

Corporate Medical Policy

Bioengineered Skin and Tissue

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Description of Procedure or Service

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

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

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.

The preferred outcomes for the healing of lower-extremity ulcers and burn wounds are the percentage of patients with complete wound healing and the time to complete wound healing. The percentage of patients with 50% wound healing and time to 50% wound healing have also been considered appropriate outcomes for these conditions. The percent change in wound area at 4 weeks is predictive of complete healing at 12 weeks in patients with diabetic foot ulcers. Thus, minimal improvement at 30 days can be considered as an indicator that a wound is unlikely to heal in patients with comorbidities known to affect wound healing.

Peripheral nerve injuries may occur as a result of trauma or acute compression. The nerve injury may result in demyelination and/or axonal degeneration, which can disrupt sensory function, motor function or both in the injured nerve. Several methods of nerve grafting have been investigated when a large gap exists between the proximal and distal ends of the injured nerve. The use of autologous nerve grafts for bridging gaps in nerve continuity is the gold standard for nerve repair, however it requires the sacrifice of healthy nerves. Nerve allograft transplantation from cadavers offers an alternative without the morbidities associated with nerve autografts, but these grafts require appropriate immunosuppression. The limitations of nerve autografting and allografting have led to the engineering of processed, acellular nerve allografts and nerve guidance conduits. Acellular nerve grafts are processed to remove antigenic factors such as

Bioengineered Skin and Tissue

Schwann cells and myelin to reduce immunogenicity, while retaining the natural basement membrane and three-dimensional extra-cellular matrix to guide axonal regeneration. Nerve conduits, also known as nerve tubulization, involves the use of nonabsorbable or absorbable single-lumen tubes, designed to bridge the gap of a sectioned nerve. The tube serves to protect the nerve during nerve regeneration and guide the regenerating axons to the distal nerve stump. A closed tube system may also allow for accumulation of neurotropic factors.

Other situations in which bioengineered skin products might substitute for living skin grafts include certain postsurgical states (e.g., breast reconstruction) in which skin coverage is inadequate for the procedure performed, or for surgical wounds in patients with compromised ability to heal. Second- and third-degree burns are another indication in which artificial skin products may substitute for auto- or allografts. Certain primary dermatologic conditions that involve large areas of skin breakdown (e.g., bullous diseases) may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. Acellular dermal matrix 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.

Related policies:

- Amniotic Membrane and Amniotic Fluid Injections
- Growth Factors in Wound Healing
- Meniscal Allograft and Collagen Meniscus Implants
- Orthopedic Applications of Stem Cell Therapy
- Plugs for Fistula Repair

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for bioengineered skin and soft tissue substitutes when it is determined to be medically necessary because the medical criteria and guidelines shown below have been met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Bioengineered Skin and Tissue Products are covered

Breast reconstructive surgery using allogeneic acellular dermal matrix products* (including, but not limited to AlloDerm®, Cortiva® [AlloMax™], AlloMend®, DermACELL™, DermaMatrix™, FlexHD®, FlexHD® Pliable™, Graftjacket®) may be considered medically necessary.

Treatment of chronic, noninfected, full-thickness diabetic lower-extremity ulcers using the following tissue-engineered skin substitutes may be considered medically necessary:

- AlloPatch®*
- Apligraf®**
- Dermagraft®**
- Integra® Omnigraft Dermal Regeneration Matrix (also known as Omnigraft) and Integra Flowable Wound Matrix.

Bioengineered Skin and Tissue

NOTE: applications will be limited to no more than the following weekly applications per wound when the criteria above are met:

- Apligraf: 4 applications
- Dermagraft: 8 applications

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 may be considered medically necessary:

- Apligraf®**
- Oasis™ Wound Matrix***

Treatment of dystrophic epidermolysis bullosa using the following tissue-engineered skin substitutes may be considered medically necessary:

- 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])****

Treatment of second- and third-degree burns using the following tissue-engineered skin substitutes may be considered medically necessary:

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

* Banked human tissue.

** FDA premarket approval.

*** FDA 510(k) cleared.

**** FDA-approved under an HDE.

With the exception of products used within the scope of FDA indications for treatment of burns and rare skin conditions such as recessive dystrophic epidermolysis bullosa, FDA approval for a specific use does not define that product as non-investigational.

When Bioengineered Skin and Tissue Products are not covered

- A. The application of **Apligraf®** has not been proven medically effective and is therefore considered investigational for all applications not listed under “When Bioengineered Skin and Tissue Products are Covered,” including, but not limited to pressure sores and acute surgical wounds. BCBSNC does not pay for investigational services.

