Bioengineered Skin and Soft Tissue Substitutes

Policy # 00572
Original Effective Date: 12/01/2017
Current Effective Date: 08/14/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Amniotic Membrane and Amniotic Fluid *is addressed separately in medical policy 00458.*

Note: This MP is not applicable to injection laryngoplasty for the treatment of vocal fold paralysis or paresis.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider breast reconstructive surgery using allogeneic acellular dermal matrix products* (including each of the following: AlloDerm®‡, AlloMend®‡, Cortiva®‡ [AlloMax™]‡, DermACELL™‡, DermaMatrix™‡, FlexHD®‡, FlexHD® Pliable™‡, Graftjacket®‡; to be **eligible for coverage.****

- When there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required,
- When there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis, or
- The inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed.

Based on review of available data, the Company may consider treatment of chronic, noninfected, full-thickness diabetic foot ulcers, which have not adequately responded following a 1-month period of conventional ulcer therapy, using the following tissue-engineered skin substitutes to be **eligible for coverage****:

- AlloPatch®‡ *- up to 6 weekly applications; if ulcer persists after initial applications and achieved greater than 50% wound closure, can approve up to 6 additional weekly applications
- Apligraf®‡ **- up to 5 applications over 5 weeks
- Dermagraft®‡ ** - up to 8 applications over 12 weeks
- Integra®‡ Omnigraft Dermal Regeneration Matrix (also known as Omnigraft) and Integra Flowable Wound Matrix- up to 2 applications total
- PriMatrix™‡- limited to one initial application and 2 additional weekly applications (up to a maximum of 3 applications total in 12 weeks) when evidence of wound healing is present (e.g., signs of epithelialization and reduction in ulcer size).

Based on review of available data, the Company may consider treatment of chronic, noninfected, partial- or full-thickness lower-extremity skin ulcers due to venous insufficiency, which have not adequately responded following a 1-month period of conventional ulcer therapy, using the following tissue-engineered skin substitutes to be **eligible for coverage.****

- Apligraf**- up to 5 applications over 5 weeks
- Oasis™‡ Wound Matrix***- up to 8 applications over 12 weeks.

Based on review of available data, the Company may consider treatment of dystrophic epidermolysis bullosa using the following tissue-engineered skin substitutes to be **eligible for coverage.****

- OrCel™‡ (for the treatment of mitten-hand deformity when standard wound therapy has failed and when provided in accordance with the humanitarian device exemption (HDE) specifications of the U.S. Food and Drug Administration [FDA])****

Based on review of available data, the Company may consider treatment of second- and third-degree burns using the following tissue-engineered skin substitutes to be **eligible for coverage.****

- Epicel®‡ (for the treatment of deep dermal or full-thickness burns comprising a total body surface area ≥30% when provided in accordance with the HDE specifications of the FDA)****
- Integra Dermal Regeneration Template™**

* Banked human tissue.
** FDA premarket approval.

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*** FDA 510(k) cleared.
**** FDA-approved under an HDE.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers all other uses of the bioengineered skin and soft tissue substitutes listed above, and when coverage criteria are not met, to be **investigational.***

Based on review of available data, the Company considers all other skin and soft tissue substitutes not listed above to be **investigational*** including but not limited to:

- ACell®‡ UBM Hydrated/Lyophilized Wound Dressing
- AlloSkin™‡
- AlloSkin™‡ RT
- Aongen™‡ Collagen Matrix
- Architect®‡ ECM, PX, FX
- ArthroFlex™‡ (Flex Graft)
- Atlas Wound Matrix
- Avagen Wound Dressing
- Biobrane®‡/Biobrane-L
- Bio-ConneKt®‡ Wound Matrix
- CollaCare®‡
- CollaCare®‡ Dental
- Collagen Wound Dressing (Oasis Research)
- CollaGUARD®‡
- CollaMend™‡
- CollaWound™‡
- Coll-e-derm
- Collexa®‡
- Collieva®‡

