BlueCross BlueShield of Alabama

Name of Policy:

Bio-Engineered Skin and Soft Tissue Substitutes

Policy #: 527
Category: Surgery

Latest Review Date: March 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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.*

Description of Procedure or Service:

Skin and Soft Tissue Substitutes

Bio-engineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), non-human tissue (xenographic), synthetic materials, or a composite of these materials. Bio-engineered 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 in the repair of a variety of soft tissues.

Bio-engineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (i.e., dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. The various ADM 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. 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 non-healing 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, non-healing lower extremity wounds represent an ongoing risk for infection, sepsis, limb amputation, and death. Bio-engineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

Other situations in which bio-engineered skin products might substitute for living skin grafts include certain postsurgical states such as 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 situation in which artificial skin products may substitute for auto- or allografts. Certain primary dermatologic conditions that involve large areas of skin breakdown, such as 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 a variety of other conditions.

For additional information on **specific ocular conditions using amniotic products**, refer to medical policy #624 ***Amniotic Membrane Transplantation for the Ocular Surface*.**

For additional information on **all other amniotic products and indications for use**, refer to medical policy #597 ***Amniotic Membrane and Amniotic Fluid Injections.***

Policy:

Effective for dates of service on or after March 14, 2018:

Covered

Treatment of **upper and lower eyelid retraction or conjunctival contraction requiring soft tissue spacer or replacement** using the following tissue-engineered skin substitute **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- AlloDerm®

Breast reconstructive surgery using the allogenic acellular dermal matrix products* AlloDerm®, AlloMax™, AlloMend®, DermACELL™, DermaMatrix™, FlexHD®, FlexHD® Pliable, GraftJacket® meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

Treatment of **chronic, noninfected, full-thickness *diabetic* lower extremity ulcers** using the following tissue-engineered skin substitutes **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

Treatment of **chronic, non-infected, partial- or full-thickness lower extremity skin ulcers *due to venous insufficiency,* which have not adequately responded following a one-month period of conventional ulcer therapy,** using the following tissue-engineered skin **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

Treatment of **dystrophic epidermolysis bullosa** using the following tissue-engineered skin substitute **meets** Blue Cross and Blue Shield of Alabama's medical criteria 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 FDA)****

Treatment of **second- and third-degree burns** using the following tissue-engineered skin substitutes **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

*Banked Human Tissue
** FDA PMA approved
*** FDA 510(k) cleared
**** FDA-approved under a humanitarian device exemption (HDE)

Non-Covered

All other uses of the bio-engineered skin and soft tissue substitutes **listed above do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational.**

All other skin and soft tissue substitutes not listed above **do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational, including, but not limited to:**

- **ACell® UBM Hydated Wound Dressing**
- **ACell® UBM Lyophilized Wound Dressing**
- **AlloSkin™**
- **AlloSkin™ RT**
- **Aongen™ Collagen Matrix**
- **Architect Extracellular Matrix**
- **ArthroFlex™ (FlexGraft)**
- **Atlas Wound Matrix**
- **Avagen Wound Dressing**
- **AxoGuard® Nerve Protector (AxoGen)**
- **Biobrane®**
- **Bio-Connekt Wound Matrix**
- **BioRenew**
- **BioSkin**
- **CollaCare®**
- **CollaCare® Dental**
- **Collagen Sponge (Innocoll)**
- **Collagen Wound Dressing (Oasis Research)**
- **CollaGuard®**
- **CollaMend™**
- **CollaSorb™**
- **CollaWound™**
- **Collexa®**
- **Collieva®**
- **Conexa™**
- **Coreleader Colla-Pad**

- **CorMatrix®**
- **Cortiva™**
- **Cymetra®**
- **Cytal™ (previously MatriStem)**
- **Dermacell**
- **Dermadapt™ Wound Dressing**
- **DermaPure™**
- **DermaSpan™**
- **DressSkin**
- **Durepair Regeneration Matrix®**
- **Endoform Dermal Template™**
- **ENDURAgen™**
- **Excellagen**
- **ExpressGraft™**
- **E-Z Derm™**
- **Flexigraft®**
- **GammaGraft**
- **GraftJacket® Xpress, injectable**
- **HA Absorbent Wound Dressing**
- **Helicoll**
- **Hyalomatrix® (Laserskin®)**
- **Hyalomatrix® PA**
- **hMatrix®**
- ~~**Integra™ Flowable Wound Matrix**~~
- **Integra™ Bilayer Wound Matrix**
- **Jaloskin®**
- **Keramatrix®**
- **Kerecis™**
- **MariGen™/Kerecis™ Omega3™**
- **MatriDerm®**
- **Matrix Collagen Wound Dressing**
- **Matrix HD™**
- **MediHoney®**
- **Mediskin®**
- **MemoDerm™**
- **Miroderm® Biologic Wound Matrix**
- **NeoForm™**
- **NuCel**
- **Oasis® Burn Matrix**
- **Oasis® Ultra Tri-Layer Matrix**
- **Pelvicol®/PelviSoft®**
- **Permacol™**
- **PriMatrix™**
- **Primatrix™ Dermal Repair Scaffold**
- **PuraPly™ wound Matrix (previously FortaDerm™)**
- **PuraPly™ AM (Antimicrobial Wound Matrix)**

- **Puros® Dermis**
- **RegenePro™**
- **Repliform®**
- **Repriza™**
- **StrataGraft**
- **Strattice™**
- **Suprathel®**
- **SurgiMend®**
- **Talymed®**
- **TenoGlide™**
- **TenSIX**
- **TheraForm™ Standard/Sheet**
- **TheraSkin®**
- **TissueMend**
- **TruSkin™**
- **Veritas® Collagen Matrix**
- **WoundEx**
- **XCM Biologic Tissue Matrix7**
- **XenMatrix™ AB**

Note:
For additional information on **specific ocular conditions using amniotic products,** refer to medical policy #624 ***Amniotic Membrane Transplantation for the Ocular Surface*.**

For additional information on **all other amniotic products and indications for use,** refer to medical policy #597 ***Amniotic Membrane and Amniotic Fluid.***

Effective for dates of service on or after June 1, 2017 and prior to March 14, 2018:
Covered
Treatment of **upper and lower eyelid retraction or conjunctival contraction requiring soft tissue spacer or replacement** using the following tissue-engineered skin substitute **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- AlloDerm®

Breast reconstructive surgery using the allogenic acellular dermal matrix products* AlloDerm®, AlloMax™, AlloMend®, DermaMatrix™, FlexHD®, GraftJacket® meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

Treatment of **chronic, noninfected, full-thickness *diabetic* lower extremity ulcers** using the **following** tissue-engineered skin substitutes **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- **AlloPatch®**
- **Apligraf®****
- **Dermagraft®****
- **Integra®** ~~Dermal Regeneration Template~~ Omnigraft Dermal Regeneration Matrix (also known as Omnigraft)

Treatment **of chronic, non-infected, partial- or full-thickness lower extremity skin ulcers *due to venous insufficiency*, which have not adequately responded following a one-month period of conventional ulcer therapy**, using the following tissue-engineered skin **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

Treatment of **dystrophic epidermolysis bullosa** using the following tissue-engineered skin substitute **meets** Blue Cross and Blue Shield of Alabama's medical criteria 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 FDA)****

Treatment of **second- and third-degree burns** using the following tissue-engineered skin substitutes **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

*Banked Human Tissue
** FDA PMA approved
*** FDA 510(k) cleared
**** FDA-approved under a humanitarian device exemption (HDE)

Non-Covered
All other uses of the bio-engineered skin and soft tissue substitutes **listed above do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational**.

All other skin and soft tissue substitutes not listed above **do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational**, **including, but not limited to:**

- ACell® UBM Hydated Wound Dressing
- ACell® UBM Lyophilized Wound Dressing
- AlloSkin™
- AlloSkin™ RT

- Aongen™ Collagen Matrix
- Architect Extracellular Matrix
- ArthroFlex™ (FlexGraft)
- Atlas Wound Matrix
- Avagen Wound Dressing
- AxoGuard® Nerve Protector (AxoGen)
- Biobrane®
- Bio-Connekt Wound Matrix
- BioRenew
- BioSkin
- CollaCare®
- CollaCare® Dental
- Collagen Sponge (Innocoll)
- Collagen Wound Dressing (Oasis Research)
- CollaGuard®
- CollaMend™
- CollaSorb™
- CollaWound™
- Collexa®
- Collieva®
- Conexa™
- Coreleader Colla-Pad
- CorMatrix®
- Cortiva™
- Cymetra®
- Cytal™ (previously MatriStem)
- Dermacell
- Dermadapt™ Wound Dressing
- DermaPure™
- DermaSpan™
- DressSkin
- Durepair Regeneration Matrix®
- Endoform Dermal Template™
- ENDURAgen™
- Excellagen
- ExpressGraft™
- E-Z Derm™
- Flexigraft®
- GammaGraft
- GraftJacket® Xpress, injectable
- HA Absorbent Wound Dressing
- Helicoll
- Hyalomatrix® (Laserskin®)
- Hyalomatrix® PA
- hMatrix®
- Integra™ Flowable Wound Matrix

- Integra™ Bilayer Wound Matrix
- Jaloskin®
- Keramatrix®
- MariGen™/Kerecis™ Omega3™
- MatriDerm®
- Matrix Collagen Wound Dressing
- Matrix HD™
- MediHoney®
- Mediskin®
- MemoDerm™
- Miroderm® Biologic Wound Matrix
- NeoForm™
- NuCel
- Oasis® Burn Matrix
- Oasis® Ultra Tri-Layer Matrix
- Pelvicol®/PelviSoft®
- Permacol™
- PriMatrix™
- Primatrix™ Dermal Repair Scaffold
- PuraPly™ wound Matrix (previously FortaDerm™)
- PuraPly™ AM (Antimicrobial Wound Matrix)
- Puros® Dermis
- RegenePro™
- Repliform®
- Repriza™
- StrataGraft
- Strattice™
- Suprathel®
- SurgiMend®
- Talymed®
- TenoGlide™
- TenSIX
- TheraForm™ Standard/Sheet
- TheraSkin®
- TissueMend
- TruSkin™
- Veritas® Collagen Matrix
- WoundEx
- XCM Biologic Tissue Matrix7
- XenMatrix™ AB