Apligraf® is contraindicated for use in the following situations:

1. The wounds are infected
2. The patient has a known allergy to bovine collagen
3. The patient has a known hypersensitivity to components in the product’s agarose shipping medium

- B. **Oasis® Wound Matrix** is contraindicated in the following situations:

1. The patient has a known allergy to porcine collagen
2. For any indications other than those listed above in the “When Covered” section of the policy

Bioengineered Skin and Tissue

- C. **Dermagraft®** is contraindicated for use in the following situations:
1. Ulcers that have signs of clinical infection
 2. Ulcers that have sinus tracts
 3. Patients with known hypersensitivity to bovine products
 4. For any indications other than those listed above in the "When Covered" section of the policy
 5. For the treatment of dystrophic epidermolysis bullosa. The manufacturer has withdrawn Dermagraft from HDE status for treatment of dystrophic epidermolysis bullosa.
- D. **Acellular Dermal Matrix Products** are considered investigational for all indications except those addressed in the "When Covered" section including but not limited to parotidectomy and recurrent hernia repair or other major abdominal cavity reconstruction.
- E. **Bioengineered skin and tissue products** are not covered for any indications other than those listed under "When Bioengineered Skin and Tissue Products are covered." Other bioengineered skin and tissue products have not been proven medically effective and are therefore considered investigational for all other applications. BCBSNC does not cover investigational services. **With the exception of products used within the scope of FDA indications for treatment of burns and rare skin conditions such as recessive dystrophic epidermolysis bullosa, FDA approval for a specific use does not define that product as non-investigational. The following list of products considered investigational may not be all-inclusive:**

ACell® UBM Hydrated Wound Dressing/ACell® UBM Lyophilized Wound Dressing - FDA approved xenograft. Indicated for use with partial and full thickness wounds and 2nd degree burns.

AlloSkin™ and **AlloSkin™ RT** - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated for use with partial and full thickness wounds.

Aongen™ Collagen Matrix - FDA approved collagen product. Indicated for use with partial and full thickness wounds and 2nd degree burns, oral wounds and skin ulcerations.

Architect® ECM, PX, FX - FDA approved matrix indicated for use as a wound dressing for the local management of moderately to heavy exuding wounds.

ArthroFlex™ (FlexGraft) - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated for shoulder reconstruction and Achilles tendon repair.

Atlas Wound Matrix - FDA approved xenograft. Indicated for use with partial and full thickness wounds and ulcerations.

Avagen Wound Dressing - FDA approved xenograft. Indicated for use with partial and full thickness wounds and 2nd degree burns and skin ulcerations.

Avance Nerve Graft (AxoGen, Inc.) - acellular, processed human peripheral nerve tissue proposed for the surgical repair of severed peripheral nerve discontinuities to support regeneration.

AxoGuard® Nerve Connector (Axogen/AxioGuard®) - Formerly marketed as Surgisis Nerve Cuff. FDA 510(k) approved xenograft indicated for peripheral nerve repair.

CollaCare® - bioactive wound dressing for management of chronic and acute wounds available in sponge, film and powder format

CollaCare® Dental - collagen matrix manufactured from purified type I collagen derived from bovine Achilles tendon

Collagen Wound Dressing (Oasis Research) - intact matrix naturally derived from porcine small intestinal submucosa, indicated for wound management

Bioengineered Skin and Tissue

Collaguard®/ Collieva® - FDA approved xenograft. Indicated for the management of superficial and deep wounds, including coverage of skin ulcers and temporary dermatoplasty in the case of lesion and burns.

Collamend™ - FDA approved xenograft indicated for hernia and abdominal wall repair.

CollaWound™ - FDA approved collagen product. Indicated for use with partial and full thickness wounds and 2nd degree burns and skin ulcerations.

Collexa® - FDA approved xenograft with polyurethane foam backing. Indicated for use with partial and full thickness wounds and 2nd degree burns and skin ulcerations.

Conexa™ - FDA approved xenograft indicated for the reinforcement of soft tissue repaired by sutures or suture anchors during tendon repair surgery including reinforcement of rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons.

Coreleader Colla-Pad - FDA approved xenograft. Indicated for use with partial and full thickness wounds, ulcerations and 2nd degree burns.

CorMatrix® - FDA approved xenograft indicated for use as an intracardiac patch for tissue repair.

Cymetra® (Micronized AlloDerm™) - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Described as an injectable micronized particulate form of AlloDerm, is indicated for the correction of soft-tissue defects requiring minimally invasive techniques, such as injection laryngoplasty.

Cytal™ (previously MatriStem®) - comprised of naturally-occurring urinary bladder matrix to maintain an intact epithelial basement membrane

DermADAPT™ Wound Dressing -FDA approved xenograft. Indicated for use with partial and full thickness wounds, ulcerations and 2nd degree burns.

Dermapure™ - decellularized dermal allograft produced from donated human tissue

DermaSpan™ - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated for the repair or replacement of damaged or inadequate integumental tissue (wound coverage). DermaSpan™ can also be used for supplemental support, protection, reinforcement or covering of tendon.

DressSkin

Durepair Regeneration Matrix®- FDA approved xenograft indicated for repair of defects in the dura mater.

Endoform Dermal Template™ - FDA approved xenograft indicated for partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns; and skin tears) and draining wounds

ENDURAgen™ -FDA approved xenograft indicated for soft tissue repair or reinforcement in plastic and reconstructive surgery of the face and head

Excellagen® - FDA approved xenograft indicated for management of wounds.

ExpressGraft™ - genetically enhanced tissue with anti-microbial factors

E-Z Derm™ - FDA approved xenograft for the treatment of partial-thickness burns and venous, diabetic, and pressure ulcers.

