; however, more studies are needed.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence
Bianchi et al. (2019) conducted an analysis to assess if intention-to-treat (ITT) and per-protocol (PP) both demonstrate superiority of EpiFix over standard moist dressings as a treatment for venous leg ulcers (VLU). The data analyzed was collected an RCT that compared VLU treatment with EpiFix versus standard wound care. One hundred and twenty-eight patients were 1:1 randomized between the two groups, 64 to the EpiFix group and 64 to the standard care group with a primary outcome of the incidence of healing at 12 weeks. The healing rate of the ITT group was 50% for EpiFix and 31% for standard wound care. The healing rate of the PP group was 60% for EpiFix and 35% for standard wound care. Within both ITT and PP analyses, these differences were statistically significant; $P = 0.0473$, ITT and $P = 0.0128$, PP. The authors concluded that the Kaplan-Meier plot of time to heal within 12 weeks for the ITT and PP populations demonstrated a superior wound-healing trajectory for EpiFix compared to standard wound care alone.

Farivar et al. (2019) conducted a study to evaluate the efficacy of cryopreserved placental tissue wound matrix (Grafix) in the management of chronic venous leg ulcers. Twenty-one patients were included in the study for a total of 30 VLUs, all of which were men. The patients were enrolled only after failing 12 weeks of standard wound therapy, and therefore served as their own control. The average area of the VLUs before Grafix initiation was 12.2 cm^2 (SD, ±14.6 cm2; range, 3.3-12.3 cm^2), and after Grafix treatment there was a mean reduction in wound surface area by 79% (SD, ±27.3%; $P < .001$ compared with standard therapy) after a mean treatment time of 10.9 weeks. Eighty percent of VLUs were reduced in size by half compared with 25% with standard therapy ($P < .001$), and complete wound healing was achieved in 53% (16/30) of VLUs refractory to standard therapy. The results led the authors to conclude that adjunct therapy with a skin substitute, such as Grafix, provides superior wound healing than standard therapy alone; however, larger RCTs are needed to confirm these findings.

National and Specialty Organizations

The **International Society for Burn Injury (ISBI)** (2016) published the *ISBI Practice Guidelines for Burn Care*. The aim was to provide guidance for those with burns to improve care overall. The ISBI also defined the most effective and efficient methods of evaluation and management of burn injuries. The document recommends that following excision or debridement, a deep burn wound should be covered with autograft skin or an appropriate skin substitute.

The **Wound Healing Society (WHS)** published *WHS Guidelines Update: Diabetic Foot Ulcer Treatment Guidelines* (Lavery et al. 2020) that offered support for use of skin substitutes by assigning a Level 1 recommendation of the evidence that cellular and acellular skin equivalents improve DFU healing.

The **Society for Vascular Surgery (SVS)**, **American Podiatric Medical Association (APMA)**, and the **Society for Vascular Medicine (SVM)** jointly published *The Management of Diabetic Foot: A Clinical Practice Guideline by the Society for Vascular Surgery* (Hingorani et al. 2016). The guideline offers recommendations regarding prevention, examination for peripheral neuropathy, education for patients and their families, and strategies for glycemic control to reduce DFUs manifestation and complications. The guideline also offers recommendations on the treatment of DFUs, including the use of biologics (platelet-derived growth factor, living cellular therapy, extracellular matrix products, amniotic membrane products) to aid in the healing of chronic DFUs that have not shown improvement with conventional therapy after at least 4 weeks.

The **Agency for Healthcare Research and Quality (AHRQ)** published a Technology Assessment Program Technical Brief on *Skin Substitutes for Treating Chronic Wounds* (Snyder et al. 2020) in which different skin substitute products commercially available in the United States used to treat chronic wounds are described and examined for classification. In addition, the brief identified and assessed RCTs and suggested best practices for future studies on skin substitutes. The authors concluded "Studies rarely reported clinical outcomes, such as amputation, wound recurrence at least 2 weeks after treatment ended, or patient-related outcomes, such as return to function, pain, exudate, and odor. The lack of studies examining the efficacy of most skin substitute products and the need for better-designed and reported studies providing more clinically relevant data in this field are this Technical Brief's clearest implications."

The **International Work Group on Diabetic Foot (IWGDF)** published *Guidelines on Interventions to Enhance Healing of Foot Ulcers in People with Diabetes* (Chen et al. 2024) in which the recommendation was made to consider the use of placental derived products in DFUs that have not improved with standard therapy, the products are recommended to be used as an adjunct therapy to conventional wound management.