Note:
For additional information on **specific ocular conditions using amniotic products**, refer to medical policy #624 ***Amniotic Membrane Transplantation for the Ocular Surface*.**

For additional information on **all other amniotic products and indications for use**, refer to medical policy #597 ***Amniotic Membrane and Amniotic Fluid.***

Effective for dates of service on or after July 1, 2016 and prior to June 1, 2017:
Covered
Treatment of **upper and lower eyelid retraction or conjunctival contraction requiring soft tissue spacer or replacement** using the following tissue-engineered skin substitute **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- AlloDerm®

Breast reconstructive surgery using allogenic acellular dermal matrix products* (i.e., AlloDerm®, AlloMax™, DermaMatrix™, FlexHD®, GraftJacket®) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

Treatment of **chronic, noninfected, full-thickness *diabetic* lower extremity ulcers** using the **following** tissue-engineered skin substitutes **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- **Apligraf®****
- **Dermagraft®****
- **Integra®** Dermal Regeneration Template
- Amniotic membrane Graft* (including **Biovance®**, **Epifix®**, **Grafix™**)

Treatment **of chronic, non-infected, partial- or full-thickness lower extremity skin ulcers *due to venous insufficiency,* which have not adequately responded following a one-month period of conventional ulcer therapy**, using the following tissue-engineered skin **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

Treatment of **dystrophic epidermolysis bullosa** using the following tissue-engineered skin substitutes **meets** Blue Cross and Blue Shield of Alabama's medical criteria 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 FDA)****

Treatment of **second- and third-degree burns** using the following tissue-engineered skin substitutes **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

*Banked Human Tissue
** FDA PMA approved
*** FDA 510(k) cleared
**** FDA-approved under a humanitarian device exemption (HDE)

Non-Covered
All other uses of the bio-engineered skin and soft tissue substitutes **listed above do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational**.

All other skin and soft tissue substitutes not listed above **do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational**, including, but not limited to:

- ACell® UBM Hydated Wound Dressing
- ACell® UBM Lyophilized Wound Dressing
- Affinity™
- AlloPatch HD™
- AlloSkin™
- AlloSkin™ RT
- Allowrap™
- Alphaplex™ with MariGen Omega3™
- AmnioBand™
- AmnioExCel or BioDExCel™
- Amniofix®
- AmnioGen
- AmnioGraft®
- AmnioMatrix
- AmnioPro
- Aongen™ Collagen Matrix
- Architect Extracellular Matrix
- ArthroFlex™ (FlexGraft)
- Atlas Wound Matrix
- Avagen Wound Dressing
- Avaulta Plus™
- AxoGuard® Nerve Protector (AxoGen)
- Biobrane®
- Bio-Connekt Wound Matrix
- BioDfence/BioDfactor
- BioDMatrix Dry Flex
- BioRenew
- BioSkin

- CellerateRX®
- Clarix® Flo
- Collagen Sponge (Innocoll)
- Collagen Wound Dressing (Oasis Research)
- Collaguard®
- CollaSorb™
- CollaWound™
- Collexa®
- Collieva®
- Conexa™
- Coreleader Colla-Pad
- CorMatrix®
- CRXa™
- Cymetra®
- Dermacell
- Dermadapt™ Wound Dressing
- Dermapure™
- Dermavest™
- DressSkin
- Durepair Regeneration Matrix®
- Endoform Dermal Template™
- ENDURAgen™
- Epifix®, injectable
- Excellagen
- E-Z Derm™
- FortaDerm™ Wound Dressing
- GammaGraft
- GraftJacket® Xpress, injectable
- GUARDIAN
- HA Absorbent Wound Dressing
- Helicoll
- Hyalomatrix® (Laserskin®)
- Hyalomatrix® PA
- hMatrix®
- Integra™ Flowable Wound Matrix
- Integra™ Bilayer Wound Matrix
- Jaloskin®
- Keramatrix®
- MariGen
- MatriDerm®
- MatriStem® Burn Matrix
- MatriStem® Micromatrix
- MatriStem® Wound Matrix
- Matrix Collagen Wound Dressing
- Matrix HD™
- MediHoney®

- Mediskin®
- MemoDerm™
- Neox 100
- Neox 1K
- Neox® Flo
- NuShield™
- Oasis® Burn Matrix
- Oasis® Ultra Tri-Layer Matrix
- Permacol™
- Plurivest™
- PriMatrix™
- Primatrix™ Dermal Repair Scaffold
- Puros® Dermis
- Repliform®
- Repriza™
- Revitalon™
- SIS Wound Dressing II
- SS Matrix™
- Stimulen™ Collagen
- StrataGraft
- Strattice™
- Suprathel®
- SurgiMend®
- Talymed®
- TenoGlide™
- TenSIX
- TheraForm™ Standard/Sheet
- TheraSkin®
- Unite™ Biomatrix
- Veritas® Collagen Matrix
- WoundEx
- XCM Biologic Tissue Matrix7

Note: For additional information on **specific ocular conditions**, refer to medical policy 624 *Amniotic Membrane Transplantation for the Ocular Surface*.

Effective for dates of service on or after January 9, 2014 and prior to July 1, 2016:

Covered

Treatment of **upper and lower eyelid retraction or conjunctival contraction requiring soft tissue spacer or replacement** using the following tissue-engineered skin substitute **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- AlloDerm®

Breast reconstructive surgery using allogenic acellular dermal matrix products* (i.e., AlloDerm®, AlloMax™, DermaMatrix™, FlexHD®, GraftJacket®) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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Treatment of **chronic, noninfected, full-thickness *diabetic* lower extremity ulcers** using the **following** tissue-engineered skin substitutes **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

- Apligraf®**
- Dermagraft®**

Treatment **of chronic, non-infected, partial- or full-thickness lower extremity skin ulcers *due to venous insufficiency*, which have not adequately responded following a one-month period of conventional ulcer therapy**, using the following tissue-engineered skin **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

Treatment of **dystrophic epidermolysis bullosa** using the following tissue-engineered skin substitutes **meets** Blue Cross and Blue Shield of Alabama's medical criteria 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 FDA)****

Treatment of **second- and third-degree burns** using the following tissue-engineered skin substitutes **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage:

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

*Banked Human Tissue
** FDA PMA approved
*** FDA 510(k) cleared
**** FDA-approved under a humanitarian device exemption (HDE)

Non-Covered

All other uses of the bio-engineered skin and soft tissue substitutes **listed above do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational**.

All other skin and soft tissue substitutes not listed above **do not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and are considered **investigational**, including, but not limited to:

- ACell® UBM Hydated Wound Dressing
- ACell® UBM Lyophilized Wound Dressing
- Affinity™
- AlloPatch HD™
- AlloSkin™
- AlloSkin™ RT
- Allowrap™
- Alphaplex™ with MariGen Omega3™
- AmnioBand™
- Amniofix®
- Aongen™ Collagen Matrix
- ArthroFlex™ (FlexGraft)
- Atlas Wound Matrix
- Avagen Wound Dressing
- Avaulta Plus™
- Biobrane®
- BioDfence/BioDfactor
- Biovance®
- CellerateRX®
- Clarix® Flo
- Collagen Sponge (Innocoll)
- Collagen Wound Dressing (Oasis Research)
- Collaguard®
- CollaSorb™
- CollaWound™
- Collexa®
- Collieva®
- Conexa™
- Coreleader Colla-Pad
- CorMatrix®
- CRXa™
- Cymetra®
- Dermadapt™ Wound Dressing
- Dermapure™
- Dermavest™
- DressSkin
- Durepair Regeneration Matrix®
- Endoform Dermal Template™
- ENDURAgen™
- Epifix®
- Excellagen
- E-Z Derm™

- FortaDerm™ Wound Dressing
- GammaGraft
- Grafix® core
- Grafix® prime
- GraftJacket® Xpress, injectable
- GUARDIAN
- HA Absorbent Wound Dressing
- Helicoll
- Hyalomatrix® (Laserskin®)
- Hyalomatrix® PA
- hMatrix®
- Integra™ Flowable Wound Matrix
- Integra™ Bilayer Wound Matrix
- Jaloskin®
- MariGen
- MatriDerm®
- MatriStem® Burn Matrix
- MatriStem® Micromatrix
- MatriStem® Wound Matrix
- Matrix Collagen Wound Dressing
- Matrix HD™
- MediHoney®
- Mediskin®
- MemoDerm™
- Neox® Flo
- Neox 1K
- NuShield™
- Oasis® Burn Matrix
- Oasis® Ultra Tri-Layer Matrix
- Permacol™
- PriMatrix
- Primatrix™ Dermal Repair Scaffold
- Puros® Dermis
- Repliform®
- Repriza™
- Revitalon™
- SIS Wound Dressing II
- SS Matrix™
- Stimulen™ Collagen
- StrataGraft
- Strattice™ (xenograft)
- Suprathel®
- SurgiMend®
- Talymed®
- TenoGlide™
- TheraForm™ Standard/Sheet

- TheraSkin®Unite™
- Unite® Biomatrix
- Veritas® Collagen Matrix

Note: For additional information on **specific ocular conditions**, refer to medical policy 624 *Amniotic Membrane Transplantation for the Ocular Surface*.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The literature search for this policy was performed through November 6, 2017.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The primary end points of interest for trials of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration for industry in developing products for treatment of chronic cutaneous ulcer and burn wounds:

1. Incidence of complete wound closure.
2. Time to complete wound closure (reflecting accelerated wound closure).

3. Incidence of complete wound closure following surgical wound closure.
4. Pain control.

Following is a summary of key literature to date.