FlexiGraft® - demineralized natural bone fibers

GammaGraft - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated for the treatment of venous stasis ulcers; diabetic foot ulcers; full-thickness ulcers; Mohs surgery sites; skin graft donor sites; partial thickness wounds; burns; areas of dermabrasion; temporary coverage of exposed abdominal viscera, including small bowel and liver; exposed pericranium and cranium; fasciotomy sites

Bioengineered Skin and Tissue

GraftJacket® Xpress, injectable - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated for deep tunneling chronic wounds.

hMatrix® - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated to replace damaged or inadequate integumental tissue, wound covering, abdominal wall repair, breast reconstruction, soft tissue grafting in craniomaxillofacial applications.

Hyalomatrix® PA/ Jaloskin® - FDA approved bilayer of an esterified hyaluronan scaffold beneath a silicone membrane. The scaffold delivers hyaluronan to the wound bed, and the silicone membrane acts as a temporary epidermal barrier. The matrix is indicated as a staging treatment for burn wounds.

Integra™ Bilayer Wound Matrix – porous matrix of cross-linked bovine tendon collagen, glycosaminoglycan and semi-permeable polysiloxane that provides a scaffold for cellular invasion and capillary growth

MariGen™/Kerecis™ Omega3™ - fish skin acellular dermal graft

MatriDerm® - acellular dermal substitute

Matrix HD™ - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated for use in repair of tendon and muscle fascia.

Mediskin®- FDA approved in 2012. Xenograft wound matrix indicated as a temporary skin substitute in burns, abrasions, donor sites, decubitus and chronic ulcers.

MemoDerm™ - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated for use in repair of tendon and ligament repair as well a chronic diabetic foot ulcers.

Miroderm® biologic wound matrix – wound matrix product derived from porcine liver

NeoForm Dermis™ - Gamma-irradiated preserved human allograft dermis used in breast reconstruction

NeuraGen™ Nerve Guide (Integra LifeSciences Corp.) is proposed to be used in cases where a nerve is completely severed. It is a semi-permeable absorbable bovine collagen tube that is designed to be used as an interface for damaged nerves and the surrounding tissue by creating a conduit for axonal growth across the gap between the ends of the severed nerve.

NeuraWrap™ Nerve Protector (Integra LifeSciences Corp.) is an absorbable collagen implant that provides a non-constricting encasement for injured peripheral nerves for protection of the neural environment.

Oasis® Burn Matrix - FDA approved xenograft indicated for the treatment of partial-thickness burns. It is not indicated for treatment of third degree burns.

Oasis® Wound Matrix - intact matrix naturally derived from porcine small intestinal submucosa indicated for the management of wounds

Oasis® Ultra Tri-Layer Matrix - FDA approved xenograft derived from porcine small intestinal mucosa. It is indicated for the management of partial and full-thickness wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wound, trauma wounds, and draining wounds. This product is similar to Oasis® Wound Matrix but is in triple layer structure.

Pelvicol®/Pelvisoft® - FDA approved xenograft indicated for pelvic reconstruction.

Permacol™ - FDA approved xenograft indicated for soft tissue repair or reinforcement in plastic and reconstructive surgery of the face and head and inguinal hernia repair.

PriMatrix™ - FDA approved xenograft indicated for treatment of partial and full thickness wounds, pressure, diabetic, and venous ulcers, second-degree burns, surgical wounds-donor sites/grfts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence, trauma wounds-abrasions, lacerations, and skin tears, tunneled/undermined wounds, draining wounds.

PriMatrix® Dermal Repair Scaffold – derived from fetal bovine dermis rich in Type III collagen

Bioengineered Skin and Tissue

PuraPly™ Wound Matrix (previously FortaDerm™) – single layer fenestrated sheet of biocompatible porcine-derived collagen

PuraPly™ AM (Antimicrobial Wound Matrix) – collagen sheet coated with antimicrobial

Puros® Dermis - Regulated by RTI Biologics and the FDA guidelines for banked human tissue. Indicated for use in for the repair, replacement, reconstruction or augmentation of periodontal tissue.

RegenePro™ - purified Type I bovine collage provides matrix for tissue in-growth

Repliform® - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated for the repair or replacement of damaged or inadequate integumental tissue such to repair enteroceles, rectoceles and/or cystoceles and for pelvic floor reinforcement.

Repriza™ - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated for use in breast reconstruction, abdominal wall reconstruction, and augmentation of soft tissue irregularities.

StrataGraft® - viable, full-thickness product in development for severe burns and complex skin defects

Strattice™ - FDA approved xenograft indicated for the reinforcement of soft tissues repaired by sutures or suture anchors, during rotator cuff surgery. Indications for use also include the repair of hernias and/or body wall defects which require the use of reinforcing or bridging material to obtain the desired surgical outcome.

Suprathel® - synthetic one-time application wound and burn dressing

SurgiMend® - FDA approved xenograft indicated for plastic and reconstructive surgery, muscle flap reinforcement, and hernia repair.

Talymed® - FDA approved wound matrix comprised of shortened fibers of poly-Nacetylglucosamine, isolated from microalgae. Indicated for treatment of diabetic ulcers, venous ulcers, pressure wounds, ulcers caused by mixed vascular etiologies, full thickness and partial thickness wounds, second degree burns, surgical wounds-donor sites/grafts, post-Moh's surgery, post-laser surgery, and other bleeding surface wounds, abrasions, lacerations, traumatic wounds healing by secondary intention, chronic vascular ulcers and dehisced surgical wounds.