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Codes

Code	Description
15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

HCPCS (Healthcare Common Procedure Coding System) Codes

Code	Description
C5271	Application of low-cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5272	Application of low-cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5273	Application of low-cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low-cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C5275	Application of low-cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low-cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (list separately in addition to code for primary procedure)
C5277	Application of low-cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (list separately in addition to code for primary procedure)
C9250	Human plasma fibrin sealant, vapor-heated, solvent-detergent (Artiss), 2ml
Q4101	Apligraf per square centimeter
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) or Integra Omnigraft dermal regeneration matrix, per sq cm
Q4106	Dermagraft per square centimeter
Q4107	GRAFTJACKET, per sq cm
Q4108	Integra matrix, per square centimeter
Q4121	TheraSkin, per sq cm
Q4122	DermACELL, DermACELL AWM or DermACELL AWM Porous, per sq cm~~F~~
Q4124	OASIS ultra tri-layer wound matrix, per sq cm
Q4132	Grafix core and grafixpl core, per square centimeter
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per sq cm
Q4151	AmnioBand or Guardian, per sq cm
Q4168	AmnioBand, 1 mg
Q4182	Transcyte per square centimeter
Q4186	Epifix, per square centimeter
A2012	Suprathel, per sq cm
A4100	Skin substitute, FDA-cleared as a device, not otherwise specified
Q4100	Skin substitute, not otherwise specified [use for others not specified]
Q4110	Primatrix, per square centimeter
Q4111	Gammagraft, per sq cm
Q4112	Cymetra, injectable, 1cc
Q4113	Graftjacket xpress, injectable, 1cc
Q4114	Integra flowable wound matrix, injectable, 1cc
Q4115	Alloskin, per sq cm

Q4116	Alloderm, per square centimeter
Q4117	Hyalomatrix, per sq cm
Q4118	Matristem micromatrix, 1mg
Q4123	AlloSkin RT, per sq cm
Q4125	Arthroflex, per square centimeter
Q4126	MemoDerm, DermaSpan, TranZgraft or IntéguPly, per sq cm
Q4127	Talymed, per sq cm
Q4128	FlexHD, or AllopatchHD, per sq cm
Q4130	Strattice tm, per square centimeter
Q4134	Hmatrix, per sq cm
Q4135	Mediskin, per sq cm
Q4136	E-Z Derm, per sq cm
Q4137	Amnioexcel, amnioexcel plus or biodexcel, per square centimeter
Q4138	Biodfense dryflex, per square centimeter
Q4139	Amniomatrix or biodmatrix, injectable, 1 cc
Q4140	BioDFence, per square centimeter
Q4141	Alloskin AC, per square centimeter
Q4142	Xcm biologic tissue matrix, per square centimeter
Q4143	Repriza, per square centimeter
Q4145	Epifix, injectable, 1 mg
Q4146	Tensix, per square centimeter
Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per square centimeter
Q4148	Neox Cord 1K, Neox Cord RT, or Clarix Cord 1K, per square centimeter
Q4149	Excellagen, 0.1 cc
Q4150	Allowrap DS or dry, per square centimeter
Q4152	DermaPure, per sq cm
Q4153	Dermavest and Plurivest, per sq cm
Q4154	Biovance, per sq cm
Q4155	Neox Flo or Clarix Flo 1 mg
Q4156	Neox 100 or Clarix 100, per sq cm
Q4157	Revitalon, per sq cm
Q4158	Kerecis Omega3, per sq cm
Q4159	Affinity, per sq cm
Q4160	Nushield, per square centimeter
Q4161	bio-ConneKt wound matrix, per sq cm
Q4162	Woundex flow, bioskin flow, 0.5cc
Q4163	Woundex, bioskin, per sq cm
Q4164	Helicoll, per square cm
Q4165	Keramatrix or Kerasorb, per sq cm
Q4166	Cytal, per square centimeter
Q4167	Truskin, per square centimeter
Q4169	Artacent wound, per sq cm
Q4170	Cygnus, per sq cm
Q4171	Interfyl, 1 mg
Q4173	Palingen or Palingen Xplus, per sq cm
Q4174	Palingen or promatrx, 0.36 mg per 0.25 cc
Q4175	Miroderm, per sq cm
Q4176	Neopatch or Therion, per square centimeter
Q4177	Floweramnioflo, 0.1 cc
Q4178	FlowerAmnioPatch, per sq cm
Q4179	Flowerderm, per square centimeter
Q4180	Revita, per square centimeter
Q4181	Amnio wound, per square centimeter