Oculoplastic Procedures
Several retrospective observational case series were noted in the literature for the use of bioengineered grafts in oculoplastic procedures. Li et al compared the efficacy of hard palate grafts with acellular human dermis grafts (i.e., AlloDerm®) in lower eyelid surgery for lid retraction following blepharoplasty in 25 patients. Shorr et al reviewed the safety and applications of the same type of grafts (i.e., AlloDerm®) in 63 patients with lower eyelid retraction following blepharoplasty, refractory upper eyelid retraction related to thyroid disorder (i.e., Grave's disease), contracted socket repair in anophthalmia, exposed implants, and hypoglobus. Liao et al investigated the efficacy of these grafts (AlloDerm®) in the management of lower lid retraction in 32 patients with Grave's ophthalmopathy. Rubin et al reviewed 23 cases using these same type grafts (i.e., AlloDerm®) for the treatment of lower eyelid retraction, sulcus defects, implant coverage, and periorbital contour defects. All of the reviews concluded that the use of the acellular human dermal allograft (i.e., AlloDerm®) provided a safe and effective alternative to currently used autologous materials, namely hard palate grafts and dermal/fat grafts, and other alloplastic materials. Authors cite ease of use; prevention of a second operative site needed with autologous grafting, and decreased patient discomfort as added rationale for the use of acellular human dermal allografts. All reviews noted long-term data were needed for head to head comparisons of these grafts with conventional materials. There were no randomized, controlled studies noted, nor were there any reviews for grafts other than the AlloDerm® product in the oculoplastic procedures.

Breast Reconstruction
A variety of breast reconstruction techniques are used postmastectomy, including implant-based (immediate or delayed following use of a tissue expander) and those using autologous tissue flaps. Some of these techniques have been used with acellular dermal matrix (ADM) to provide additional support or tissue coverage. The literature on ADM for breast reconstruction consists primarily of retrospective, uncontrolled series.

A 2013 study used data from the American College of Surgeon's National Surgical Quality Improvement Program to compare ADM-assisted tissue-expander breast reconstruction (n=1717) to submuscular tissue-expander breast reconstruction (n=7442) after mastectomy. Complication rates did not differ significantly between the ADM-assisted (5.5%) and the submuscular tissue-expander groups (5.3%; p=0.68). Rates of reconstruction-related complications, major complications, and 30-day reoperation did not differ significantly between cohorts.

Systematic Reviews
A 2016 meta-analysis by Lee and Mun included 23 studies (total N=6199 cases) on implant-based breast reconstruction that were published between February 2011 and December 2014. The analysis included one RCT and three prospective comparative cohort studies; the remainder was retrospective comparative cohort studies. Use of ADM did not affect the total complication rate (see Table 1). ADM significantly increased the risk of major infection, seroma, and flap

necrosis, but reduced risks of capsular contracture and implant malposition. Use of ADM allowed for significantly greater intraoperative expansion (mean difference [MD], 79.63; 95% confidence interval [CI], 41.99 to 117.26; p<0.001) and percentage of intraoperative filling (MD=13.30; 95% CI, 9.95 to 16.65; p<0.001), and reduced the frequency of injection to complete expansion (MD = -1.56; 95% CI, -2.77 to -0.35; p=0.01).

Table 1. Meta-Analysis of Breast Reconstruction Outcomes with and without ADM

Outcome Measure	Relative Risk	95% Confidence Interval	p
Infection	1.42	1.02 to 1.99	0.04
Seroma	1.41	1.12 to 1.78	0.004
Mastectomy flap necrosis	1.44	1.11 to 1.87	0.006
Unplanned return to the operating room	1.09	0.63 to 1.90	NS
Implant loss	1.00	0.68 to 1.48	NS
Total complications	1.08	0.87 to 1.34	NS
Capsular contracture	0.26	0.15 to 0.47	<0.001
Implant malposition	0.21	0.07 to 0.59	0.003

Adapted from Lee and Mun (2016).
ADM: acellular dermal matrix

AlloDerm

Randomized Controlled Trials

In 2012, McCarthy et al reported a multicenter blinded randomized controlled trial of AlloDerm in 2-Stage expander/implant reconstruction. Seventy patients were randomized to AlloDerm acellular dermal matrix-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. The trial was adequately powered to detect clinically significant differences in immediate postoperative pain, but underpowered for detection of a secondary end point of pain during tissue expansion. There were no significant differences between the groups in the primary outcomes of immediate postoperative pain (54.6 AlloDerm and 42.8 control on a 100-point visual analog score) or pain during the expansion phase (17.0 AlloDerm and 4.6 control), or in the secondary outcome of rate of tissue expansion (91 days AlloDerm and 108 days control) and patient-reported physical well-being. There was no significant difference in adverse events, although the total number of adverse events was small.

Comparisons between Products

AlloDerm vs AlloMax

Hinchcliff et al (2017) conducted an RCT that compared AlloDerm with AlloMax (n=15 each) for implant-based breast reconstruction. Complications were assessed 7, 14, and 30 days postoperatively and biopsies of the ADMs were taken during implant exchange. Vessel density in the AlloMax biopsies was higher than in the AlloDerm biopsies. Complications were reported in 26.1% of AlloMax cases and 8.0% of AlloDerm cases; these complication rates did not differ statistically with the 30 patients in this trial.

AlloDerm vs DermaMatrix

Mendenhall et al (2017) conducted an RCT that compared AlloDerm with DermaMatrix in 111 patients (173 breasts). There were no significant differences in overall rates of complications (AlloDerm, 15.4%; DermaMatrix, 18.3%; p=0.8) or implant loss (AlloDerm, 2.2%; DermaMatrix, 3.7%; p=0.5) between the 2 ADMs.

AlloDerm versus FlexHD

A 2014 retrospective review by Liu et al compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts). Eighty-one percent of the sample was immediate reconstructions; 165 used AlloDerm, and 97 used FlexHD. Mean follow-up was 6.4 months. Compared with breast reconstruction without use of AlloDerm or FlexHD, ADM had a higher rate of delayed healing (20.2% vs 10.3%), although this finding might be related to differences in fill volumes. In univariate analysis, there were no significant differences in complications (return to the operating room, surgical site infection, seroma, hematoma, delayed healing, or implant loss) between AlloDerm and FlexHD. In multivariate analysis, there were no significant differences between AlloDerm or FlexHD for the return to the operating room, surgical site infection, seroma, or delayed healing. Independent risk factors for implant loss included the use of FlexHD, single-stage reconstruction, and smoking.

AlloDerm vs FlexHD Pliable and DermACELL

Chang and Liu (2017) reported on a prospective comparison of FlexHD Pliable (32 breasts), AlloDerm (22 breasts), and DermACELL (20 breasts) in breast reconstruction. The choice of ADM was based on different years when each ADM was available for use at the investigators' institution; patient demographics were comparable between groups. The pieces of ADM used were all the same size (8 × 16 cm) to eliminate an effect of size on outcomes. The time to drain removal was longer with AlloDerm (26 days) than with FlexHD (20 days) or DermACELL (15 days; p=0.001). Complications were low (four in the Flex Pliable group, two in the AlloDerm group, one in the DermACELL group), with no significant differences between groups. At the time of exchange for a permanent implant or free flap reconstruction, all grafts had completely incorporated into the mastectomy skin flaps. No patients developed complications requiring removal of the ADM.

Pittman et al (2017) reported a retrospective pilot study of the use of AlloDerm (50 breasts) and DermACELL (50 breasts). The choice of ADM was based on products available during different years and patient demographics were similar between the two groups. Patients in the DermACELL group had a significantly lower incidence of "red breast syndrome" (0% vs 26%, p=0.001) and fewer days until drain removal (15.8 days vs 20.6 days, p=0.017). There were no significant differences in the rates of other complications.

Strattice

Dikmans et al (2017) reported on early safety outcomes from an open-label multicenter RCT that compared porcine ADM-assisted one-stage expansion with two-stage implant-based breast reconstruction (see Table 2). One-stage breast reconstruction with porcine ADM was associated with a higher risk of surgical complications, reoperation, and with removal of implant, ADM, or both (see Table 3). The trial was stopped early due to safety concerns, but it cannot be determined from this study design whether the increase in complications was due to the use of the xenogenic ADM or to the comparison between 1-stage and 2-stage reconstruction.

Table 2. Summary of Key RCT Characteristics

					Interventions	
Author	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Dikmans et al (2017)	EU	8	2013-2015	Women intending to undergo skin-sparing mastectomy and immediate IBBR	59 patients (91 breasts) undergoing 1-stage IBBR with ADM	62 women (92 breasts) undergoing 2-stage IBBR

ADM: acellular dermal matrix; IBBR: implant-based breast reconstruction; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Outcomes

Study	Surgical Complications	Severe Adverse Events	Reoperation	Removal of Implant, ADM, or Both
Dikmans et al (2017)				
1-stage with ADM, n (%)	27 (46)	26 (29)	22 (37)	24 (26)
2-stage with ADM, n (%)	11 (18)	5 (5)	9 (15)	4 (5)
OR (95% CI)	3.81 (2.67 to 5.43)		3.38 (2.10 to 5.45)	8.80 (8.24 to 9.40)
p	<0.001		<0.001	<0.001

ADM: acellular dermal matrix; CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial.