TenoGlide™ - FDA approved matrix of cross-linked collagen and Glycosaminoglycan, indicated for use as tendon protector sheath.

TenSIX™ Acellular Dermal Matrix - indicated for the repair or replacement of integumental tissue and used for protecting, reinforcing and covering tendons.

TheraForm™ - approved Collagen product indicated for second-degree burns, chronic ulcers and other topical wound managements.

TheraSkin® - Regulated by the American Association of Tissue banks and the FDA guidelines for banked human tissue. Indicated to promote healing of ulcerated and burn wounds.

TissueMend - FDA approved xenograft indicated for reinforcement of soft tissues repaired by sutures or suture anchors, during tendon repair surgery, including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps or other tendons.

TruSkin™ - cryopreserved skin allograft that serves as an alternative to fresh skin grafts

Veritas® Collagen Matrix - FDA approved xenograft indicated for repair of complex abdominal wall reconstruction procedures.

XCM Biologic/Medeor Matrix - FDA approved xenograft indicated for the reinforcement and repair of soft tissue where weakness exists including, but not limited to: defects of the thoracic wall, suture line reinforcement, muscle flap reinforcement, hernia repair and soft tissue reconstructive procedures.

XenMatrix™ AB – antibacterial-coated, non-crosslinked porcine dermal graft

Policy Guidelines

Bioengineered Skin and Tissue

Breast Reconstruction

For individuals who are undergoing breast reconstruction who receive allogeneic ADM products, the evidence includes a randomized controlled trial (RCT) and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. A recent systematic review found no difference in overall complication rates with ADM allograft compared to 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, including but not limited to when the use of ADM allows a single-stage reconstruction, the available evidence may be considered sufficient to permit conclusions about health outcomes that 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. Clinical input indicated that the various acellular dermal matrix (ADM) products used in breast reconstruction have similar efficacy. The products listed are those that have been identified for use in breast reconstruction. Additional ADM products may become available for this indication.

Tendon Repair

For individuals who are undergoing tendon repair who receive Graftjacket ADM, the evidence includes 1 RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. One RCT identified improved outcomes with Graftjacket ADM allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of patients is needed to evaluate 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, quality of life, 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 Dermal Regeneration Template, the evidence includes RCTs. Relevant outcomes are disease specific survival, symptoms, change in disease status, morbid events, and quality of life. RCTs have demonstrated the efficacy of AlloPatch (reticular ADM), Apligraf and Dermagraft (living cell therapy), and Integra Dermal Regeneration Template (biosynthetic) over the standard of care. 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 other ADM products, cryopreserved skin allograft, or xenogenic skin substitutes, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Additional study with a larger number of subjects is needed to compare the effect of other human ADM products, cryopreserved skin allograft (TheraSkin) and xenogenic skin substitutes (eg, Oasis Wound Matrix, PriMatrix) to the standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. RCTs have demonstrated the efficacy of Apligraf living cell therapy and xenogenic Oasis Wound Matrix over the standard of care. 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,

Bioengineered Skin and Tissue

morbid events, and quality of life. In a moderately large RCT, Dermagraft was not shown to be more effective than controls for the primary or secondary end points in the entire population and was only slightly more effective than controls (an 8%-15% increase in healing) in subgroups of patients with ulcer durations of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of the xenogenic PriMatrix skin substitute versus the current standard of care. 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 disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. OrCel was approved under a humanitarian drug exemption for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. Outcomes have been reported in small series (eg, 5 patients). 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, quality of life, and treatment-related morbidity. Overall, there are few skin substitutes approved, and the evidence is limited for each product. Epicel (living cell therapy) has received Food and Drug Administration 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.

Peripheral Nerve Repair

There is insufficient scientific evidence in the peer-reviewed medical literature to support the efficacy of either acellular, allogeneic nerve grafts or nerve conduits for bridging defects resulting from peripheral nerve injuries. The published literature for processed, acellular nerve grafts consists of small case series and registry data, and for nerve conduits, a small randomized trial and small case series. Study limitations include non-standardized assessment of clinical outcomes, lack of comparator groups, small group size and lack of long-term follow-up.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbnsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes:

Application of skin replacements and skin substitutes is reported with CPT codes 15040-15278.

Nerve repair with allograft is reported with CPT codes 64910, 64912, 64913

Codes 15040-15261 are specific to autografts and tissue-cultured autografts.

Codes 15271-15278 are specific to skin substitute grafts.

Code 15777 is a specific add-on code for use of these materials as an implant.

HCPCS modifiers:

JC: skin substitute used as a graft

Bioengineered Skin and Tissue

JD: skin substitute not used as a graft

Product specific codes:

Q4100 - Q4108, Q4110 - Q4118, Q4121 - Q4128, Q4130, Q4134 - Q4136, Q4141 - Q4143, Q4146, Q4147, Q4149, Q4152, Q4158, Q4161, Q4164 - Q4167, Q4172, Q4175, Q4176, Q4179, Q4180, Q4182, Q4222, Q4226, , C1849, C9349, C9352 - C9356, C9358, C9360, C9361, C9363, C9364

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Consultant Review - 1/94

Physician Advisory Group - 3/95

BCBSA Medical Policy Reference manual (Growth Factors for Wound Healing S9055)

MPAG Review - 3/99

Specialty Matched Consultant Advisory Panel - 10/2000

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Schonfeld WH, Villa KF, Fastenau JM, Mazonson PD, Falanga V. An economic assessment of Apligrar (Graftskin) for the treatment of hard-to-heal venous leg ulcers. *Wound Repair Regen.* 2000 Jul-Aug;8(4):251-7.