Q4183	Surgigraft, per sq cm
Q4184	Cellesta or Cellesta Duo, per sq cm
Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4187	Epicord, per square centimeter
Q4188	AmnioArmor, per sq cm
Q4189	Artacent ac, 1 mg
Q4190	Artacent AC, per sq cm
Q4191	Restorigin, per square centimeter
Q4192	Restorigin, 1 cc
Q4193	Coll-e-derm, per square centimeter
Q4194	Novachor, per square centimeter
Q4195	PuraPly, per square cm
Q4196	PuraPly AM, per square cm
Q4197	Puraply XT, per square cm
Q4198	Genesis amniotic membrane, per square centimeter
Q4200	SkinTE, per sq cm
Q4201	Matrion, per square centimeter
Q4202	Keroxx (2.5g/cc), 1cc
Q4203	Derma-Gide, per sq cm
Q4204	Xwrap, per square centimeter
Q4205	Membrane graft or membrane wrap, per square centimeter
Q4206	Fluid flow or fluid gf, 1 cc
Q4208	Novafix, per sq cm
Q4209	SurGraft, per sq cm
Q4211	Amnion Bio or AxoBioMembrane, per sq cm
Q4212	Allogen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta Cord, per sq cm
Q4215	Axolotl ambient or axolotl cryo, 0.1 mg
Q4216	Artacent Cord, per sq cm
Q4217	WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm
Q4218	SurgiCORD, per sq cm
Q4219	SurgiGRAFT-DUAL, per sq cm
Q4220	BellaCell HD or Surederm, per sq cm
Q4221	Amniowrap2, per square centimeter
Q4222	ProgenaMatrix, per sq cm
Q4224	Human Health Factor 10 Amniotic Patch (HHF10-P), per sq cm
Q4225	Amniobind or derma tl, per sq cm
Q4226	MyOwn Skin, includes harvesting and preparation procedures, per sq cm
Q4227	AmnioCoreTM, per sq cm
Q4229	Cogenex Amniotic Membrane, per sq cm
Q4230	Cogenex Flowable Amnion, per 0.5 cc
Q4231	Corplex P, per cc
Q4232	Corplex, per sq cm
Q4233	SurFactor or NuDyn, per 0.5 cc
Q4234	XCellerate, per sq cm
Q4235	AMNIOREPAIR or AltiPly, per sq cm
Q4236	carePATCH, per sq cm
Q4237	Cryo-Cord, per sq cm
Q4238	Derm-Maxx, per sq cm
Q4239	Amnio-Maxx or Amnio-Maxx Lite, per sq cm
Q4240	CoreCyte, for topical use only, per 0.5 cc
Q4241	PolyCyte, for topical use only, per 0.5 cc

Q4242	AmnioCyte Plus, per 0.5 cc
Q4245	AmnioText, per cc
Q4246	CoreText or ProText, per cc
Q4247	Amniotext patch, per sq cm
Q4248	Dermacyte Amniotic Membrane Allograft, per sq cm
Q4249	AMNIPLY, for topical use only, per sq cm
Q4250	AmnioAmp-MP, per sq cm
Q4254	Novafix DL, per sq cm
Q4255	REGUaRD, for topical use only, per sq cm
Q4256	MLG-Complete, per sq cm
Q4257	Relese, per sq cm
Q4258	Enverse, per sq cm
Q4262	Dual Layer Impax Membrane, per sq cm
Q4263	SurGraft TL, per sq cm
Q4264	Cocoon Membrane, per sq cm
Q4265	Neostim TL, Per Square Centimeter
Q4266	Neostim Membrane, Per Square Centimeter
Q4267	Neostim DL, Per Square Centimeter
Q4268	Surgraft FT, Per Square Centimeter
Q4269	Surgraft XT, Per Square Centimeter
Q4270	Complete SL, Per Square Centimeter
Q4271	Complete FT, Per Square Centimeter
Q4279	Vendaje ac, per square centimeter
Q4287	Dermabind dl, per square centimeter
Q4288	Dermabind ch, per square centimeter
Q4289	Revoshield + amniotic barrier, per square centimeter
Q4290	Membrane wrap-hydro, per square centimeter
Q4291	Lamellas xt, per square centimeter
Q4292	Lamellas, per square centimeter
Q4293	Acesso dl, per square centimeter
Q4294	Amnio quad-core, per square centimeter
Q4295	Amnio tri-core amniotic, per square centimeter
Q4296	Rebound matrix, per square centimeter
Q4297	Emerge matrix, per square centimeter
Q4298	Amnicore pro, per square centimeter
Q4299	Amnicore pro+, per square centimeter
Q4300	Acesso tl, per square centimeter
Q4301	Activate matrix, per square centimeter
Q4302	Complete aca, per square centimeter
Q4303	Complete aa, per square centimeter
Q4304	Grafix plus, per square centimeter
Q4311	Acesso, per square centimeter
Q4312	Acesso ac, per square centimeter
Q4313	Dermabind fm, per square centimeter
Q4314	Reeva ft, per square centimeter
Q4315	Regenelink amniotic membrane allograft, per square centimeter
Q4316	Amchoplast, per square centimeter
Q4317	Vitograft, per square centimeter
Q4318	E-graft, per square centimeter
Q4319	Sanograft, per square centimeter
Q4320	Pellograft, per square centimeter
Q4321	Renograft, per square centimeter
Q4326	Woundplus, per square centimeter

