Molina Clinical Policy
Skin and Soft Tissue Substitutes
Policy No. 357

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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 2025).

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 2025).

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.

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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

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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

1. Skin substitute products that are listed above in the medically necessary section are ONLY approved for the covered indication. Any indications other than those noted above are considered **not medically necessary**

2. Skin 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 for ANY of the following indications:
   a. Decubitus ulcer treatment
   b. Continued treatment when the ulcer fails to heal by ≥ 50% within the first 6 weeks of treatment
   c. Treatment beyond 12 weeks regardless of wound status
   d. 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
   e. Retreatment of healed ulcers (those showing greater than 75% size reduction and smaller than 1cm^2)

3. 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
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
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

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Ascent
AxoBioMembrane
Axolotl Ambient or Axolotl Cryo
Axolotl Graft or Axolotl DualGraft
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
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)
Flow, PalinGen SportFlow, ProMatrX ACF)
Phoenix Wound Matrix
Polycyte
Procenta
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
Surederm
Surfactor
surgiGRAFT
SurgiMend
Talymed
TenSIX
TheraGenesis
Therion
TissueMend
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.

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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 through 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 2026). In 2023, RTI Surgical received IDE approval for Cortiva in breast reconstruction, the study is ongoing ([2]ClinicalTrials.gov 2026). In 2023, MTF Biologics received IDE approval for FlexHD in breast reconstruction, the study is ongoing (ClinicalTrials.gov 2025).

Randomized Controlled Trials

Arnaout et al. (2021) conducted a randomized controlled trial (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 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.

Systematic Reviews and Meta-Analyses

Glynou et al. (2024) completed a systematic review and network meta-analysis to evaluate complication rates associated with several ADMs used in implant-based breast reconstruction. The analysis synthesized outcomes across 51 studies involving 7,667 patients and nearly 12,000 breasts, comparing short- and long-term complication rates among specific ADM types. The included products comprised human-derived matrices such as AlloDerm (Freeze-Dried, Ready-To-Use, and unspecified), DermACELL, and FlexHD, as well as xenograft materials including SurgiMend (bovine), and porcine-derived matrices like Strattice, ARTIA, and Braxon. While overall complication profiles across ADM types were broadly similar, the analysis identified a notably higher risk profile for AlloDerm Freeze-Dried, which exhibited the highest rates of wound dehiscence (3.1%), implant failure (11.8%), and infections (11.0%). In contrast, AlloDerm Ready-To-Use demonstrated significantly lower complication rates, with the network meta-analysis confirming reduced risks of infection, explantation, and wound dehiscence compared to AlloDerm Freeze-Dried. Porcine-derived ADMs were associated with the highest rates of seroma formation (10.3%), hematoma (2.7%), and

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shared a similarly elevated infection rate (11.2%). Capsular contracture was infrequent across all ADM types, with no significant differences observed. Despite the variability in specific outcomes, the study concluded that most ADM products performed comparably, and that further high-quality, long-term comparative studies are needed to account for potential confounders such as patient characteristics, surgical technique, and provider experience.

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 deep partial-thickness 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 were 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 to 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/cm^2 per patient for Mepilex Ag and $0.56/cm^2 per patient for Suprathel. The authors concluded that both dressings were viable treatments for burn wounds.

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Systematic Reviews and Meta-Analyses

Susini et al. (2025) conducted a systematic review to evaluate biological skin substitutes (BSS) and tissue-engineered skin substitutes (TESS) for partial and full-thickness burns in pediatric patients. The review included 29 studies, which mostly consisted of observational and retrospective studies, case series, and small RCTs, for a total of 2676 patients. 12 studies evaluated BSS products, while 17 studies evaluated TESS products. Primary outcomes included healing time, burn size, measured as percentage of total body surface area (TBSA), perioperative complications, and technical or surgical outcomes. Among BSS patients, the mean age was 4 years old (range 1-17), the mean treated burn size was 22.9% TBSA (range 3-50%), and the weighted mean healing time was 15 days (range 10-26 days). Among TESS patients, the mean age was 6 years old (range 1-17), mean TBSA was 36.2% (range 3-73%), and the mean healing time was also 15 days (range 5-33). While the average healing time was similar between TESS and BSS, the mean TBSA was higher among TESS studies, which suggests its preferential use in more extensive burns. Complication rates were generally low (< 10%) and infection was the most frequent adverse event. Among TESS products, acellular matrices such as Integra and NovoSorb were associated with shorter healing times, whereas cellular products such as OrCel and Apligraf showed favorable long-term integration but were used in smaller case series. Overall, trends indicate comparable safety and efficacy profiles between BSS and TESS, with acellular substitutes being the most widely used in pediatric practice. The authors concluded that while BSS and TESS are safe and effective reconstructive options when autograft is contraindicated or unlikely to succed, the overall level of evidence remains low to moderate. Surgical debridement, early excision, and autograft skin replacement currently represents the gold standard for partial and full-thickness pediatric burns.