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Bioengineered Skin and Tissue

Pollak RA, Edington H, Jensen J, Kroeker, et al. A human dermal replacement for the treatment of diabetic foot ulcers. *Wounds: A Compendium of Clinical Research and Practice*. 1997 November/December;9(6):175-182.

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ECRI. (2001,December). Bioengineered composite skin substitute for donor sites in burn victims. Target database. Retrieved on 5/10/2004 from http://www.target.ecri.org/summary/detail.aspx?doc_id=1726&q=bioengineered+skin&anm=wynneb.

Specialty Matched Consultant Advisory Panel - 7/2004

Specialty Matched Consultant Advisory Panel - 6/2006

TEI Biosciences. (2007). PriMatrix™: Dermal repair scaffold. Retrieved 12/3/07 from <http://www.teibio.com/PriMatrix.aspx>.

Stryker Corporation. Product Overview Orthobiologics: TissueMend Soft Tissue Repair Matrix. Retrieved 12/3/07 from <http://strykercorp.com/jointreplacements/sites/orthobiologics/tissuemend/index.php>.

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Specialty Matched Consultant Advisory Panel - 6/2008

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Policy Implementation/Update Information

1/94	Original Policy Issued.
3/95	Reviewed: Remains investigational
9/95	Reaffirmed: Remains investigational
10/96	Reaffirmed
3/99	Reaffirmed
8/99	Reformatted, Description of procedure changed, Medical Term Definitions added.
10/00	Specialty Matched Consultant Advisory Panel review. No change recommended in criteria. System coding changes. Medical Policy Advisory Group. No change in criteria. Approve.
10/02	Name changed from Keratinocyte Allografts to Bioengineered Skin for the Treatment of Skin Ulcers. Description section expanded. Changed from investigational to covered for certain indications. Specialty Matched Consultant Advisory Panel review.
4/03	Date of Last Review changed to 10/2002 when review was done by the Specialty Matched Consultant Advisory Panel and policy was updated. Date of Next Review changed to 2 years later - 10/2004.
9/03	Added Dermagraft as a covered product with specific criteria. Sources added. Added codes J7342 and J7350. Removed code 15350.

Bioengineered Skin and Tissue

- 12/03 Billing/Coding section updated for consistency.
- 9/9/04 Policy name changed from Bioengineered Skin for the Treatment of Skin Ulcers to Bioengineered Skin. Specialty Matched Consultant Advisory Panel review 7/14/2004. Added information in Description of Procedure or Service section to include burns. Added statement in Policy section indicating "BCBSNC will provide coverage for bioengineered skin for the treatment of burns when it is determined to be medically necessary because the medical criteria and guidelines shown below have been met." In section regarding When Bioengineered Skin is Covered, added "C. Bioengineered skin may be considered medically necessary in the treatment of burns when all of the following criteria are met. 1. When the product has full FDA approval. and 2. When the product is used within the scope of the FDA indications." Removed reference to Biobrane in that it is a biosynthetic wound dressing for burns and does not apply to this policy. Added HCPCS code Q0183. References added. Notification given 9/9/2004. Effective date 11/11/2004.
- 1/6/05 First quarter 2005 HCPCS codes J7343, J7344 added to Billing/Coding section of policy.
- 1/5/06 Added new 2006 CPT codes 15150, 15151, 15152, 15155, 15156, 15157, 15170, 15171, 15175, 15176, 15300, 15301, 15320, 15321, 15330, 15331, 15335, 15336, 15340 15341, 15360, 15361, 15365, 15366, 15420, 15421, 15430, 15431, and HCPCS code J7341 to "Billing/Coding" section. Deleted CPT codes 15342 and 15343.
- 7/24/06 Specialty Matched Consultant Advisory Panel review 6/20/2006. Updated "Description of Procedure or Service" section to include information regarding specific products. Added "rare skin conditions" to the "Policy" statement. The following changes were made to the "When Bioengineered Skin is Covered" section. Removed the statement "The ulcers are not infected". Changed the wording regarding "standard wound care" to "clinically appropriate therapy". Under B. changed statement from indicating 4 applications to "Applications will be limited to no more than 6 pieces per wound when the above criteria are met." Added additional indication under C. "rare skin conditions such as recessive dystrophic epidermolysis bullosa". Added the following product names under "When Bioengineered Skin is Not Covered"; "EZ Derm®, Mediskin®, Alloderm®, Oasis®, Surgis®, Acticoat®, and GraftJacket. Removed deleted HCPCS code Q0183. References added.
- 1/17/07 Added the following new 2007 HCPCS codes, J7345 and J7346 to "Billing/Coding" section. Deleted HCPCS code, J7350.
- 4/23/07 Added CPT codes 15400 and 15401 to "Billing/Coding" section.
- 01/14/08 Added information to the "Description" section regarding "Primatrix™ (formerly known as DressSkin) and TissueMend®". "Primatrix, DressSkin, and TissueMend" added to "Key Words". Added new 2008 HCPCS codes; "J7347, J7348, and J7349" to "Billing/Coding" section. Removed HCPCS code J7345.
- 7/28/08 Specialty Matched Consultant Advisory Panel review 6/23/08. Added "Celaderm® is an allograft that contains active keratinocytes made from epithelial cells of the foreskin. Although metabolically active they are not capable of proliferating. The product has not received FDA approval at this time." to the "Description section. Added to "Alloderm" under the "When Not Covered" section "is considered investigational for all indications including but not limited to breast reconstruction and recurrent hernia repair." and added "Celladerm®" to the list. Updated the rationale in the "Policy Guidelines" section. References added.