Section Summary: Breast Reconstruction

Results from systematic reviews 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, rates of 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 studies may be considered sufficient to permit informed decision-making about risks and benefits of using allogeneic ADM for breast reconstruction.

Tendon Repair

Graftjacket

In 2012, Barber et al reported an industry-sponsored multi-center randomized controlled trial of augmentation with GraftJacket acellular human dermal matrix for arthroscopic repair of large (>3 cm) rotator cuff tears involving two tendons. Twenty-two patients were randomized to GraftJacket augmentation, and 20 patients were randomized to no augmentation. At a mean follow-up of 24 months (range, 12 to 38 months) the American Shoulder and Elbow Surgeons (ASES) score improved from 48.5 to 98.9 in the GraftJacket group and from 46.0 to 94.8 in the control group (p=0.035). The Constant score improved from 41 to 91.9 in the GraftJacket group and from 45.8 to 85.3 in the control group (p=0.008). The University of California, Los Angeles score was not significantly different between the groups. Gadolinium-enhanced magnetic resonance imaging (MRI) scans showed intact cuffs in 85% of repairs in the GraftJacket group and 40% of repairs in the control group. However, no correlation was found between MRI

findings and clinical outcomes. Rotator cuff re-tears occurred in three patients (14%) in the GraftJacket group and nine patients (45%) in the control group.

Section Summary: Tendon Repair
One small RCT was identified that found improved outcomes with Graftjacket ADM allograft for rotator cuff repair. Although results of this trial were promising, additional study with a larger number of patients is needed to evaluate consistency of findings and determine the effects of this technology with greater certainty.

Surgical Repair of Hernias or Parastomal Reinforcement
A 2013 systematic review evaluated the clinical effectiveness of acellular collagen-based scaffolds for the repair of incisional hernias. The bioprosthetic materials could be harvested from bovine pericardium, human cadaveric dermis, porcine small intestine mucosa, porcine dermal collagen, or bovine dermal collagen. Products included in the search were Surgisis, Tutomesh, Veritas, AlloDerm, FlexHD, AlloMax, CollaMend, Permacol, Strattice, FortaGen, ACell, DermaMatrix, XenMatrix, and SurgiMend. Sixty publications with 1212 repairs were identified and included in the review, although meta-analysis could not be performed. There were four level III studies (two AlloDerm, two Permacol); the remainder was level IV or V. The largest number of publications were on AlloDerm (n=27) and Permacol (n=18). No publications on incisional hernia repair were identified for AlloMax, FortaGen, DermaMatrix, or ACell. The overall incidence of a surgical site occurrence (eg, postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, mechanical failure) was 82.6% for porcine small intestine mucosa, 50.7% for xenogenic dermis, 48.3% for human dermis, and 6.3% for xenogenic pericardium. No comparative data were identified that could establish superiority to permanent synthetic meshes.

AlloDerm as an Overlay
In 2007, Espinosa-de-los-Monteros and colleagues retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases. They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

Comparisons between Products
AlloDerm versus Surgisis Gold
Gupta et al compared the efficacy and complications associated with the use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair in 2006. The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine submucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen seven to ten days after discharge from the hospital and at six weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in eight hernia recurrences (24%). Fifteen of the AlloDerm patients (45%) developed a diastasis or bulging at the repair site. Seroma formation was only a problem in two patients.

AlloDerm versus FlexHD
A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery. From 2005 to 2007, AlloDerm was used to repair large (>200 cm^2) symptomatic complicated ventral hernia that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD was used to repair large complicated ventral hernia in patients meeting the same criteria (n=40). The two groups were comparable at baseline. At one-year follow-up, all of the AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, or true recurrence) requiring a second repair. Eleven patients (31%) in the FlexHD group required a second repair. This comparative study is limited by the use of non-concurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

FlexHD vs Strattice
Roth et al (2017) reported on a prospective study assessing clinical and quality of life outcomes following complex hernia repair with a human (FlexHD) or porcine (Strattice) ADM. The study was funded by the Musculoskeletal Transplant Foundation, which prepares and supplies FlexHD. Patients were enrolled if they had a hernia at least 6 cm in the transverse dimension, active or prior infection of the abdominal wall, and/or enterocutaneous fistula requiring mesh removal. Eighteen (51%) of the 35 patients had undergone a previous hernia repair. After abdominal wall repair with the ADM, 20 (57%) patients had a surgical site occurrence, and nearly one-third had hospital readmission. The type of biologic material did not impact hernia outcomes. There was no comparison with synthetic mesh in this study, limiting interpretation.

Strattice versus Synthetic Mesh
In 2014, Bellows et al reported early results of an industry-sponsored multicenter RCT that compared Strattice (non-cross-linked porcine ADM, n=84) to a standard synthetic mesh (n=88) for the repair of inguinal hernias. The study was designed by the surgeons and was patient-and assessor-blinded to reduce risk of bias. Allocation concealment continued through two years of follow-up. The primary outcome was resumption of activities of daily living at one year. Secondary outcomes included complications, recurrences, or chronic pain (i.e., pain that did not disappear by three months postsurgery). At three-month follow-up, there were no significant differences in either the occurrence or type of wound events (RR=0.98; 95% CI: 0.52 to 1.86). Pain was reduced from one to three days postoperative in the group treated with Strattice, but at three month follow-up pain scores did not differ significantly between groups.

Strattice versus No Reinforcement
Also in 2014, THE PRISM Study Group reported a multicenter double-blinded randomized trial of Strattice for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies. Patients were randomly assigned to undergo standard stoma construction with no reinforcement (n=58) or stoma construction with Reconstructive Dermal Matrix as parastomal reinforcement (n=55). At 24-month follow-up (n=75), the incidence of parastomal hernias was similar for the two groups (13.2% of controls, 12.2% of study group).

Section Summary: Surgical Repair of Hernias or Parastomal Reinforcement
Current evidence does not support a benefit of ADMs in hernia repair or prevention of parastomal hernia. Additional RCTs are needed to compare biologic mesh with synthetic mesh and to determine if there is a patient population that would benefit from these products.

Diabetic Lower Extremity Ulcers
Systematic Reviews
A 2016 Cochrane review evaluated skin substitutes for the treatment of diabetic foot ulcers. Seventeen trials (total N=1655 participants) were included in the meta-analysis. Most trials identified were industry-sponsored, and an asymmetric funnel plot indicated publication bias. Pooled results of published trials found that skin substitutes increased the likelihood of achieving complete ulcer closure compared with standard of care (SOC) alone (RR=1.55; 95% CI, 1.30 to 1.85). Use of skin substitutes also led to a statistically significant reduction in amputations, (RR=0.43; 95% CI, 0.23 to 0.81), although the absolute risk difference was small. Analysis by individual products found a statistically significant benefit on ulcer closure for Apligraf, EpiFix, and Hyalograft-3D. The products that did not show a statistically significant benefit for ulcer closure were Dermagraft, Graftjacket, Kaloderm, and OrCel. Individual RCTs are described next.

Martinson and Martinson (2016) conducted an industry-sponsored analysis of Medicare claims data (13,193 treatment episodes) to compare efficacy and cost of skin substitutes for the management of diabetic foot ulcers. Included in the analysis were treatment episodes with Apligraf (37%), Dermagraft (42%), Oasis (19%), and Cytal (MatriStem, 2%). The mean number of applications was 3.24 for Apligraf, 4.48 for Oasis, 5.53 for Cytal, and 5.96 for Dermagraft. All comparisons were statistically significant. Healing at 90 days was modestly but statistically higher for Oasis (63%) and Cytal (62%) than for Apligraf (58%) or Dermagraft (58%). Amputation rates were similar after treatment with the 4 products, ranging from 1.3% for Oasis to 2.1% for Cytal.

Guo et al (2017) reported a systematic review of ADM for the treatment diabetic foot ulcer. Most data were from an RCT of Integra Dermal Regeneration Template, which is a bilayer product with the outer layer composed of a thin silicone film and not a pure ADM.

Apligraf, Dermagraft, AlloPatch, Integra Dermal Regeneration Template, or Integra Flowable Wound Matrix
Apligraf
In 2001, Veves and colleagues reported on a randomized prospective study on the effectiveness of Apligraf (previously called Graftskin), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers. The study involved 24 centers in the U.S.; 208 patients were randomly assigned to ulcer treatment either with Graftskin (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical debridement and adequate foot off-loading, was provided in both groups. Apligraf was applied at the beginning of the study and weekly thereafter for a maximum of four weeks (maximum of five applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Apligraf-treated patients achieved complete wound healing compared with 36 (38%) in the control group (p=0.0042). The Kaplan-Meier median time to

complete closure was 65 days for Apligraf, significantly lower than the 90 days observed in the control group (p=0.0026). The rate of adverse reactions was similar between the two groups, except osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf group. The authors concluded that application of Apligraf for a maximum of four weeks resulted in a higher healing rate when compared with state-of-the-art treatment and was not associated with any significant side effects. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf, in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.

In 2010, Steinberg and colleagues reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of non-infected diabetic foot ulcers. The design and patient population of this study were similar to the 208-subject United States study (described above) which led to FDA-approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with a non-infected neuropathic diabetic foot ulcer present for at least two weeks were enrolled in these prospective, multicenter, randomized, controlled, open-label studies that compared Apligraf use in conjunction with standard therapy (sharp debridement, standard wound care, and off-loading) against standard therapy alone. Pooling of data was performed because of the similarity and consistency of the two studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration that was significantly longer in the European study (21 months, compared to 10 months in the U.S. study). Reported adverse events by 12 weeks were comparable across treatment groups in the two studies. Efficacy measures demonstrated superiority of Apligraf treatment over control-treated groups in both studies. Combining the data from both studies, 55.2% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared to 34.3% (46/134) of control subjects (p=0.0005), and Apligraf subjects had a significantly shorter time to complete wound closure (p=0.0004). The authors concluded that both the EU and U.S. studies exhibited superior efficacy and comparable safety for subjects treated with Apligraf compared to control subjects, and the studies provide evidence of the benefit of Apligraf in treating diabetic foot ulcer (DFU).