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 provides 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 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 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

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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.

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

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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 needed 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 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-

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epithelialization without drainage or dressing needs, confirmed at two consecutive visits two weeks apart. 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 = 0·235). 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 = 0·029). 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 = 0·223). 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.

Systematic Reviews and Meta-Analyses

Mathe et al. (2026) conducted a systematic review and meta-analysis to assess the outcomes and complications of skin allografts in the healing of DFUs and VLUs. The review included 19 RCTs for a total of 1303 participants. Biologic skin allografts included Theraskin, Apligraf, Amnioexcel, Amnioband, EpiCord, and EpiFix. 14 RCTs compared an allograft with standard care, while the remaining RCTs involved direct product comparisons or multiple product comparisons with standard care. Outcomes included complete wound closure, percent wound-area reduction, time to healing, and complications. Wound closure was measured as the proportion of ulcers that were completely closed by 12 weeks, while percent wound-area reduction was measured by decrease in wound surface area from baseline. Theraskin had the highest mean closure rate at 84.7%, followed by Amnioband at 83%, EpiCord at 81%, EpiFix at 80%, Apligraf at 54%, and Amnioexcel at 37.5%. Among the 3 allograft products with data on percent wound-area reduction, Amnioband was the highest, with a mean reduction of 88.9%, followed by Theraskin at 77.8% and EpiFix at 66%, but these differences were not statistically significant (p = 0.0601). Compared with standard of care, EpiFix

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had a mean wound closure advantage of 48%, followed by Amnioband at 46.5%, Theraskin at 40%, and Apligraf at 20.5%, and the advantage difference between products was not statistically significant (p = 0.0601). Adverse events included cellulitis, osteomyelitis, re-ulceration, amputation, bleeding, and infections outside the treated wound. Across the studies that reported on safety outcomes, allograft treated groups generally had fewer complications or adverse events than standard care groups; however, definitions of adverse events and reported methods varied substantially. Limitations include heterogeneity in ulcer type, baseline wound size, patient age, standard-care protocols, application schedules, and eligibility criteria. The authors concluded that all measured allografts significantly improved wound healing outcomes in DFUs and VLUEs compared to controls, with varying degrees of efficacy, and that the findings support the use of biologic skin allografts as an adjunct treatment for complex lower extremity wounds.

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 VLUs. The data analyzed was collected from 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.

Dystrophic Epidermolysis Bullosa
A retrospective clinical study conducted in Australia between 1977 and 1998 evaluated the use of Composite Cultured Skin (CCS), later known as OrCel, in seven pediatric patients with recessive dystrophic epidermolysis bullosa (RDEB) undergoing surgical release of mitten hand deformities. CCS was used alongside autografts and surgical flaps to cover wounds and donor sites following contracture release. The study found that CCS contributed to reduced autograft harvesting and demonstrated favorable healing at treated sites. In some cases, donor areas previously covered with CCS were successfully re-harvested in later procedures. While the time interval between surgeries did not significantly differ from those without CCS, outcomes were influenced by evolving surgical techniques, disease severity, and adherence to physical therapy. These findings, along with other clinical data, supported the FDA's March 2001 Humanitarian Device Exemption (HDE H990013) approval of OrCel for this rare EB indication (U.S. Food and Drug Administration. Summary of Safety and Probable Benefit: Composite Cultured Skin (OrCel), HDE H990013. Silver Spring (MD): FDA; 2001. Later that year, in September 2001, OrCel was granted Premarket Approval (PMA P010016, product code MGR) for the treatment of fresh, clean, split-thickness donor site wounds in burn patients. In 2006, the FDA issued an approvable letter for a supplemental HDE for a cryopreserved version of OrCel for the same RDEB indication, though final approval was not granted. OrCel has been evaluated in clinical studies for chronic wounds, including diabetic foot ulcers, but evidence remains limited. In a 2016 Cochrane review (Santema et al.), OrCel showed a non-significant trend toward improved healing, but the confidence interval was wide, and the quality of evidence was low.

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 ISBI highlighted that blood products and skin substitutes are extremely important for large early burn excisions.

The **Wound Healing Society (WHS)** published updated *WHS Guidelines Update: Diabetic Foot Ulcer Treatment Guidelines* (Lavery et al. 2024) that offered support for use of skin substitutes by reaffirming 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.

The 2024 **Wounds International** Consensus on Skin Substitutes recommends the use of biological matrices and tissue-engineered products for chronic wounds that fail to respond to standard care after four weeks. Developed by an international panel of wound care experts, the guideline clarifies product categories, defines appropriate use cases, and offers practical guidance for selecting and applying skin substitutes in clinical practice. It emphasizes the importance of extracellular matrix support in hard-to-heal wounds and aims to improve patient outcomes through informed, evidence-based use of advanced therapies.