Bioengineered Skin and Tissue

- 1/5/09 Added new HCPCS codes: Q4100, Q4101, Q4102, Q4103, Q4104, Q4105, Q4106, Q4107, Q4108, Q4109, Q4110, Q4111, Q4112, Q4113, and Q4114 to the "Billing/Coding" section. Removed deleted HCPCS codes: J7340, J7341, J7342, J7343, J7344, J7346, J7347, J7348, and J734.
- 2/2/09 Reviewed with Senior Medical Director 1/20/09. The investigational status of Alloderm for the use in breast reconstruction has changed and now may be medically necessary when specific criteria is met. "Policy" statement updated. Added the following statement to the "Description" section; "Alloderm has been researched as a support mechanism for breast reconstruction, difficult hernia repairs and after parotidectomy to avoid Frey's syndrome." Added the following indications to the "When Covered" section: "C. Alloderm (an acellular allograft) may be considered medically necessary for use in breast reconstruction surgery." Reference to breast reconstruction with Allograft was removed in the "When Not Covered" section and reworded to indicate; "E. Alloderm® is considered investigational for all indications except those addressed in the "When Covered" section including but not limited to parotidectomy and recurrent hernia repair or other major abdominal cavity reconstruction." Revised "Policy Guidelines" section and added the following statement; "The use of Alloderm in breast reconstruction can be particularly useful in women who have insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is require, or when there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis or when the infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks are needed.". References added.
- 8/3/09 Added new HCPCS codes Q4115 and Q4116 to "Billing/Coding" section. (btw)
- 10/26/09 Added the following statement to the "Description" section; "***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician. Changed the wording in the "When Covered" section under B. Dermagraft from "Applications will be limited to no more than 6 pieces per wound when the above criteria are met." to "Applications will be limited to no more than 8 weekly applications per wound when the above criteria are met." Reviewed with Senior Medical Director 9/16/09. References added. (btw)
- 6/22/10 Policy Number(s) removed. (amw)
- 10/26/10 Added new product information to "Description" section for Cymetra®, C-Qur™, Avaulta Plus™, Collamend, Cuffpatch™, DermaMatrix Acellular Dermis, E-Z Derm™, Integra™ Matrix Wound Dressing, Mediskin®, Oasis™, OrthADAPT™, Pelvicol®, Pelvisoft®, PriMatrix, Strattice™, Surgimend®, Surgisis®, Unite™. These products have been added to the "What is not Covered" section. Updated references. Specialty Matched Consultant Advisory Panel review 9/2010. Added HCPCS codes C9358, C9360, C9363 and C9364 to Billing/Coding section. (mco)
- 1/4/11 Added new product information for Matristem®, Hyalomatrix®, Endoform Dermal Template™, and Theraskin®. Added the following codes to reflect the 2011 HCPCS coding updates: C9367, G0440, G0411, Q4117, Q4118, Q4119, Q4120, and Q4121. Deleted code Q4109(mco)
- 1/18/11 Senior Medical Director review 1/2011. Changed title of policy from "Bioengineered Skin" to "Bioengineered Skin and Tissue." Added new product information to "Description" section for CorMatrix® pericardial patch and Veritas® Collagen Matrix. The products were also added to the "When not Covered" section. References updated. Reformatted the "When not Covered" section. (mco)