- Conexa™‡
- Coreleader Colla-Pad
- CorMatrix®‡
- Cymetra™ (Micronized AlloDerm™‡
- Cytal™‡ (previously MatriStem®)‡
- Dermadapt™‡ Wound Dressing
- Derma-gide
- DermaPure™‡
- DermaSpan™‡
- DressSkin
- Durepair Regeneration Matrix®‡
- Endoform Dermal Template™‡
- *ENDURA*Gen™‡
- Excellagen
- ExpressGraft™‡
- E-Z Derm™‡
- FlowerDerm™‡
- GammaGraft
- Geistlich Derma-Gide™‡
- Gentrix™‡ Surgical Matrix (previously MatriStem®‡ Surgical Matrix)
- Graftjacket®‡ Xpress, injectable
- Helicoll™‡
- Hyalomatrix®‡
- Hyalomatrix®‡ PA
- hMatrix®‡
- InnovaBurn®‡
- InnovaMatrix®‡
- InnovaMatrix®‡ XL
- Integra™‡ Bilayer Wound Matrix
- Integra®‡ Matrix Wound Dressing (previously Avagen)
- IntéguPly®‡
- Keramatrix®‡

- Kerecis™‡ Omega 3
- Keroxx™‡
- MatriDerm®‡
- Matrix HD™‡
- MicroMatrix®‡
- Miroderm®‡
- Miro3D
- Mediskin®‡
- MemoDerm™‡
- Microderm®‡ biologic wound matrix
- MyOwn skin
- NeoForm™‡
- NuCel
- Oasis®‡ Burn Matrix
- Oasis®‡ Ultra
- Ologen™‡ Collagen Matrix
- Omega3 Wound (originally Merigen wound dressing)
- Pelvicol®‡/PelviSoft®‡
- Permacol™‡
- Progenamatrix
- Puracol®‡ and Puracol®‡ Plus Collagen Wound Dressings
- PuraPly™‡ Wound Matrix (previously FortaDerm™)‡
- PuraPly™‡ AM (Antimicrobial Wound Matrix)
- Puros®‡ Dermis
- ReCell
- RegenePro™‡
- Repliform®‡
- Repriza™‡
- Resolve Matrix™‡
- SkinTE™‡
- StrataGraft®‡
- Strattice™‡ (xenograft)

- Suprathel®‡
- SurgiMend®‡
- Talymed®‡
- TenoGlide™‡
- TenSIX™‡ Acellular Dermal Matrix
- TissueMend
- TheraForm™‡ Standard/Sheet
- TheraSkin®‡
- TransCyte™‡
- TruSkin™‡
- Veritas®‡ Collagen Matrix
- Wound Matrix™‡
- XCM Biologic®‡ Tissue Matrix
- XenMatrix™‡ AB.

Policy Guidelines

Clinical input has indicated that the various acellular dermal matrix products used in breast reconstruction have similar efficacy. The products listed are those that have been identified for use in breast reconstruction. Additional acellular dermal matrix products may become available for this indication.

Non-healing of diabetic wounds is defined as an ulcer that fails to demonstrate > 50% wound area reduction after a minimum of 4 weeks of standard wound therapy.

All ulcers subjected to sustained or frequent pressure and stress (ie, pressure-related heel ulcers or medial/lateral foot ulcers) or repetitive moderate pressure (plantar foot ulcers) benefit from pressure reduction, which is accomplished with mechanical offloading. Offloading devices include total contact casts, cast walkers, shoe modifications, and other devices to assist in ambulation.

In published study, AlloPatch was applied weekly for up to 12 weeks. At 6 weeks 65% of the treated diabetic foot ulcers healed (compared with 5% that received standard of care alone). If the patient did not achieve greater than 50% wound closure at 6 weeks, trial participants were withdrawn from

the study. At 12 weeks, the proportions of diabetic foot ulcers healed were 80% with AlloPatch and 20% with standard of care. Mean time to heal was 40 days for the AlloPatch group.

According to the manufacturer, the safety and the effectiveness of Apligraf have not been established for individuals receiving greater than 5 device applications.
Most studies of Dermagraft reported using up to 8 applications over 12 weeks.