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

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

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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)

Code	Description
C9250	Human plasma fibrin sealant, vapor-heated, solvent-detergent (artiss), 2 ml
Q4101	Apligraf, per square centimeter (add-on, list separately in addition to primary procedure)
Q4102	Oasis wound matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4103	Oasis burn matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4104	Integra bilayer matrix wound dressing (bmwd), per square centimeter (add-on, list separately in addition to primary procedure)
Q4105	Integra dermal regeneration template (drt) or integra omnigraft dermal regeneration matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4107	Graftjacket, per square centimeter (add-on, list separately in addition to primary procedure)
Q4108	Integra matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4121	Theraskin, per square centimeter (add-on, list separately in addition to primary procedure)
Q4122	Dermacell, dermacell awm or dermacell awm porous, per square centimeter (add-on, list separately in addition to primary procedure)
Q4124	Oasis ultra tri-layer wound matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4132	Grafix core and grafixpl core, per square centimeter (add-on, list separately in addition to primary procedure)
Q4133	Grafix prime, grafixpl prime, stravix and stravixpl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4151	Amnioband or guardian, per square centimeter (add-on, list separately in addition to primary procedure)
Q4168	Amnioband, 1 mg
Q4182	Transcyte, per square centimeter (add-on, list separately in addition to primary procedure)
Q4186	Epifix, per square centimeter (add-on, list separately in addition to primary procedure)
A2012	Suprathel, per square centimeter (add-on, list separately in addition to primary procedure)
A4100	Non-sheet form skin substitute, fda cleared as a device, not otherwise specified (list in addition to primary procedure)
Q4110	Primatrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4111	Gammagraft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4112	Cymetra, injectable, 1 cc
Q4113	Graftjacket xpress, injectable, 1 cc
Q4114	Integra flowable wound matrix, injectable, 1 cc
Q4115	Alloskin, per square centimeter (add-on, list separately in addition to primary procedure)
Q4116	Alloderm, per square centimeter (add-on, list separately in addition to primary procedure)
Q4117	Hyalomatrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4118	Matristem micromatrix, 1 mg
Q4123	Alloskin rt, per square centimeter (add-on, list separately in addition to primary procedure)
Q4125	Arthroflex, per square centimeter (add-on, list separately in addition to primary procedure)
Q4126	Memoderm, dermaspan, tranzgraft or integuply, per square centimeter (add-on, list separately in addition to primary procedure)
Q4127	Talymed, per square centimeter (add-on, list separately in addition to primary procedure)
Q4128	Flex hd, or allopatch hd, per square centimeter (add-on, list separately in addition to primary procedure)

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Q4130	Strattice tm, per square centimeter (add-on, list separately in addition to primary procedure)
Q4134	Hmatrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4135	Mediskin, per square centimeter (add-on, list separately in addition to primary procedure)
Q4136	Ez-derm, per square centimeter (add-on, list separately in addition to primary procedure)
Q4137	Amnioexcel, amnioexcel plus or biodexcel, per square centimeter (add-on, list separately in addition to primary procedure)
Q4138	Biodfence dryflex, per square centimeter (add-on, list separately in addition to primary procedure)
Q4139	Amniomatrix or biodmatrix, injectable, 1 cc
Q4140	Biodfence, per square centimeter (add-on, list separately in addition to primary procedure)
Q4141	Alloskin ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4142	Xcm biologic tissue matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4143	Repriza, per square centimeter (add-on, list separately in addition to primary procedure)
Q4145	Epifix, injectable, 1 mg
Q4146	Tensix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4147	Architect, architect px, or architect fx, extracellular matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4148	Neox cord 1k, neox cord rt, or clarix cord 1k, per square centimeter (add-on, list separately in addition to primary procedure)
Q4149	Excellagen, 0.1 cc
Q4150	Allowrap ds or dry, per square centimeter (add-on, list separately in addition to primary procedure)
Q4152	Dermapure, per square centimeter (add-on, list separately in addition to primary procedure)
Q4153	Dermavest and plurivest, per square centimeter (add-on, list separately in addition to primary procedure)
Q4154	Biovance, per square centimeter (add-on, list separately in addition to primary procedure)
Q4155	Neoxflo or clarixflo, 1 mg
Q4156	Neox 100 or clarix 100, per square centimeter (add-on, list separately in addition to primary procedure)
Q4157	Revitalon, per square centimeter (add-on, list separately in addition to primary procedure)
Q4158	Kerecis omega3, per square centimeter (add-on, list separately in addition to primary procedure)
Q4159	Affinity, per square centimeter (add-on, list separately in addition to primary procedure)
Q4160	Nushield, per square centimeter (add-on, list separately in addition to primary procedure)
Q4161	Bio-connekt wound matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4162	Woundex flow, bioskin flow, 0.5 cc
Q4163	Woundex, bioskin, per square centimeter (add-on, list separately in addition to primary procedure)
Q4164	Helicoll, per square centimeter (add-on, list separately in addition to primary procedure)
Q4165	Keramatrix or kerasorb, per square centimeter (add-on, list separately in addition to primary procedure)
Q4166	Cytal, per square centimeter (add-on, list separately in addition to primary procedure)
Q4167	Truskin, per square centimeter (add-on, list separately in addition to primary procedure)
Q4169	Artacent wound, per square centimeter (add-on, list separately in addition to primary procedure)
Q4170	Cygnus, per square centimeter (add-on, list separately in addition to primary procedure)
Q4171	Interfyl, 1 mg
Q4173	Palingen or palingen xplus, per square centimeter (add-on, list separately in addition to primary procedure)
Q4174	Palingen or promatrx, 0.36 mg per 0.25 cc
Q4175	Miroderm, per square centimeter (add-on, list separately in addition to primary procedure)
Q4176	Neopatch or therion, per square centimeter (add-on, list separately in addition to primary procedure)
Q4177	Floweramnioflo, 0.1 cc
Q4178	Floweramniopatch, per square centimeter (add-on, list separately in addition to primary procedure)
Q4179	Flowerderm, per square centimeter (add-on, list separately in addition to primary procedure)
Q4180	Revita, per square centimeter (add-on, list separately in addition to primary procedure)
Q4181	Amnio wound, per square centimeter (add-on, list separately in addition to primary procedure)
Q4183	Surgigraft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4184	Cellesta or cellesta duo, per square centimeter (add-on, list separately in addition to primary procedure)