Bioengineered Skin and Tissue

- 5/24/11 Medical Director review 5/2011. Under “When Covered” section A-1, replaced the word “venous” with “vascular” and in section A-1-d, added “including restoration by vascular bypass grafting, stenting or other means.” In section 2, deleted the words “diabetic” from the criteria for neuropathic foot ulcers. (mco)
- 7/01/11 Added new code to “Billing/Coding” section: C9365. Added new product to “Not Covered” section: Oasis Ultra Tri-Layer Matrix. (mco)
- 11/8/11 Specialty Matched Consultant Advisory Panel review 9/2011. Updated “Description” section. “When Covered” section re-formatted. Added new products to the “When not Covered” section and alphabetized product list. FDA indications provided for all products listed in policy. Added C9354 to “Billing/Coding” section. References updated. (mco)
- 12/30/11 Deleted the following codes from “Billing/Coding” section: 15170, 15171, 15175, 15176, 15330, 15331, 15335, 15336, , 15340, 15341, 15360, 15361, 15365, 15366, 15400, 15401, 15420, 15421, 15430, 15431, C9365, G0440, G0441. Added the following codes to “Billing/Coding” section: 15271, 15272, 15273, 15274, 15275, 15276, 15277, 15278, 15777, C9366, Q4122, Q4123, Q4124, Q4125, Q4126, Q4127, Q4128, Q4129, Q4130. New codes will be effective 1/1/2012. Added new product “Epifix®” to “When not Covered” section. (mco)
- 3/20/12 New policy criteria as follows: “BCBSNC will provide coverage for Apligraf® bioengineered skin, **Oasis® Wound Matrix** and Dermagraft® for the treatment of skin ulcers when it is determined to be medically necessary because the medical criteria and guidelines shown below have been met.” “When Covered” section revised to state, “A.The applications of Apligraf® and ~~Dermagraft®~~ **Oasis Wound Matrix®** are covered for the treatment of vascular ulcers when all of the following criteria are met: 1.When used in conjunction with standard therapy, 2. The ulcers have not healed by at least 50% after clinically appropriate therapy, 3.The ulcers intended for treatment are partial or full thickness venous stasis ulcers, and 4.The patient has adequate arterial blood supply to the involved limb, including restoration by vascular bypass grafting, stenting or other means.” “When not Covered” section updated to include the following statements: “B.Oasis® Wound Matrix is contraindicated in the following situations: 1.The patient has a known allergy to porcine collagen 2.For any indications other than those listed above in the “When Covered” section of the policy.” Added the following statement to the “When not Covered” section: “With the exception of products used within the scope of FDA indications for treatment of burns and rare skin conditions such as recessive dystrophic epidermolysis bullosa, FDA approval for a specific use does not define that product as non-investigational.” References updated. Medical Director review 3/2012. (mco)
- 6/29/12 C9368 and C9369 added to “Billing/Coding” section. Added new products to “When not Covered” section: Grafix® CORE and Grafix® PRIME. (mco)
- 7/10/12 Revised the FDA information for product EZ Derm™ to state: “FDA 510(k) approved xenograft for the treatment of partial-thickness burns and venous, diabetic, and pressure ulcers.”(mco)
- 10/16/12 Specialty Matched Consultant Advisory Panel review 9/2012. Added new products to the “When not Covered” section: AmnioFix®, Axogen/AxioGuard, DermaCell™, DuraGen®, Neox™1K/Neox™100, NuCell™/NuShield™, Restore Orthobiologic Soft Tissue Implant, SpinalMend™, TissueMend, Unite®Biomatrix, XCM Biologic, DermaSpan™ and DuraGen® Dural Graft and DuraGen® Plus. (mco)
- 1/1/13 Description section updated to remove non-covered product information. Non-covered product information is now specifically addressed in the “When not Covered” section. “When not Covered” section updated to include new products: hMatrix®, C-QUR Edge™, C-QUR V-Patch™ and C-QUR Lite™ V-Patch. Also added the following statement to the “When not Covered” section: **“With the exception of products used within the scope of**

Bioengineered Skin and Tissue

FDA indications for treatment of burns and rare skin conditions such as recessive dystrophic epidermolysis bullosa, FDA approval for a specific use does not define that product as non-investigational. Deleted C9366, C9368, C9369 and added Q4131, Q4132, Q4133, Q4134, Q4135, Q4136 to Billing/Coding section. Medical Director review 12/2012. (mco)

- 2/26/13 References updated. Added the following statement to the Description section and to the “When not Covered” section: “Dermagraft had been FDA approved by a Humanitarian Device Exemption (HDE) for the treatment of dystrophic epidermolysis bullosa. The manufacturer has since withdrawn Dermagraft from HDE status.” (mco)
- 10/15/13 Specialty Matched Consultant Advisory Panel review 9/2013. Medical Director review 9/2013. References updated. New products added to the “When not Covered” section. (mco)
- 12/31/13 C5271, C5272, C5273, C5274, C5275, C5276, C5277, C5278, Q4137, Q4138, Q4139, Q4140, Q4141, Q4142, Q4143, Q4145, Q4146, Q4147, Q4148, Q4149 added to Billing/Coding section. New products added to the “When not Covered” section. (mco)
- 4/1/14 Description section updated. Added the following statement to the “When Covered” section: “D. Breast reconstructive surgery using allogeneic acellular dermal matrix products (i.e., AlloDerm®, AlloMax™, DermaMatrix™, FlexHD®, GraftJacket®) may be considered medically necessary.” “When Covered” section re-formatted. Updated “When not Covered” section to include new products and to remove products that are now considered medically necessary for use in breast reconstruction surgery. Deleted code C9367 from Billing/Coding section. Policy Guidelines updated. References updated. Medical Director review 3/2014. (mco)
- 10/28/14 Specialty Matched Consultant Advisory Panel review 9/2014. Medical Director review 9/2014. (mco) (td)
- 12/30/14 Added Codes Q4150, Q4151, Q4152, Q4153, Q4154, Q4155, Q4156, Q4157, Q4158, Q4159, Q4160 and C9349 to the Billing/Coding section effective 1/1/15. (td)
- 2/24/15 References updated. Policy Statement updated to include Epifix® coverage if meets medical necessity criteria. When Covered section updated to include Epifix considered medically necessary for the treatment of chronic, non-infected full-thickness diabetic or neuropathic lower extremity ulcers. When Not Covered section updated to include additional products and to remove Epifix. Medical Director review 2/2015. (td)
- 3/10/15 When Covered section revised to cover 5 applications for Epifix. Policy Statement unchanged. (td)
- 7/1/15 When Not Covered section revised to add the trade name PuraPly. The trade name for the product has been changed from "Fortaderm" to "PuraPly" effective July 1, 2015. References updated. Billing/Coding section updated to include code C9356. (td)
- 10/30/15 Specialty Matched Consultant Advisory Panel review 9/30/2015. Medical Director review 9/2015. (td)
- 12/30/15 Billing/Coding section updated to include codes: Q4161, Q4162, Q4163, Q4164, Q4165; effective 1/1/16. When Covered section updated to include additional products. (td)
- 7/26/16 Description section extensively revised. Specific products removed from the Policy statement which is revised to read: **BCBSNC will provide coverage for bioengineered skin and soft tissue substitutes when it is determined to be medically necessary**