In 2010, Kirsner and colleagues reported on analysis of 2,517 patients with diabetic neuropathic foot ulcers who were treated between 2001 and 2004. The study was a retrospective analysis using a wound-care database; the patients received advanced biological therapy i.e., Apligraf (446 patients), Regranex, or Procuren. The analysis found that advanced biological therapy was used, on average, within 28 days from the first wound clinic visit and associated with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biological therapy were 31.2% more likely to heal than wounds first treated with topical recombinant growth factor (p<0.001) and 40.0% more likely to heal than those first treated with platelet releasate (p=0.01). Wound size, wound grade, duration of wound, and time to initiation of advanced biological therapy affected the time to healing.

Dermagraft

A 2003 pivotal multi-center FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft or control. Over the course of the 12-week study, patients received up to eight applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91% compared to 78% for the control group.

Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious adverse events were attributed to Dermagraft. Ulcer infections developed in 10.4% of the Dermagraft patients compared to 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group (19% vs. 32.5%). Retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft (5.5% vs 12.6%, p=0.031). Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

AlloPatch
AlloPatch Pliable human reticular acellular dermis was compared to SOC in a 2017 industry-sponsored multicenter trial by Zelen et al. The trial was powered to detect a 45% difference between groups in percent healing at six weeks with 20 patients per group. Evaluation of the outcome measures was not blinded. At six weeks, 65% (13/20) of wounds treated with AlloPatch had healed compared to 5% (1/20) in the SOC-alone group ($p<0.001$) After adjusting for wound area at baseline, the hazard ratio for healing was 168 (95% CI, 10 to 2704; $p<0.001$), , indicating a lack of precision in the estimate. Per protocol, ten patients in the SOC group and one in the AlloPatch group exited the study at six weeks because their wounds failed to reduce in area by at least 50%. According to ITT analysis with last observation carried forward, the percentage of wounds healed at 12 weeks was 80% in the AlloPatch group compared to 20% in the SOC group. However, because there was a high (50%) withdrawal rate in the SOC group, this result has a high risk of bias.

Integra Omnigraft Dermal Regeneration Template or Integra Flowable Wound Matrix
Integra Dermal Regeneration Template is a biosynthetic skin substitute that is FDA approved for life- threatening thermal injury. The Foot Ulcer New Dermal Replacement Study (FOUNDER) multicenter study (32 sites) on the Integra Template for chronic non-healing diabetic foot ulcers was conducted under an FDA-regulated investigational device exemption. A total of 307 patients with at least 1 chronic diabetic foot ulcer were randomized to treatment with the Integra Template or a control condition (0.9%sodium chloride gel). Treatment was given for 16 weeks or until wound closure. There was a modest increase in wound closure with the Integra Template (51% vs 32%, p=0.001) and a shorter median time to closure (43 days vs 78 days, p=0.001). There was a strong correlation between investigator-assessed and computerized planimetry assessment of wound healing (r=0.97). Kaplan-Meier analysis showed the greatest difference between groups in wound closure up to 10 weeks, with diminishing differences after 10 weeks. Strengths of the study included adequate power to detect an increase in wound healing of 18%, which was considered to be clinically significant, secondary outcomes of wound closure and time to wound closure by computerized planimetry, and intention-to-treat (ITT) analysis.

Integra Flowable Wound Matrix is composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. It is supplied as a granular product that is mixed with saline. Campitiello et al (2017) published an RCT that compared the flowable matrix with wet dressing in 46 patients who had Wagner grade 3 diabetic foot ulcers. The ulcers had developed over 39 weeks. Complete healing at six weeks was achieved in significantly more patients in the Integra Flowable Wound Matrix group than in the control group, while the risk of rehospitalization and major amputation was reduced with Integra Flowable Wound Matrix (see Table 4).

Table 4. Probability of Wound Healing with IFWM vs SOC

Study	Complete Wound Healing	Rehospitalization	Major Amputation
Campitiello et al (2017)			
IFWM, n (%)	20 (86.95)	2 (6.69)	1 (4.34)
SOC, n (%)	12 (52.17)	10 (43.47)	7 (30.43)
RR (95% CI)	1.67 (1.09 to 2.54)	0.10 (0.01 to 0.72)	0.16 (0.02 to 1.17)
p	0.010	0.001	0.028

CI: confidence interval; IFWM: Integra Flowable Wound Matrix; RR: relative risk; SOC: standard of care.

Section Summary: Apligraf, Dermagraft, AlloPatch, or Integra for Diabetic Lower-Extremity Ulcers

RCTs have demonstrated the efficacy of Apligraf, Dermagraft, AlloPatch, Integra Dermal Regeneration Template, and Integra Flowable Wound Matrix over SOC for the treatment of diabetic lower-extremity ulcers.

Bioengineered Skin Substitutes Other than Apligraf, Dermagraft, AlloPatch, or Integra

GraftJacket Regenerative Tissue Matrix

Brigido et al reported a small (n=40) randomized pilot study of GraftJacket compared with conventional treatment for chronic non-healing diabetic foot ulcers in 2004. Control patients received conventional therapy with debridement, wound gel with gauze dressing, and off-loading. GraftJacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the GraftJacket group. Preliminary one-month results showed that after a single treatment, ulcers treated with GraftJacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs. 15%), width (50% vs. 23%), area (73% vs. 34%), and depth (89% vs. 25%). With follow-up to four weeks, no data were reported on the proportion with complete closure or the mean time to heal. All of the grafts were incorporated into the host tissue.

In 2009, Reyzelman et al reported an industry-sponsored multicenter randomized study that compared a single application of GraftJacket versus standard of care in 86 patients with diabetic foot ulcers. Offloading was performed using a removable cast walker. Ulcer size at presentation was 3.6cm^2 in the GraftJacket group and 5.1cm^2 in the control group. Eight patients, six in the study group and two in the control group, did not complete the trial. At 12 weeks, complete healing was observed in 69.6% of the GraftJacket group and 46.2% of controls. After adjusting for ulcer size at presentation, a statistically significant difference in non-healing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks versus 6.8 weeks for the control group. The authors did not report if this difference was statistically significant. The median time to healing was 4.5 weeks for GraftJacket (range, 1–12 weeks) and 7.0 weeks for control (range 2–12 weeks). Kaplan-Meier survivorship analysis for time to complete healing at 12 weeks showed a significantly lower non-healing rate for the study group (30.4%) compared with the control group (53.9%). The authors commented that a single application of GraftJacket, as used in this study, is often sufficient for complete healing. This study is limited by the small study population, differences in ulcer size at baseline. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant.

In 2015, Reyzelman and Bazarov reported an industry-sponsored meta-analysis of GraftJacket for diabetic foot ulcers that included the two studies described above and a third RCT by Brigido et al (2006) with 28 patients (total N=154 patients). The time to heal was estimated for the 2004 study by Brigido, based on the average wound reduction per week. The estimated difference in time to heal was considerably larger for Brigido's 2004 study (-4.30 weeks) than for the other two studies that measured the difference in time to heal (-1.58 weeks and -1.10 weeks). Analysis of the proportion of wounds that healed included studies by Brigido (2006) and Reyzelman (2009). The OR in the smaller study by Brigido was considerably larger with a lack of precision in the estimate (OR=15.0; 95% CI, 2.26 to 99.64), and the combined OR (3.75; 95% CI, 1.72 to 8.19) was not significant when analyzed using a random-effects model. Potential sources of bias, noted by Reyzelman and Bazarov, included publication and reporting biases, study selection biases, incomplete data selection, post hoc manipulation of data, and subjective choice of analytic methods. Overall, results of these studies do not provide convincing evidence that GraftJacket is more effective than SOC for healing diabetic foot ulcers.

DermACELL versus GraftJacket Regenerative Tissue Matrix or SOC
DermACELL and GraftJacket are both composed of human ADM. In 2016, Walters et al reported a multicenter randomized comparison of DermACELL, GraftJacket, or SOC (2:1:2 ratio) in 168 patients with diabetic foot ulcers. The study was sponsored by LifeNet Health, a nonprofit organ procurement association and processor for DermACELL. At 16 weeks, the proportion of completely healed ulcers was 67.9% for DermACELL, 47.8% for GraftJacket, and 48.1% for SOC. The 20% difference in completely healed ulcers was statistically significant for DermACELL versus SOC (p=0.039). The mean time to complete wound closure did not differ significantly for DermACELL (8.6 weeks), Graftjacket (8.6 weeks), and SOC (8.7 weeks).

A second report from this study was published in 2017. This analysis compared DermACELL with SOC and did not include the Graftjacket arm. The authors reported that either one or two applications DermACELL led to a greater proportion of wounds healed compared with SOC in per protocol analysis (see Table 5), but there was no significant difference between DermACELL (one or two applications) and SOC when analyzed by intention-to-treat. For the group of patients who received only a single application, the percentage of patients who achieved complete wound healing was significantly higher than SOC at 16 and 24 weeks, but not at 12 weeks. Although reported as ITT analysis, results were analyzed only for the group who received a single application of DermACELL. This would not typically be considered ITT unless the number of DermACELL applications was prespecified.