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Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4187	Epicord, per square centimeter (add-on, list separately in addition to primary procedure)
Q4188	Amnioarmor, per square centimeter (add-on, list separately in addition to primary procedure)
Q4189	Artacent ac, 1 mg
Q4190	Artacent ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4191	Restorigin, per square centimeter (add-on, list separately in addition to primary procedure)
Q4192	Restorigin, 1 cc
Q4193	Coll-e-derm, per square centimeter (add-on, list separately in addition to primary procedure)
Q4194	Novachor, per square centimeter (add-on, list separately in addition to primary procedure)
Q4195	Puraply, per square centimeter (add-on, list separately in addition to primary procedure)
Q4196	Puraply am, per square centimeter (add-on, list separately in addition to primary procedure)
Q4197	Puraply xt, per square centimeter (add-on, list separately in addition to primary procedure)
Q4198	Genesis amniotic membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4199	Cygnus matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4200	Skin te, per square centimeter (add-on, list separately in addition to primary procedure)
Q4201	Matrion, per square centimeter (add-on, list separately in addition to primary procedure)
Q4202	Keroxx (2.5g/cc), 1cc
Q4203	Derma-gide, per square centimeter (add-on, list separately in addition to primary procedure)
Q4204	Xwrap, per square centimeter (add-on, list separately in addition to primary procedure)
Q4205	Membrane graft or membrane wrap, per square centimeter (add-on, list separately in addition to primary procedure)
Q4206	Fluid flow or fluid gf, 1 cc
Q4208	Novafix, per square cenitmeter (add-on, list separately in addition to primary procedure)
Q4209	Surgraft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4211	Amnion bio or axobiomembrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4212	Allogen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta cord, per square centimeter (add-on, list separately in addition to primary procedure)
Q4215	Axolotl ambient or axolotl cryo, 0.1 mg
Q4216	Artacent cord, per square centimeter (add-on, list separately in addition to primary procedure)
Q4217	Woundfix, biowound, woundfix plus, biowound plus, woundfix xplus or biowound xplus, per square centimeter (add-on, list separately in addition to primary procedure)
Q4218	Surgicord, per square centimeter (add-on, list separately in addition to primary procedure)
Q4219	Surgigraft-dual, per square centimeter (add-on, list separately in addition to primary procedure)
Q4220	Bellacell hd or surederm, per square centimeter (add-on, list separately in addition to primary procedure)
Q4221	Amniowrap2, per square centimeter (add-on, list separately in addition to primary procedure)
Q4222	Progenamatrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4224	Human health factor 10 amniotic patch (hhf10-p), per square centimeter (add-on, list separately in addition to primary procedure)
Q4225	Amniobind or dermabind tl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4226	Myown skin, includes harvesting and preparation procedures, per square centimeter
Q4227	Amniocore, per square centimeter (add-on, list separately in addition to primary procedure)
Q4229	Cogenex amniotic membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4230	Cogenex flowable amnion, per 0.5 cc
Q4232	Corplex, per square centimeter (add-on, list separately in addition to primary procedure)
Q4233	Surfactor or nudyn, per 0.5 cc
Q4234	Xcellerate, per square centimeter (add-on, list separately in addition to primary procedure)
Q4235	Amniorepair or altiply, per square centimeter (add-on, list separately in addition to primary procedure)
Q4236	Carepatch, per square centimeter (add-on, list separately in addition to primary procedure)