Integra Omnigraft Dermal regeneration Matrix may need second application depending on the progress of wound, however 62% of individuals who received only a single Omnigraft application experienced healing of their wound.

Oasis Wound Matrix per study report had on average 8 applications with number needed to treat for complete wound closure 5 (95% CI ranged from 3-39).

Background/Overview

Skin and Soft Tissue Substitutes

Bioengineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (eg, dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. Acellular dermal matrix (ADM) products can differ in a number of ways, including as species source (human, bovine, porcine), tissue source (eg dermis, pericardium, intestinal mucosa), additives (eg antibiotics, surfactants), hydration (wet, freeze-dried), and required preparation (multiple rinses, rehydration).

Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species (eg, bovine, porcine). Skin substitutes may also be composed of dermal cells, epidermal cells, or a combination of dermal and epidermal cells, and may provide growth factors to stimulate healing. Bioengineered skin substitutes can be used as either temporary or permanent wound coverings.

Applications

There are a large number of potential applications for artificial skin and soft tissue products. One large category is nonhealing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal

adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, nonhealing lower-extremity wounds represent an ongoing risk for infection, sepsis, limb amputation, and death. Bioengineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

Other situations in which bioengineered skin products might substitute for living skin grafts include certain postsurgical states (eg, breast reconstruction) in which skin coverage is inadequate for the procedure performed, or for surgical wounds in individuals with compromised ability to heal. Second- and third-degree burns are another indication in which artificial skin products may substitute for auto- or allografts. Certain primary dermatologic conditions that involve large areas of skin breakdown (eg, bullous diseases) may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. ADM products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and other conditions.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

A large number of artificial skin and soft-tissue products are commercially available or in development. The following section summarizes commercially available skin and soft-tissue substitutes that have substantial relevant evidence on efficacy. Information on additional products is available in a 2020 Technical Brief on skin substitutes for treating chronic wounds that was commissioned by the Agency for Healthcare Research and Quality.

Acellular Dermal Matrix Products

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

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In 2017, FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps).

HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

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

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

- AlloDerm (LifeCell Corp.) is an ADM (allograft) tissue-replacement product created from native human skin and processed so that the basement membrane and cellular matrix remain intact. Originally, AlloDerm required refrigeration and rehydration before use. It is currently available in a ready-to-use product stored at room temperature. An injectable micronized form of AlloDerm (Cymetra) is available.
- Cortiva (previously marketed as AlloMax Surgical Graft and before that NeoForm) is an acellular non-cross-linked human dermis allograft.
- AlloPatch (Musculoskeletal Transplant Foundation) is an acellular human dermis allograft derived from the reticular layer of the dermis and marketed for wound care. This product is also marketed as FlexHD for postmastectomy breast reconstruction.

- FlexHD and the newer formulation FlexHD Pliable (Musculoskeletal Transplant Foundation) are acellular hydrated reticular dermis allograft derived from donated human skin.
- DermACELL (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL and PRESERVON.
- DermaMatrix (Synthes) is a freeze-dried ADM derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation.
- DermaPure (Tissue Regenix Wound Care) is a single-layer decellularized human dermal allograft for the treatment of acute and chronic wounds.
- GraftJacket Regenerative Tissue Matrix (also called GraftJacket Skin Substitute; KCI) is an acellular regenerative tissue matrix that has been processed from human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells while preserving dermal structure. GraftJacket Xpress is an injectable product.

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

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

In March 2021, FDA issued a Safety Communication to inform individuals, caregivers, and health care providers that certain ADM products used in implant-based breast reconstruction may have a higher chance for complications or problems. An FDA analysis of patient-level data from real-world

use of ADMs for implant-based breast reconstruction suggested that 2 ADMs—FlexHD and Allomax—may have a higher risk profile than others.

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

FDA product codes: FTM, OXF.

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

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

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

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

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

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

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

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

Oasis Wound Matrix (Cook Biotech) is a collagen scaffold (extracellular matrix) derived from porcine small intestinal submucosa. In 2000, it was cleared for marketing by FDA through the 510(k) process for the management of partial- and full-thickness wounds, including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds. FDA Product code: KGN.