Q4327	Duoamnion, per square centimeter
Q4328	Most, per square centimeter
Q4329	Singlay, per square centimeter
Q4330	Total, per square centimeter
Q4331	Axolotl graft, per square centimeter
Q4332	Axolotl dualgraft, per square centimeter
Q4333	Ardeograft, per square centimeter
Q4334	Amnioplast 1, per square centimeter
Q4335	Amnioplast 2, per square centimeter
Q4336	Artacent c, per square centimeter
Q4337	Artacent trident, per square centimeter
Q4338	Artacent velos, per square centimeter
Q4339	Artacent vericlen, per square centimeter
Q4340	Simpligraft, per square centimeter
Q4341	Simplimax, per square centimeter
Q4342	Theramend, per square centimeter
Q4343	Dermacyte ac matrix amniotic membrane allograft, per square centimeter
Q4344	Tri-membrane wrap, per square centimeter
Q4345	Matrix hd allograft dermis, per square centimeter
Q4346	Shelter dm matrix, per square centimeter
Q4347	Rampart dl matrix, per square centimeter
Q4348	Sentry sl matrix, per square centimeter
Q4349	Mantle dl matrix, per square centimeter
Q4350	Palisade dm matrix, per square centimeter
Q4351	Enclose tl matrix, per square centimeter
Q4352	Overlay sl matrix, per square centimeter
Q4353	Xceed tl matrix, per square centimeter
Q4322	Caregraft, per square centimeter
Q4323	Alloply, per square centimeter
Q4324	Amniotx, per square centimeter
Q4325	Acapatch, per square centimeter
A2001	Innovamatrix AC Per Sq Cm
A2002	Mirragen Advanced Wound Matrix Per Sq Cm
A2004	Xcellistem Per Sq Cm
A2005	Microlyte Matrix Per Sq Cm
A2006	Novosorb Synpath Dermal Matrix Per Sq Cm
A2007	Restrata Per Sq Cm
A2008	Theragenesis Per Sq Cm
A2009	Symphony Per Sq Cm
A2010	Apis Per Sq Cm
A2011	Supra SDRM, per sq cm
A2013	Innovamatrix FS, per sq cm
A2019	Kerecis Omega3 Marigen Shield, Per Square Centimeter
A2020	Ac5 Advanced Wound System (Ac5)
A2021	Neomatrix, Per Square Centimeter

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APPROVAL HISTORY

02/12/2025	Policy revised. Removed general age restriction, removed products AlloMax and Biobrane L, added products StrataGraft for burn wounds and DermACELL AWM for VSUs. Updated multiple product indications to align more stringently with manufacturer-stated indications. IRO peer reviewed on January 29, 2025, by a practicing physician board certified in plastic surgery.
08/14/2024	Policy reviewed. Added coverage criteria indications for the use of skin substitutes in breast reconstruction and in the treatment of dystrophic epidermolysis bullosa. Added specific skin substitutes to already covered indications. IRO Peer Reviewed on July 31, 2024, by a practicing physician board certified in Plastic Surgery.
04/10/2024	Policy reviewed. No changes to coverage criteria. Updated Summary of Medical Evidence and References.
12/13/2023	Coding and Billing section updated.
04/13/2023	Policy reviewed. Criteria consolidated. Criteria specific to line of business removed. Coverage in case of acute burn updated. Coverage of EpiFix sheet form clarified. Coding updated. AMR Peer Review. Policy reviewed on April 4, 2023, by a practicing, board-certified physician in Wound Care.
02/09/2022	Policy reviewed, included Actigraft as non-covered.
12/08/2021	Policy reviewed; no changes to criteria; added HCPCS code Q4155 and removed Q4131; added national / specialty items from ASPS, ISBI, WHS SVS/APMA/SVM and updated references.
02/08/2021	Policy reviewed, clinical criteria updated with additional and comprehensive wound specific recommendations for burns, diabetic foot ulcers and venous leg ulcers. Coding updated with all products available. Contraindications and limitations updated; guidelines and references sections revised, condensed, and updated. AMR Peer Review. Policy reviewed on January 13, 2021, by an Advanced Medical Reviews (AMR) practicing, board-certified physician in Plastic Surgery.
04/23/2020	New policy. AMR Peer Review. Policy reviewed on January 3, 2020, by an Advanced Medical Reviews (AMR) practicing, board-certified physician in Plastic Surgery.

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