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Q4237	Cryo-cord, per square centimeter (add-on, list separately in addition to primary procedure)
Q4238	Derm-maxx, per square centimeter (add-on, list separately in addition to primary procedure)
Q4239	Amnio-maxx or amnio-maxx lite, per square centimeter (add-on, list separately in addition to primary procedure)
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 square centimeter (add-on, list separately in addition to primary procedure)
Q4248	Dermacyte amniotic membrane allograft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4249	Amniply, for topical use only, per square centimeter (add-on, list separately in addition to primary procedure)
Q4250	Amnioamp-mp, per square centimeter (add-on, list separately in addition to primary procedure)
Q4251	Vim, per square centimeter (add-on, list separately in addition to primary procedure)
Q4253	Zenith amniotic membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4259	Celera dual layer or celera dual membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4260	Signature apatch, per square centimeter (add-on, list separately in addition to primary procedure)
Q4261	Tag, per square centimeter (add-on, list separately in addition to primary procedure)
Q4285	Nudyn dl or nudyn dl mesh, per square centimeter (add-on, list separately in addition to primary procedure)
Q4286	Nudyn sl or nudyn slw, per square centimeter (add-on, list separately in addition to primary procedure)
Q4252	Vendaje, per square centimeter (add-on, list separately in addition to primary procedure)
Q4254	Novafix dl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4255	Reguard, for topical use only, per square centimeter (add-on, list separately in addition to primary procedure)
Q4256	Mlg-complete, per square centimeter (add-on, list separately in addition to primary procedure)
Q4257	Relese, per square centimeter (add-on, list separately in addition to primary procedure)
Q4258	Enverse, per square centimeter (add-on, list separately in addition to primary procedure)
Q4262	Dual layer impax membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4263	Surgraft tl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4264	Cocoon membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4265	Neostim tl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4266	Neostim membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4267	Neostim dl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4268	Surgraft ft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4269	Surgraft xt, per square centimeter (add-on, list separately in addition to primary procedure)
Q4270	Complete sl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4272	Esano a, per square centimeter (add-on, list separately in addition to primary procedure)
Q4273	Esano aaa, per square centimeter (add-on, list separately in addition to primary procedure)
Q4274	Esano ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4275	Esano aca, per square centimeter (add-on, list separately in addition to primary procedure)
Q4276	Orion, per square centimeter (add-on, list separately in addition to primary procedure)
Q4278	Epieffect, per square centimeter (add-on, list separately in addition to primary procedure)
Q4271	Complete ft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4279	Vendaje ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4280	Xcell amnio matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4281	Barrera sl or barrera dl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4282	Cygnus dual, per square centimeter (add-on, list separately in addition to primary procedure)

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Q4283	Biovance tri-layer or biovance 3l, per square centimeter (add-on, list separately in addition to primary procedure)
Q4284	Dermabind sl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4287	Dermabind dl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4288	Dermabind ch, per square centimeter (add-on, list separately in addition to primary procedure)
Q4289	Revoshield + amniotic barrier, per square centimeter (add-on, list separately in addition to primary procedure)
Q4290	Membrane wrap-hydro, per square centimeter (add-on, list separately in addition to primary procedure)
Q4291	Lamellas xt, per square centimeter (add-on, list separately in addition to primary procedure)
Q4292	Lamellas, per square centimeter (add-on, list separately in addition to primary procedure)
Q4293	Acesso dl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4294	Amnio quad-core, per square centimeter (add-on, list separately in addition to primary procedure)
Q4295	Amnio tri-core amniotic, per square centimeter (add-on, list separately in addition to primary procedure)
Q4296	Rebound matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4297	Emerge matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4298	Amniocore pro, per square centimeter (add-on, list separately in addition to primary procedure)
Q4299	Amniocore pro+, per square centimeter (add-on, list separately in addition to primary procedure)
Q4300	Acesso tl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4301	Activate matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4302	Complete aca, per square centimeter (add-on, list separately in addition to primary procedure)
Q4303	Complete aa, per square centimeter (add-on, list separately in addition to primary procedure)
Q4304	Grafix plus, per square centimeter (add-on, list separately in addition to primary procedure)
Q4305	American amnion ac tri-layer, per square centimeter (add-on, list separately in addition to primary procedure)
Q4306	American amnion ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4307	American amnion, per square centimeter (add-on, list separately in addition to primary procedure)
Q4308	Sanopellis, per square centimeter (add-on, list separately in addition to primary procedure)
Q4309	Via matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4310	Procenta, per 100 mg
Q4354	Palingen dual-layer membrane and dual-layer palingen x-membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4360	Amchoplast fd, per square centimeter (add-on, list separately in addition to primary procedure)
Q4311	Acesso, per square centimeter (add-on, list separately in addition to primary procedure)
Q4312	Acesso ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4313	Dermabind fm, per square centimeter (add-on, list separately in addition to primary procedure)
Q4314	Reeva ft, per square cenitmeter (add-on, list separately in addition to primary procedure)
Q4315	Regenelink amniotic membrane allograft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4316	Amchoplast, per square centimeter (add-on, list separately in addition to primary procedure)
Q4317	Vitograft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4318	E-graft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4319	Sanograft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4320	Pellograft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4321	Renograft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4326	Woundplus, per square centimeter (add-on, list separately in addition to primary procedure)
Q4327	Duoamnion, per square centimeter (add-on, list separately in addition to primary procedure)
Q4328	Most, per square centimeter (add-on, list separately in addition to primary procedure)
Q4329	Singlay, per square centimeter (add-on, list separately in addition to primary procedure)
Q4330	Total, per square centimeter (add-on, list separately in addition to primary procedure)
Q4331	Axolotl graft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4332	Axolotl dualgraft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4333	Ardeograft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4334	Amnioplast 1, per square centimeter (add-on, list separately in addition to primary procedure)