Table 5. Probability of Wound Healing in Per Protocol Analysis of DermACELL vs SOC

Study	Single Application			1 or 2 Applications		
	% With Wound Healing at 12 Wk	**% With Wound Healing at 16 Wk**	**% With Wound Healing at 24 Wk**	**% With Wound Healing at 12 Wk**	**% With Wound Healing at 16 Wk**	**% With Wound Healing at 24 Wk**
Cazzell et al (2017)						
DermACELL, %	65.0%	82.5%	89.7%	NR	67.9%	83.7%
SOC, %	41.1%	48.1%	67.3%	NR	48.1%	67.3%
HR (95% CI)	1.97 (1.1 to 3.5)	2.40 (1.4 to 4.1)	2.11 (1.3 to 3.5)		1.72 (1.04 to 2.83)	1.55 (0.98 to 2.44)
p	0.012	<0.001	<0.001	*NS*	0.028	0.049

CI: confidence interval; HR: hazard ratio; NR; not reported; *NS*: not significant; SOC: standard of care.

Theraskin versus Dermagraft

Sanders et al (2014) reported a small (n=23) industry-funded randomized comparison of Theraskin (human skin allograft with living fibroblasts and keratinocytes) versus Dermagraft (human-derived fibroblasts cultured on mesh) for diabetic foot ulcers. Wound size at baseline ranged from 0.5 to 18.02 cm^2; the average wound size was about 5cm^2 and was similar for the two groups (p=0.51). Grafts were applied according to manufacturer's instructions over the first 12 weeks of the study until healing, with an average of 4.4 Theraskin grafts (every two weeks) compared with 8.9 Dermagraft applications (every week). At week 12, complete wound healing was observed in 63.6% of ulcers treated with Theraskin and 33.3% of ulcers treated with Dermagraft (p<0.049). At 20 weeks, complete wound healing was observed in 90.9% of the Theraskin-treated ulcers compared with 66.67% of the Dermagraft group (p=0.428).

TheraSkin vs Apligraf

DiDomenico et al (2011) compared TheraSkin to Apligraf for the treatment of diabetic foot ulcers in a small (N=29) RCT. The risk of bias in this study is uncertain, because reporting did not include a description of power analysis, statistical analysis, method of randomization, or blinding. The percentage of wounds closed at 12 weeks was 41.3% in the Apligraf group and 66.7% in the TheraSkin group. Results at 20 weeks were not substantially changed from those at 12 weeks, with 47.1% of wounds closed in the Apligraf group and 66.7% closed in the TheraSkin group. The percentage healed in the Apligraf group was lower than expected based on prior studies. The average number of grafts applied was similar for both groups at 1.53 for Apligraf and 1.38 for TheraSkin. The low number of dressing changes may have influenced results, with little change in the percentage of wounds closed between 12 and 20 weeks. An adequately powered trial with blinded evaluation of wound healing and a standard treatment regimen would permit greater certainty on the efficacy of this product.

Cytal (MatriStem) vs Dermagraft

Frykberg et al (2017) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cytal, a porcine urinary bladder–derived extracellular matrix) versus Dermagraft in 56 patients with diabetic foot ulcers. The mean duration of ulcers before treatment was 263 days (range, 30-1095 days). The primary outcome was the percent wound closure with up to 8 weeks of treatment using blinded evaluation of photographs. Intention-to-treat (ITT) analysis found complete wound closure in five (18.5%) wounds treated with Cytal compared to

two (6.9%) wounds treated with Dermagraft (p=NS). Quality of life, measured by the Diabetic Foot Ulcer Scale, improved from 181.56 to 151.11 in the Cytal group and from 184.46 to 195.73 in the Dermagraft group (p=0.074). It should be noted that this scale is a subjective measure and patients were not blinded to treatment. Power analysis indicated that 92 patients would be required; further recruitment is ongoing for completion of the study.

PriMatrix™
In 2014, Kavros et al reported a prospective multicenter study of PriMatrix (a xenograft fetal bovine dermal collagen matrix) for the treatment of chronic diabetic foot ulcers in 55 patients. The average duration of ulcers before treatment was 286, and the average area was 4.34 cm^2. Of the 46 patients who completed the study, 76% healed by 12 weeks with an average of two applications of PriMatrix. For the intention-to-treat population, 64% of wounds healed by 12 weeks.

In 2011, Karr published a retrospective comparison of PriMatrix (a xenograft fetal bovine dermal collagen matrix) and Apligraf in 40 diabetic foot ulcers. The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. Included were diabetic foot ulcers of four weeks' duration, at least $1cm^2$ and depth to subcutaneous tissue, healthy tissue at the ulcer, adequate arterial perfusion to heal, and able to off-load the diabetic ulcer. The time to complete healing for PriMatrix was 38 days with 1.5 applications compared to 87 days with two applications for Apligraf. Although promising, additional studies with a larger number of subjects is needed to compare the efficacy of PriMatrix to current standard of care or advanced wound therapies.

Oasis™ Wound Matrix vs Regranex Gel
Niezgoda and colleagues (2015) compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix, an acellular wound care product, to Regranex Gel. This industry-sponsored randomized controlled multicenter trial conducted at nine outpatient wound care clinics and involved 73 patients with at least one diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix (n=37) or Regranex Gel (n=36) and a secondary dressing. Wounds were cleansed and debrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks of treatment, 18 (49%) Oasis-treated patients had complete wound closure compared with ten (28%) Regranex-treated patients. Oasis treatment met the non-inferiority margin, but did not demonstrate that healing in the Oasis group was statistically superior (p=0.055). Post-hoc subgroup analysis showed no significant difference in incidence of healing in patients with Type I diabetes (33% vs. 25%) but a significant improvement in patients with Type II diabetes (63% vs. 29%). There was also an increased healing of plantar ulcers in the Oasis group (52% vs. 14%). These post-hoc findings are considered hypothesis-generating. Additional study with a larger number of subjects is needed to evaluate the effect of Oasis treatment in comparison with the current standard of care.

Section Summary: Diabetic Lower-Extremity Ulcers
Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients 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.

Lower Extremity Ulcers Due to Venous Insufficiency

Apligraf or Oasis Wound Matrix

Apligraf

Falanga and colleagues reported a multicenter randomized trial of Apligraf (human skin equivalent) in 1998. A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or compression therapy and treatment with Apligraf. Apligraf was applied up to a maximum of five (mean 3.3) times per patient during the initial three weeks. The primary endpoints were the percentage of patients with complete healing by six months after initiation of treatment and the time required for complete healing. At six months' follow-up, the percentage of patients healed was increased with Apligraf (63% vs. 49%), and the median time to complete wound closure was reduced (61 vs. 181 days). Treatment with Apligraf was found to be superior to compression therapy in healing larger (>1,000 mm^2) and deeper ulcers and ulcers of more than six months' duration. There were no symptoms or signs of rejection, and the occurrence of adverse events was similar in both groups. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (Graftskin), in conjunction with good local wound care, met the TEC criteria for the treatment of venous ulcers that fail to respond to conservative management.

Oasis Wound Matrix

In 2005, Mostow et al reported an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment with Oasis Wound Matrix (xenogeneic collagen scaffold derived from porcine small intestinal mucosa) versus standard of care in 120 patients with chronic ulcers due to venous insufficiency that were not adequately responding to conventional therapy. Healing was assessed weekly for up to 12 weeks, with follow-up performed after six months to assess recurrence. After 12 weeks of treatment, there was a significant improvement in the percentage of wounds healed in the Oasis group (55% vs. 34%). After adjusting for baseline ulcer size, patients in the Oasis group were three times more likely to achieve healing than those in the standard care group. Patients in the standard care group whose wounds did not heal by the 12^{th} week were given the option to cross over to Oasis treatment. Of the healed patients treated with Oasis wound matrix and seen for the six-month follow-up, none experienced ulcer recurrence.

A research group in Europe has described two comparative studies of the Oasis matrix for mixed arteriovenous. In a 2007 quasi-randomized study, Romanelli et al compared the efficacy of two extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid). A total of 54 patients with mixed arterial/venous leg ulcers were assigned to the two arms based on order of entry into the study; 50 patients completed the study. Patients were followed up twice a week, and the dressings were changed more than once a week, only when necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis-treated ulcers compared with 46.2% of Hyaloskin-treated ulcers. Oasis treatment significantly increased the time to dressing change (mean of 6.4 vs. 2.4 days), reduced pain on a 10-point scale (3.7 vs. 6.2), and improved patient comfort (2.5 vs. 6.7).

In a 2010 trial, Romanelli et al compared Oasis with a moist wound dressing (SOC) in 23 patients with mixed arterial/venous ulcers and 27 patients with venous ulcers. The study was described as randomized, but the method of randomization was not described. After the eight-week study period, patients were followed up monthly for six months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis-treated ulcers at eight weeks, compared to 65% of the standard of care group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks as compared with 8.3 weeks for the standard of care group. Treatment with Oasis also increased the time to dressing change (5.2 vs. 2.1 days) and the percentage of granulation tissue formed (65% vs. 38%).

Subsection Summary: Apligraf or Oasis Wound Matrix for Lower-Extremity Ulcers due to Venous Insufficiency

RCTs have demonstrated the efficacy of Apligraf or Oasis Wound Matrix over SOC for lower-extremity ulcers due to venous insufficiency. Evidence is considered sufficient for these products.

Bioengineered Skin Substitutes Other than Apligraf or Oasis Wound Matrix for Lower-Extremity Ulcers due to Venous Insufficiency

Dermagraft

Dermagraft living cell therapy has been approved by FDA for repair of diabetic foot ulcers. Use of Dermagraft for venous ulcers is an off-label indication. In 2013, Harding el al reported an open-label multicenter RCT that compared Dermagraft plus compression therapy (n=186) versus compression therapy alone (n=180). The study had numerous inclusion/exclusion criteria that restricted the study population to patients who had nonhealing ulcers with compression therapy but had capacity to heal. Intention-to-treat analysis revealed no significant difference between the two groups in the primary outcome measure, the proportion of patients with completely healed ulcers by 12 weeks (34% Dermagraft vs 31% control). Prespecified subgroup analysis revealed a significant improvement in the percent of ulcers healed for ulcers of 12 months or less in duration (52% vs 37%) and for ulcers of 10cm or less (47% vs 39%). There were no significant differences in the secondary outcomes of time to healing, complete healing by week 24, and percent reduction in ulcer area.