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

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

TheraSkin (Soluble Systems) is a cryopreserved split-thickness human skin allograft composed of living fibroblasts and keratinocytes and an extracellular matrix in epidermal and dermal layers. TheraSkin is derived from human skin allograft supplied by tissue banks compliant with the

American Association of Tissue Banks and FDA guidelines. It is considered a minimally processed human cell, tissue, and cellular- and tissue-based product by FDA.

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

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

Biosynthetic Products
Biobrane/Biobrane-L (Smith & Nephew) is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially embedded into the film. The fabric creates a complex 3-dimensional structure of trifilament thread, which chemically binds collagen. Blood/sera clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs. FDA product code: FRO.

Integra Dermal Regeneration Template (also marketed as Omnigraft Dermal Regeneration Matrix; Integra LifeSciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It was approved by FDA for use in the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable because of the physiologic condition of the patient and for certain diabetic foot ulcers. Integra Matrix Wound Dressing and Integra Meshed Bilayer Wound Matrix are substantially equivalent skin substitutes and were cleared for marketing by FDA through the 510(k) process for other indications. Integra Bilayer Matrix Wound Dressing (Integra LifeSciences) is designed to be used in conjunction with negative pressure wound

therapy. The meshed bilayer provides a flexible wound covering and allows drainage of wound exudate. FDA product code: MDD.

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

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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

Breast Reconstruction
For individuals who are undergoing breast reconstruction who receive allogeneic ADM products, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life (QOL), and treatment-related morbidity. A systematic review found no difference in overall complication rates with ADM allograft compared with standard procedures for breast reconstruction. Reconstructions with ADM have been reported to

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

Tendon Repair
For individuals who are undergoing tendon repair who receive Graftjacket, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, QOL, and treatment-related morbidity. The RCT identified found improved outcomes with the Graftjacket ADM allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of individuals is needed to evaluate the consistency of the effect. The evidence is insufficient to determine the effects of the technology on health outcomes.

Surgical Repair of Hernias or Parastomal Reinforcement
For individuals who are undergoing surgical repair of hernias or parastomal reinforcement who receive acellular collagen-based scaffolds, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, QOL, and treatment-related morbidity. Several comparative studies including RCTs have shown no difference in outcomes between tissue-engineered skin substitutes and either standard synthetic mesh or no reinforcement. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

Diabetic Lower-Extremity Ulcers
For individuals who have diabetic lower-extremity ulcers who receive AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. RCTs have demonstrated the efficacy of AlloPatch (reticular ADM), Apligraf and Dermagraft (living cell therapy), and Integra (biosynthetic) over the standard of care (SOC). The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have diabetic lower-extremity ulcers who receive ADM products other than AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of individuals who only

required a single application of the ADM. Studies are needed to further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of GraftJacket, TheraSkin, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Lower-Extremity Ulcers due to Venous Insufficiency
For individuals who have lower-extremity ulcers due to venous insufficiency who receive Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. RCTs have demonstrated the efficacy of Apligraf living cell therapy and xenogenic Oasis Wound Matrix over the SOC. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have lower-extremity ulcers due to venous insufficiency who receive bioengineered skin substitutes other than Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and QOL. In a moderately large RCT, Dermagraft was not shown to be more effective than controls for the primary or secondary endpoints in the entire population and was only slightly more effective than controls (an 8%-15% increase in healing) in subgroups of individuals with ulcer duration of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of the xenogenic PriMatrix skin substitute versus the current SOC. The evidence is insufficient to determine the effects of the technology on health outcomes.

Dystrophic Epidermolysis Bullosa
For individuals who have dystrophic epidermolysis bullosa who receive OrCel, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, morbid events, and QOL. OrCel was approved under a humanitarian drug exemption for use in individuals with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. Outcomes have been reported in small series (eg, 5 individuals). The evidence is insufficient to determine the effects of the technology on health outcomes.