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Q4335	Amnioplast 2, per square centimeter (add-on, list separately in addition to primary procedure)
Q4336	Artacent c, per square centimeter (add-on, list separately in addition to primary procedure)
Q4337	Artacent trident, per square centimeter (add-on, list separately in addition to primary procedure)
Q4338	Artacent velos, per square centimeter (add-on, list separately in addition to primary procedure)
Q4339	Artacent vericlen, per square centimeter (add-on, list separately in addition to primary procedure)
Q4340	Simpligraft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4341	Simplimax, per square centimeter (add-on, list separately in addition to primary procedure)
Q4342	Theramend, per square centimeter (add-on, list separately in addition to primary procedure)
Q4343	Dermacyte ac matrix amniotic membrane allograft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4344	Tri-membrane wrap, per square centimeter (add-on, list separately in addition to primary procedure)
Q4345	Matrix hd allograft dermis, per square centimeter (add-on, list separately in addition to primary procedure)
Q4346	Shelter dm matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4347	Rampart dl matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4348	Sentry sl matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4349	Mantle dl matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4350	Palisade dm matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4351	Enclose tl matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4352	Overlay sl matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4353	Xceed tl matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4322	Caregraft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4323	Alloply, per square centimeter (add-on, list separately in addition to primary procedure)
Q4324	Amniotx, per square centimeter (add-on, list separately in addition to primary procedure)
Q4325	Acapatch, per square centimeter (add-on, list separately in addition to primary procedure)
A2001	Innovamatrix ac, per square centimeter (add-on, list separately in addition to primary procedure)
A2002	Mirragen advanced wound matrix, per square centimeter (add-on, list separately in addition to primary procedure)
A2004	Xcellistem, 1 mg
A2005	Microlyte matrix, per square centimeter (add-on, list separately in addition to primary procedure)
A2006	Novosorb synpath dermal matrix, per square centimeter (add-on, list separately in addition to primary procedure)
A2007	Restrata, per square centimeter (add-on, list separately in addition to primary procedure)
A2008	Theragenesis, per square centimeter (add-on, list separately in addition to primary procedure)
A2009	Symphony, per square centimeter (add-on, list separately in addition to primary procedure)
A2010	Apis, per square centimeter (add-on, list separately in addition to primary procedure)
A2011	Supra sdrm, per square centimeter (add-on, list separately in addition to primary procedure)
A2013	Innovamatrix fs, per square centimeter (add-on, list separately in addition to primary procedure)
A2014	Omeza collagen matrix, per 100 mg
A2015	Phoenix wound matrix, per square centimeter (add-on, list separately in addition to primary procedure)
A2016	Permeaderm b, per square centimeter (add-on, list separately in addition to primary procedure)
A2017	Permeaderm glove, each
A2018	Permeaderm c, per square centimeter (add-on, list separately in addition to primary procedure)
A2022	Innovaburn or innovamatrix xl, per square centimeter (add-on, list separately in addition to primary procedure)
A2023	Innovamatrix pd, 1 mg
A2024	Resolve matrix or xenopatch, per square centimeter (add-on, list separately in addition to primary procedure)
A2025	Miro3d, per cubic centimeter (add-on, list separately in addition to primary procedure)
A2026	Restrata minimatrix, 5 mg
A2027	Matriderm, per square centimeter (add-on, list separately in addition to primary procedure)
A2028	Micromatrix flex, per mg
A2029	Mirotract wound matrix sheet, per cubic centimeter (add-on, list separately in addition to primary procedure)