PriMatrix™

In 2011, Karr published a retrospective comparison of PriMatrix and Apligraf in 28 venous stasis ulcers. The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Criteria were venous stasis ulcers of four weeks' duration, at least 1sq cm and depth to subcutaneous tissue, healthy tissue at the ulcer, adequate arterial perfusion to heal, and able to tolerate compression therapy. The time to complete healing for PriMatrix was 32 days with 1.3 applications compared to 63 days with 1.7 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

Section Summary: Lower Extremity Ulcers due to Venous Insufficiency

In a moderately large RCT, Dermagraft was not shown to be more effective than controls in the primary or secondary end points for the entire population and was slightly more effective than

controls (an 8%-15% increase in healing) only in subgroups of patients 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 PriMatrix treatment in comparison with the current standard of care.

Dystrophic Epidermolysis Bullosa
OrCel™ was approved under an HDE 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. Because this is a rare disorder, it is unlikely that there will be randomized controlled trials to evaluate whether OrCel improves health outcomes for this condition. HDE status has been withdrawn for Dermagraft for this indication.

Fivenson et al (2003) reported the off-label use of Apligraf in five patients with recessive dystrophic epidermolysis bullosa who underwent syndactyly release.

Section Summary: Dystrophic Epidermolysis Bullosa
Dystrophic epidermolysis bullosa is a rare disorder. Because this is a rare disorder, it is unlikely that RCTs will be conducted to evaluate whether OrCel improves health outcomes for this condition. Therefore, the HDE for OrCel is considered sufficient.

Deep Dermal Burns
Epicel
One case series from 2000 described the treatment of 30 severely burned patients with Epicel®. The cultured epithelial autografts were applied to a mean 37% of total body surface area. Epicel® achieved permanent coverage of a mean 26% of total body surface area, an area greater than that covered by conventional autografts (a mean 25%). Survival was 90% in these severely burned patients.

Integra Dermal Regeneration Template
A 2013 study compared Integra versus split-thickness skin graft or viscose cellulose sponge (Cellonex), using three test sites of 10 x 5 cm on each of ten burn patients. The surrounding burn area was covered with meshed autograft. Biopsies were taken from each site on days three, seven, fourteen, and twenty-one, and at three months and twelve months. The tissue samples were stained and examined for markers of inflammation and proliferation. The Vancouver Scar Scale was used for scar assessment. At 12-month follow-up, the three methods resulted in similar clinical appearance, along with similar histologic and immunohistochemical findings.

In 2007, Branski et al reported a randomized trial of Integra compared with a standard autograft-allograft technique in 20 children with an average burn size of 73% total body surface area (71% full-thickness burns) in 2007. Once vascularized (about 14-21 days), the Silastic epidermis was stripped and replaced with thin (0.05-0.13 mm) epidermal autograft. There were no significant differences between the Integra group and controls in burn size (70% vs. 74% total body surface area), mortality (40% vs. 30%), and length of stay (41 vs. 39 days – all respectively). Long-term follow-up revealed a significant increase in bone mineral content and density (24 months) and improved scarring in terms of height, thickness, vascularity, and pigmentation (12 months and 18-24 months) in the Integra group. No differences were observed between the groups in the

time to first reconstructive procedure, cumulative reconstructive procedures required during two years, and the cumulative operating room time required for these procedures. The authors concluded that Integra can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

In 2003, Heimback and colleagues reported a multicenter (13 U.S. burn care facilities) postapproval study involving 222 burn injury patients (36.5% total body surface area, range one-95%) who were treated with Integra® Dermal Regeneration Template. Within two to three weeks, the dermal layer regenerated, and a thin epidermal autograft was placed. The incidence of infection was 16.3%. Mean take rate (absence of graft failure) of Integra was 76.2%; the median take rate was 98%. The mean take rate of epidermal autograft placed over Integra was 87.7%; the median take rate was 95%.

TransCyte
TransCyte is no longer commercially available.

Earlier studies included a 2001 report by Lukish et al that found improved healing in 20 consecutive cases of pediatric burns greater than 7% TBSA that underwent wound closure using TransCyte compared to the previous 20 consecutive burn cases greater than 7% TBSA that received standard therapy. In 2006, Amani et al found significant improvement in healing in 110 consecutive patients who had deep partial-thickness burns treated with TransCyte as compared to results from the American Burn Association Patient Registry for similar burns.

Section Summary: Deep Dermal Burns
Epicel is FDA-approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a TBSA of 30% or more, with patient survival of 90%. Integra Dermal Regeneration Template has been compared with autograft in a within-subject study and with autograft-allograft in a small RCT with ten patients per group. Outcomes are at least as good as with autograft or allograft, with a reduction in scarring and without risks associated with cadaver skin. This product has also been studied in a large series with over 222 burn patients, showing a take rate of 76% and with a take rate of epidermal autograft placed over Integra of 87.7%.

Other
Punch Biopsy Wounds
Baldursson et al (2015) reported a double-blinded RCT with 81 patients (162 punch biopsy wounds) that compared Kerecis Omega3 Wound (derived from fish skin) with Oasis SIS ECM (porcine small intestinal submucosa extracellular matrix). The primary outcome (the percentage of wounds healed at 28 days) was similar for the fish skin ADM (95%) and the porcine SIS ECM (96.3%). The rate of healing was faster with Kerecis Omega3 (p=0.041). At 21 days, 72.5% of the fish skin ADM group had healed compared with 56% of the porcine SIS ECM group. Interpretation of this study is limited because it did not include an accepted control condition for this indication.

Split-Thickness Donor Sites
There is limited evidence to support the efficacy of OrCel compared to the standard of care for the treatment of split-thickness donor sites. Still et al examined the safety and efficacy of

bilayered OrCel to facilitate wound closure of split-thickness donor sites in 82 severely burned patients. Each patient had two designated donor sites that were randomized to receive a single treatment of either OrCel or the standard dressing (Biobrane-L). The healing time for OrCel sites was significantly shorter than for sites treated with a standard dressing, enabling earlier re-cropping. OrCel sites also exhibited a non-significant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

Miscellaneous

In addition to indications reviewed above, off-label uses of bio-engineered skin substitutes have included pressure ulcers, inflammatory ulcers such as pyoderma gangrenosum and vasculitis, scleroderma digital ulcers, post-keloid removal wounds, genetic conditions, and variety of other conditions. In addition, products that have been FDA approved/cleared for one indication (e.g., lower extremity ulcers) have been used off-label in place of other FDA approved/cleared products (e.g., for burns). No controlled trials were identified for these indications.

Summary of Evidence

Breast Reconstruction

For individuals who are undergoing breast reconstruction who receive allogeneic acellular dermal matric products, the evidence includes a RCT and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment related morbidity. Results from a 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 breast tissue for coverage, including but not limited to when the use of ADM allows a single-stage reconstruction, the available noncomparative studies 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 qualitatively 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 ADM, the evidence includes one RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life and treatment related morbidity. One RCT identified found improved outcomes with GraftJacket ADM allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of subjects 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 incudes RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Several comparative studies including RCTs show no difference in outcome between tissue-

engineered skin substitutes and either standard synthetic mesh or no reinforcement. The evidence is insufficient to determine the effects of the technology on 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, Dermagraft (living cell therapy), and Integra Dermal Regeneration Template (biosynthetic) over the standard of care. Several amniotic membrane products have also been shown to improve healing. The evidence is sufficient to determine qualitatively 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 disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients 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 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 qualitatively 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 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 (living cell therapy) was approved FDA approval under a humanitarian device exemption for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heals wounds created by the surgery, including those at donor sites. Outcomes have been reported in small series (e.g., five patients). This is a rare disorder and it is unlikely that there will be randomized controlled trials. Therefore, the HDE for OrCel is considered sufficient. OrCel is considered medically necessary for this condition.

Deep Dermal Burns

For individuals who have deep dermal burns who receive bioengineered skin substitutes (i.e., 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.

Clinical Input Received 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 two physician specialty societies and three 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 non-ocular burns (biosynthetic only). Input on the equivalency of products within these categories was mixed.

2014 Input

In response to requests, input was received from three physician specialty societies and four 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, 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 bio-engineered 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 (e.g., EpiFix) to be medically necessary for any indication.

Practice Guidelines and Position Statements

American Society of Plastic Surgeons and Wound Healing Society

Review of the literature for 2013 guidelines from the American Society of Plastic Surgeons (ASPS) found that evidence suggests that the use of ADM, although increasingly common in postmastectomy expander/implant breast reconstruction, can result in increased risk of complications in the presence of certain risk factors. The ASPS notes that cellular dermal matrix is currently used to increase soft tissue coverage, support the implant pocket, improve contour and reduce pain with expansion. However, evidence to support these improved surgical outcomes are limited. Some evidence suggests that use of ADM is associated with increased postoperative complications, specifically related to infection and seroma. Overall, the ASPS found that evidence on ADM products in postmastectomy expander/implant breast reconstruction is varied and conflicting, and gave a Grade C recommendation based on level III evidence that surgeons should evaluate each clinical case individually and objectively determine the use of ADM.

National Institute for Health and Care Excellence

In 2016, the U.K.'s National Institute for Health and Care Excellence (NICE) published clinical guidelines on the prevention and management of diabetic foot problems. NICE recommends 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.