Deep Dermal Burns
For individuals who have deep dermal burns who receive bioengineered skin substitutes (ie, Epicel, Integra Dermal Regeneration Template), the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related morbidity. Overall, few skin substitutes have been approved, and the evidence is limited for each product. Epicel (living cell therapy) has received FDA approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. Comparative studies have demonstrated improved outcomes for biosynthetic skin substitute Integra Dermal Regeneration Template for the treatment of burns. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Clinical Input
Clinical input has been obtained on several occasions. The input considered ADM products to be medically necessary for breast reconstruction under select conditions and for the various products to be similar in efficacy. Input was mixed on the efficacy of xenogenic products for other indications. It was concluded that, based on the extensive data from case series and clinical input on the usefulness of this procedure in providing inferolateral support for breast reconstruction, this procedure was medically necessary for breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin post mastectomy skin flaps that are at risk of dehiscence or necrosis; or when the inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2016 Input
In response to requests, input was received from 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2016. Input was requested on the equivalency of products within the categories of amniotic membrane, living cell therapies, and biosynthetic skin substitutes for the treatment of diabetic foot ulcers and nonocular burns (biosynthetic only). Input on the equivalency of products within these categories was mixed.

2014 Input
In response to requests, input was received from 3 physician specialty societies and 4 academic medical centers while this policy was under review in 2014. In addition to questions on medical necessity for different indications, input was specifically requested on the equivalency of products within the different categories (eg, acellular dermal matrix [ADM], living cell therapy, xenogeneic collagen scaffold, amniotic membrane). Five reviewers addressed the use of ADM products for breast reconstruction and most considered the various ADM products (AlloDerm, AlloMax, DermaMatrix, FlexHD, Graftjacket) to have similar outcomes when used for breast reconstructive surgery, although differences in firmness and stretch of the products were noted. Six reviewers addressed questions on bioengineered skin and soft tissue substitutes for diabetic and venous lower-extremity ulcers. Responses were mixed, although most reviewers considered living cell therapies to be equivalent for these indications. Most reviewers did not consider xenogeneic ADM products (eg, PriMatrix) or amniotic membrane (eg, EpiFix) to be medically necessary for any indication.

2012 Input
In response to requests, input was received from 3 physician specialty societies and 2 academic medical centers while this policy was under review in 2012. Most reviewers supported the indications and products described in this policy. Input was requested on the use of an interpositional spacer after parotidectomy. Support for this indication was mixed. Some reviewers suggested use of other products and/or additional indications; however, the input on these products/indications was not uniform. Reviewers provided references for the additional indications; these were subsequently reviewed.

2009 Input
In response to requests, input was received from 1 physician specialty society (2 physicians) and 1 academic medical center while this policy was under review in 2009. All reviewers indicated that on

use of AlloDerm in breast reconstruction surgery should be available for use during breast reconstructive surgery.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence
In 2019, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems. The Institute recommended that clinicians "consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The Centers for Medicare & Medicaid Services (CMS) issued the following national coverage determination: porcine (pig) skin dressings are covered, if reasonable and necessary for the individual patient as an occlusive dressing for burns, donor sites of a homograft, and decubiti and other ulcers if the item is furnished on a different date of service as the primary service.

In 2019, CMS reported that it is finalizing the proposal to continue the policy established in CY 2018 to assign skin substitutes to the low cost or high-cost group. In addition, CMS presented several payment ideas to change how skin substitute products are paid and solicited comments on these ideas to be used for future rulemaking.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04537520[a]	Interventional Multi-Center Post Market Randomized Controlled Open-Label Clinical Trial Comparing Kerecis Omega3 Wound Versus SOC in Hard to Heal Diabetic Foot Wounds	229	Dec 2022
NCT04257370[a]	An Open Label, Randomized Controlled Study to Compare Healing of Severe Diabetic Foot Ulcers and Forefoot Amputations in Diabetics With and Without Moderate Peripheral Arterial Disease Treated With Kerecis Omega3 Wound and SOC vs. SOC Alone	330	Oct 2022
NCT02587403[a]	A Randomized, Prospective Study Comparing Fortiva™‡ Porcine Dermis vs. Strattice™‡ Reconstructive Tissue Matrix in Individuals Undergoing Complex Open Primary Ventral Hernia Repair	120	Jun 2022
Unpublished			
NCT02322554	The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers	50,000	Jan 2020 (status unknown)
NCT03935386[a]	A Prospective Randomized Clinical Trial Comparing Multi-layer Bandage Compression Therapy With and Without a Biologically Active Human Skin Allograft for the Treatment of Chronic Venous Leg Ulcers	100	Dec 2020 (status unknown)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 12/01/2017
Current Effective Date: 08/14/2023