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A2019	Kerecis omega3 marigen shield, per square centimeter (add-on, list separately in addition to primary procedure)
A2020	Ac5 advanced wound system (ac5)
A2021	Neomatrix, per square centimeter (add-on, list separately in addition to primary procedure)
A2030	Miro3d fibers, per milligram
A2031	Mirodry wound matrix, per square centimeter (add-on, list separately in addition to primary procedure)
A2032	Myriad matrix, per square centimeter (add-on, list separately in addition to primary procedure)
A2033	Myriad morcells, 4 milligrams
A2034	Foundation drs solo, per square centimeter (add-on, list separately in addition to primary procedure)
A2035	Corplex p or theracor p or allacor p, per milligram
Q4355	Abiomend xplus membrane and abiomend xplus hydromembrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4356	Abiomend membrane and abiomend hydromembrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4357	Xwrap plus, per square centimeter (add-on, list separately in addition to primary procedure)
Q4358	Xwrap dual, per square centimeter (add-on, list separately in addition to primary procedure)
Q4359	Choriply, per square centimeter (add-on, list separately in addition to primary procedure)
Q4361	Epixpress, per square centimeter (add-on, list separately in addition to primary procedure)
Q4362	Cygnus disk, per square centimeter (add-on, list separately in addition to primary procedure)
Q4363	Amnio burgeon membrane and hydromembrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4364	Amnio burgeon xplus membrane and xplus hydromembrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4365	Amnio burgeon dual-layer membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4366	Dual layer amnio burgeon x-membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4367	Amniocore sl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4368	Amchothick, per square centimeter (add-on, list separately in addition to primary procedure)
Q4369	Amnioplast 3, per square centimeter (add-on, list separately in addition to primary procedure)
Q4372	Amchoplast excel, per square centimeter (add-on, list separately in addition to primary procedure)
Q4370	Aeroguard, per square centimeter (add-on, list separately in addition to primary procedure)
Q4371	Neoguard, per square centimeter (add-on, list separately in addition to primary procedure)
Q4373	Membrane wrap lite, per square centimeter (add-on, list separately in addition to primary procedure)
Q4376	Duograft aa, per square centimeter (add-on, list separately in addition to primary procedure)
Q4375	Duograft ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4377	Trigraft ft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4378	Renew ft matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4379	Amniodefend ft matrix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4380	Advograft one, per square centimeter (add-on, list separately in addition to primary procedure)
Q4382	Advograft dual, per square centimeter (add-on, list separately in addition to primary procedure)
Q4390	Ascendion, per square centimeter (add-on, list separately in addition to primary procedure)
Q4383	Axolotl graft ultra, per square centimeter (add-on, list separately in addition to primary procedure)
Q4384	Axolotl dualgraft ultra, per square centimeter (add-on, list separately in addition to primary procedure)
Q4391	Amnioplast double, per square centimeter (add-on, list separately in addition to primary procedure)
Q4386	Acesso trifaca, per square centimeter (add-on, list separately in addition to primary procedure)
Q4385	Apollo ft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4397	Summit aaa, per square centimeter (add-on, list separately in addition to primary procedure)
Q4387	Neothelium ft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4388	Neothelium 4l, per square centimeter (add-on, list separately in addition to primary procedure)
Q4389	Neothelium 4l+, per square centimeter (add-on, list separately in addition to primary procedure)
Q4395	Acelagraft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4396	Natalin, per square centimeter (add-on, list separately in addition to primary procedure)