Bioengineered Skin and Tissue

because the medical criteria and guidelines shown below have been met. “When Covered” section reformatted and new products added. Policy Guidelines section extensively revised. Deleted the following products from the “investigational” list: AmnioBand, Biovance, Grafix CORE, Grafix PRIME and Neox 1K. Rationale added for individual indications. (an)

- 8/30/16 Corrected typo in Description section. No other change to policy. (an)
- 10/25/16 Specialty Matched Consultant Advisory Panel review 9/28/2016. Policy accepted as written. (an)
- 12/30/16 Amnioband®/Guardian added back to the list of Investigational products. Added codes *Q4166, Q4167, Q4168, Q4169, Q4170, Q4171, Q4172, Q4173, Q4174, Q4175* to the Billing/Coding section. (an)
- 2/24/17 Minor change to Description section. AlloMend added to list of products covered for breast reconstructive surgery. AlloPatch added to list of products covered for chronic, noninfected, full-thickness diabetic lower-extremity ulcers. List of investigation/noncovered products was extensively revised. All amniotic membrane and amniotic fluid injection deleted from this list—refer to policy titled: **Amniotic Membrane and Amniotic Fluid Injections**. Policy Guidelines section updated. Billing/Coding section updated. (an)
- 4/28/17 Note regarding application limit for Epifix was removed from this policy and moved to policy titled “Amniotic Membrane and Amniotic Fluid Injections.” (an)
- 5/26/17 DermACELL™ added back to the list of Investigational products. (an)
- 6/30/17 In the When Covered section, the bullet points under breast reconstructive surgery were deleted. The following statement was added to the Policy Guidelines section for Breast Reconstruction: Clinical input indicated that the various acellular dermal matrix (ADM) products used in breast reconstruction have similar efficacy. The products listed are those that have been identified for use in breast reconstruction. Additional ADM products may become available for this indication. CellerateRX® (CRXa™) removed from the list of investigational products. (an)
- 7/28/17 DermACELL™ removed from the list of Investigational products. Allogeneic acellular dermal matrix products, including Dermacell, may be considered medically necessary for breast reconstructive surgery. (an)
- 9/15/17 NeoForm Dermis and Avance Nerve Graft added to list of investigational products. Integra Omnigraft deleted from investigational product list and added to bullet point under “Treatment of chronic, noninfected, full-thickness diabetic lower extremity ulcers”. Specialty Matched Consultant Advisory Panel review 8/30/2017. (an)
- 12/15/17 New codes added to Billing/Coding section, effective 1/1/2018: Q4176, Q4179, Q4180, Q4182. (an)
- 3/29/18 FlexHD® Pliable™ and Cortiva® added to list of covered products. Integra Flowable Wound Matrix moved from the Investigational products list to the “When Covered” section. The following statement from the “Not Covered” section was also added to the “When Covered” section: *With the exception of products used within the scope of FDA indications for treatment of burns and rare skin conditions such as recessive dystrophic epidermolysis bullosa, FDA approval for a specific use does not define that product as non-investigational.* Reference added. (an)

Bioengineered Skin and Tissue

- 9/7/18 Specialty Matched Consultant Advisory Panel review 8/22/2018. No change to policy statement. (an)
- 2/12/19 Added information regarding peripheral nerve grafting to Description Section. Added NeuraGen™ Nerve Guide and NeuraWrap™ Nerve Protector to list of investigational products. Rationale added to Policy Guidelines section. Codes added to Billing/Coding section: 64910, 64912, 64913, C9352, C9353, C9355, C9361. Medical Director review 1/2019. **Notification given 2/12/2019 for effective date 4/16/2019.** (an)
- 4/16/19 Reference added. Deleted information regarding NuCel/NuShield/NuShield Orthopaedics Spine. This is an amniotic membrane product. (an)
- 9/10/19 Specialty Matched Consultant Advisory Panel 8/20/19. (eel)
- 10/1/19 Coding section updated with new codes effective 10/1/19. Added codes Q4222 and Q4226. (eel)
- 6/30/20 Coding section updated with new code effective 7/1/20. Added code C1849. (eel)

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