09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. New policy.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. DermACELL and FlexHD Pliable added to medically necessary statement on breast reconstructive surgery. Integra Flowable Wound Matrix added to medically necessary statement on use of Integra Dermal Regeneration Template for diabetic lower-extremity ulcers. Several products added to investigational list.
01/01/2019	Coding update

Bioengineered Skin and Soft Tissue Substitutes

Policy # 00572
Original Effective Date: 12/01/2017
Current Effective Date: 08/14/2023

05/02/2019	Medical Policy Committee review
05/15/2019	Medical Policy Implementation Committee approval. FlexiGraft removed from investigational statement. This note was added "This MP is not applicable to injection laryngoplasty for the treatment of vocal fold paralysis or paresis."
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. No change to coverage.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. New investigational indications added.
01/07/2022	Coding Update
02/03/2022	Medical Policy Committee review
02/09/2022	Medical Policy Implementation Committee approval. MatriStem Surgical Matrix rebranded to Gentrix Surgical Matrix.
03/20/2022	Coding update
6/08/2022	Medical Policy Implementation Committee approval. AxoGuard Nerve Protector (AxoGen) removed from investigation list.
09/20/2022	Coding Update
09/28/2022	Coding Update
12/21/2022	Coding Update
01/05/2023	Medical Policy Committee review
01/11/2023	Medical Policy Implementation Committee approval. Time frames added for eligible products.
03/20/2023	Coding update
07/06/2023	Medical Policy Committee review
07/12/2023	Medical Policy Implementation Committee approval. Added ReCell as investigational. Removed PriMatrix and PriMatrix Dermal Repair Scaffold from investigational list and made PriMatrix eligible for diabetic foot ulcers with criteria.
09/20/2023	Coding update
09/27/2023	Added InnovaBurn®‡, InnovaMatrix®‡, InnovaMatrix®‡ XL. Miro3D, Resolve Matrix™‡, and Wound Matrix™‡ to the list of all other skin and soft tissue substitutes that are investigational and not listed in the eligible for coverage section.

Next Scheduled Review Date: 07/2024

Bioengineered Skin and Soft Tissue Substitutes

Policy # 00572
Original Effective Date: 12/01/2017
Current Effective Date: 08/14/2023

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	15271, 15272, 15273, 15274, 15275, 15276, 15277, 15278, 15777, 64910, 64912, 64999
HCPCS	A2002, A2004, A2005, A2006, A2007, A2008, A2009, A2010, A2011 A2012, A2013, A2014, A2015, A2016, A2017, A2018, A6460, A6461 C9354, C9356, C9358, C9360, C9363, C9364, Q4100, Q4101, Q4102, Q4103, Q4104, Q4105, Q4106, Q4107, Q4108, Q4110, Q4111, Q4112, Q4113, Q4114, Q4115, Q4116, Q4117, Q4118, Q4121, Q4122, Q4123,

	Q4124, Q4125, Q4126, Q4127, Q4128, Q4130, Q4134, Q4135, Q4136, Q4141, Q4142, Q4143, Q4146, Q4147, Q4149, Q4152, Q4158, Q4161, Q4164, Q4165, Q4166, Q4167, Q4175, Q4179, Q4180, Q4182, Q4193, Q4195, Q4196, Q4197, Q4200, Q4202, Q4203, Q4220, Q4222, Q4226, Q4238, Q4255 Delete code effective 01/01/2023: C1849 Add codes effective 04/01/2023: A2019, A2020, A2021 Add code effective 08/01/2023: C1832 Add codes effective 10/01/2023: A2022, A2023, A2024, A2025
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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