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Q4392	Grafix duo, per square centimeter (add-on, list separately in addition to primary procedure)
Q4393	Surgraft ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4394	Surgraft aca, per square centimeter (add-on, list separately in addition to primary procedure)
Q4415	Alexiguard sl-t, per square centimeter (add-on, list separately in addition to primary procedure)
Q4416	Alexiguard tl-t, per square centimeter (add-on, list separately in addition to primary procedure)
Q4417	Alexiguard dl-t, per square centimeter (add-on, list separately in addition to primary procedure)
Q4402	Xwrap 2.0, per square centimeter (add-on, list separately in addition to primary procedure)
Q4403	Xwrap dual plus, per square centimeter (add-on, list separately in addition to primary procedure)
Q4404	Xwrap hydro plus, per square centimeter (add-on, list separately in addition to primary procedure)
Q4405	Xwrap fenestra plus, per square centimeter (add-on, list separately in addition to primary procedure)
Q4406	Xwrap fenestra, per square centimeter (add-on, list separately in addition to primary procedure)
Q4407	Xwrap tribus, per square centimeter (add-on, list separately in addition to primary procedure)
Q4408	Xwrap hydro, per square centimeter (add-on, list separately in addition to primary procedure)
Q4410	Amchomatrixdl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4398	Summit ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4399	Summit fx, per square centimeter (add-on, list separately in addition to primary procedure)
Q4414	Simplichor, per square centimeter (add-on, list separately in addition to primary procedure)
Q4412	Choriofix, per square centimeter (add-on, list separately in addition to primary procedure)
Q4411	Amniomatrixf4x, per square centimeter (add-on, list separately in addition to primary procedure)
Q4409	Amniomatrixf3x, per square centimeter (add-on, list separately in addition to primary procedure)
Q4413	Cygnus solo, per square centimeter (add-on, list separately in addition to primary procedure)
Q4400	Polygon3 membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4401	Absolv3 membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4418	Biolab membrane wrap flow, per square centimeter (add-on, list separately in addition to primary procedure)
Q4419	Biolab membrane wrap lite flow, per square centimeter (add-on, list separately in addition to primary procedure)
Q4420	NuForm, per sq cm (add-on, list separately in addition to primary procedure)
Q4421	Biolab membrane wrap solo, per square centimeter (add-on, list separately in addition to primary procedure)
Q4422	A/c wrap, per square centimeter (add-on, list separately in addition to primary procedure)
Q4423	Biolab tri-membrane wrap flow, per square centimeter (add-on, list separately in addition to primary procedure)
Q4424	Revive ft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4425	Revive tl, per square centimeter (add-on, list separately in addition to primary procedure)
Q4426	Dermabind tl + or dermabind tl x, per square centimeter (add-on, list separately in addition to primary procedure)
Q4427	Dermabind dl n or dermabind dl + or dermabind dl x, per square centimeter (add-on, list separately in addition to primary procedure)
Q4428	Dermabind sl n or dermabind sl + or dermabind sl x, per square centimeter (add-on, list separately in addition to primary procedure)
Q4429	Dermabind ch n or dermabind ch x, per square centimeter (add-on, list separately in addition to primary procedure)
Q4431	PMA skin substitute product, not otherwise specified (list in addition to primary procedure)
Q4432	510(k) skin substitute product, not otherwise specified (list in addition to primary procedure)
Q4433	361 HCT/P skin substitute product, not otherwise specified (list in addition to primary procedure)
Q4435	Renati membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4436	Renati ac membrane, per square centimeter (add-on, list separately in addition to primary procedure)
Q4437	Revival ac, per square centimeter (add-on, list separately in addition to primary procedure)
Q4438	Pretect, per square centimeter (add-on, list separately in addition to primary procedure)
Q4439	Instagraft, per square centimeter (add-on, list separately in addition to primary procedure)
Q4440	Curamatrix, per square centimeter (add-on, list separately in addition to primary procedure)
A2036	Cohealyx collagen dermal matrix, per square centimeter (add-on, list separately in addition to primary

	procedure)
A2037	G4derm Plus and Suprello, per ml
A2038	Marigen pacto, per square centimeter (add-on, list separately in addition to primary procedure)
A2039	Innovamatrix fd, per square centimeter (add-on, list separately in addition to primary procedure)
A2040	Microlyte painguard, per square centimeter
A2041	Foundation drs+ duo, per square centimeter
A2042	Foundation drs+ solo, per square centimeter
A2043	Biobrane, per square centimeter
A2044	Biobrane glove, each
A2045	Novashield or novogen wound matrix, per square centimeter
G0681	Application of a premarket approval (pma), 510(k), 361 human cells, tissues or cellular and tissue-based products (hct/p) non-sheet form skin substitute for a wound surface area up to 100 sq cm; first 25 sq cm or less of wound surface area
G0682	Application of a premarket approval (pma), 510(k), 361 human cells, tissues or cellular and tissue-based products (hct/p) non-sheet form skin substitute for a 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)
G0683	Application of a premarket approval (pma), 510(k), 361 human cells, tissues or cellular and tissue-based products (hct/p) non-sheet form skin substitute graft for a wound surface greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
G0684	Application of a premarket approval (pma), 510(k), 361 human cells, tissues or cellular and tissue-based products (hct/p) non-sheet form skin substitute graft for a wound surface 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)
A2046	Dermisphere hdrt, per square centimeter (add-on, list separately in addition to primary procedure)
A2047	Lacertamatrix, per square centimeter (add-on, list separately in addition to primary procedure)
A2048	Puraply mz, per milligram
A2049	Theracor, per square centimeter (add-on, list separately in addition to primary procedure)
Q4207	Carbon life, per square centimeter (add-on, list separately in addition to primary procedure)
Q4223	Dermabind sl optic, per square centimeter (add-on, list separately in addition to primary procedure)
Q4243	Amchomatrix, per square centimeter (add-on, list separately in addition to primary procedure)
A2050	Fibrillar collagen wound dressing, per milligram

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APPROVAL HISTORY

08/12/2026 Policy reviewed. No changes to coverage criteria.
02/11/2026 Policy reviewed. No changes to coverage criteria. Updated Summary of Medical Evidence and References.
08/13/2025 Policy reviewed. No changes to coverage criteria. Updated Summary of Medical Evidence and References.
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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