Infectious Diseases Society of America

The 2012 guidelines from the Infectious Diseases Society of America (IDSA) state that for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents (weak recommendation, moderate evidence) growth factors (weak, moderate), granulocyte colony-stimulating factors (weak, moderate), hyperbaric oxygen therapy (strong, moderate), or negative pressure wound therapy (weak, low). It is emphasized that none of these measures have been shown to improve resolution of infection and that they are expensive, not universally available, may require consultation with experts, and reports supporting their utility are mostly flawed.

U.S. Preventive Services Task Force Recommendations

Not applicable

Approved by Governing Bodies:

A large number of artificial skin products that are commercially available or in development. The following summary of commercially available skin substitutes describes those products that have substantial relevant evidence on efficacy.

Acellular Dermal Matrix

Allograft acellular dermal matrix products derived from donated human skin tissue are supplied by U.S. AATB-compliant tissue banks using the standards of the American Association of Tissue Banks (AATB) and U.S. Food and Drug Administration's (FDA) guidelines. The processing removes the cellular components (i.e., epidermis and all viable dermal cells) that can lead to rejection and infection. Acellular dermal matrix products from human skin tissue are regarded as minimally processed and not significantly changed in structure from the natural material; the FDA classifies it as banked human tissue and therefore does not require FDA approval.

- AlloDerm® (LifeCell Corporation) is an acellular dermal matrix (allograft) tissue-replacement product that is created from native human skin and processed so that the basement membrane and cellular matrix remain intact. Originally, AlloDerm required refrigeration and rehydration prior to use. It is currently available in a ready-to-use product that is stored at room temperature. An injectable micronized form of AlloDerm (Cymetra) is also available.
- Cortiva® (previously marketed as AlloMax™ Surgical Graft (Bard Davol) is an acellular non-cross-linked human dermis allograft. (AlloMax was previously marketed as NeoForm™.)
- 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) is an acellular hydrated dermis derived from donated human allograft skin.
- DermaCell™ (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL® and PRESERVON®.
- DermaMatrix™ (Synthes) is a freeze dried acellular dermal matrix derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation® (MTF®).
- DermaPure™ (Tissue Regenix Wound Care Inc.) 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.

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 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 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) marketing 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. Crosslinking improves the tensile strength and long-term durability, but decreases pliability.

PriMatrix™ (TEI Biosciences) is a xenogeneic acellular dermal matrix processed from fetal bovine dermis. It is indicated through the U.S. Food and Drug Administration's (FDA) 510(k) process for partial and full-thickness wounds; diabetic, pressure, and venous stasis ulcers; surgical wounds; and tunneling, draining, and traumatic wounds.

SurgiMend® PRS (TEI Biosciences) is a xenogeneic ADM processed from fetal 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 derived from porcine small intestinal mucosa. It was cleared by the FDA's 510(k) process in 2000 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.

Living Cell Therapy

Apligraf® (Organogenesis) is a bi-layered 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 one size, with a shelf-life of 10 days. It was FDA-approved in 1998 for use in conjunction with compression therapy for the treatment of non-infected, 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.

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 FDA for repair of diabetic foot ulcers.

Theraskin® (Soluble Systems) is a cryopreserved 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 in compliance with the AATB and FDA guidelines. It is considered a minimally processed human cell, tissue, and cellular- and tissue-based product (HCT/P) by the FDA.

Epicel® (Genzyme Biosurgery) is a cultured epithelial autograft and is FDA-approved under a humanitarian device exemption (HDE) for the treatment of deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30%. It may be used in conjunction with split-thickness autografts or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns.

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

Biosynthetic Products

Biobrane®/Biobrane-L (Smith and Nephew) is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially imbedded into the film. The fabric creates a complex three dimensional structure of tri-filament thread, which chemically binds collagen. Blood/sera clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs.

Integra® Dermal Regeneration Template (marketed as Omnigraft Dermal Regeneration Matrix; Integra LifeSciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It is FDA-approved for use in post-excisional 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 that are FDA- 510(k) approved for other indications. Integra® Bilayer Wound Matrix (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.

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 to be used 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.

Key Words:

ACell®, acellular dermal matrix, AlloDerm®, AlloMax™, AlloMend, AlloSkin™ RT, ArthroFlex™ (FlexGraft), AlloSkin™, AlloSkin AC, Aongen, Apligraf®, Architect extracellular matrix, Atlas, Avagen, AvaultaPlus™, AxoGuard, Banked Human Tissue, Biobrane®, CellerateRX®, bio-engineered soft tissue substitutes, Bio-engineered skin substitutes, biosynthetic wound dressing, collagen scaffold, Collaguard, CollaSorb, CollaWound, Collexa, Collieva, Conexa™, Grafix®, Coreleader, CorMatrix®CRXa™, Cymetra®, Cytal ™, Dermacell, Dermadapt, Dermagraft®, DermaMatrix Acellular DermisDurepair Regeneration Matrix®, Dermapure™, DressSkin, dystrophic epidermolysis bullosa, Endoform Dermal Template™, ENDURAgen™, Excellagen, E-Z Derm™, FlexHD® Acellular Hydrated Dermis, GammaGraftGrafix®, GraftJacket®, hMatrix®, Helicoll, Hyalomatrix® PA, injectable, Innocoll, Integra Dermal Regeneration Template™, Integra™ Bilayer Wound Matrix, Integra™ Flowable Wound Matrix, HA, Hyalomatrix, Jaloskin, Keramatrix, Kerecis, Laserskin, living cell therapy, MariGen, MatriDerm®, MatriStem® Burn Matrix, MatriStem® Micromatrix, MatriStem® Wound Matrix, Matrix, Matrix HD™, MediHoney®, Mediskin®, MemoDerm™, Miroderm ® biologic wound matrix, Oasis® Burn Matrix, Oasis® Ultra Tri-Layer Matrix, Permacol™, OrCel™, PriMatrix, PuraPly™ wound Matrix, PuraPly™ AM, Puros, Regenerative Tissue Matrix GraftJacket®, Repliform, Repriza™, SIS, SS, Stimulen, StrataGraft, Strattice™ (xenograft), Suprathel®, SurgiMend®, Talymed®, TenoGlide™, Tensix, TheraForm, TheraSkin®Unite™, TransCyte™, TransCyte™, TruSkin™, Veritas® Collagen Matrix, Xcm biologic tissue matrix, XenMatrix™ AB, Xpress

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There are a large number of artificial skin products that are commercially available or in development. The following summary of commercially available skin substitutes describes those products that have substantial relevant evidence on efficacy.

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Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

HCPCS Codes:

C9354	Acellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm
C9358	Dermal substitute, native, nondenatured collage, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters
C9360	Dermal substitute, native, nondenatured collage, neonatal bovine origin (SurgiMend collagen Matrix), per 0.5 square centimeters
C9363	Skin substitute, Integra Meshed Bilayer Wound Matrix, per sq cm
C9364	Porcine implant, Permacol, per sq cm
C9367	Skin substitute, Endoform Dermal Template, per sq cm
Q4100	Skin substitute, not otherwise specified
Q4101	Apligraf, per sq cm

Q4102 Oasis wound matrix, per sq cm
Q4103 Oasis burn matrix, per sq cm
Q4104 Integra bilayer matrix wound dressing (BMWD), per sq cm
Q4105 Integra dermal regeneration template (DRT), or Integra Omnigraft dermal regeneration matrix, per sq cm
Q4106 Dermagraft, per sq cm
Q4107 GRAFTJACKET, per sq cm
Q4108 Integra matrix, per sq cm
Q4110 PriMatrix, per sq cm
Q4111 GammaGraft, per sq cm
Q4112 Cymetra, injectable, 1 cc
Q4113 GRAFTJACKET Express, injectable 1 cc
Q4114 Integra flowable wound matrix, injectable, 1 cc
Q4115 AlloSkin, per sq cm
Q4116 AlloDerm, per sq cm
Q4117 HYALOMATRIX, per sq cm
Q4118 MatriStem micromatrix, per sq cm
Q4121 TheraSkin, per sq cm
Q4122 Dermacell, per sq cm
Q4123 Alloskin RT, per sq cm
Q4124 Oasis Ultra Tri-Layer Wound Matrix, per sq cm
Q4125 Arthroflex, per sq cm
Q4126 Memoderm, per sq cm
Q4127 Talymed, per sq cm
Q4128 FlexHD OR Allopatch HD, per sq cm
Q4130 Strattice TM, per sq cm
Q4134 hMatrix, per sq cm
Q4135 Mediskin, per sq cm
Q4136 EZ-derm, per sq cm
Q4141 Alloskin ac, per sq cm **(Effective 01/01/14)**
Q4142 Xcm biologic tissue matrix, per sq cm **(Effective 01/01/14)**
Q4143 Repriza, per sq cm **(Effective 01/01/14)**
Q4146 Tensix, per sq cm **(Effective 01/01/14)**
Q4147 Architect, architect px, or architect fx, extracellular matrix, per sq cm **(Effective 01/01/14)**
Q4149 Excellagen, 0.1cc **(Effective 01/01/14)**
Q4152 DermaPure, per square centimeter **(Effective 01/01/16)**
Q4161 Bio-conneKt wound matrix, per square centimeter **(Effective 01/01/2016)**
Q4164 Helicoll, per square centimeter **(Effective 01/01/2016)**
Q4165 Keramatrix, per square centimeter **(Effective 01/01/2016)**
Q4166 Cytal, per sq cm **(Effective 01/01/17)**
Q4167 Truskin, per sq cm **(Effective 01/01/17)**
Q4172 PuraPly or Pura Ply AM, per sq cm **(Effective 01/01/17)**
Q4175 Miroderm, per sq cm **(Effective 01/01/17)**
Q4176 Neopatch, per square centimeter **(Effective 01/01/18)**
Q4182 Transcyte, per square centimeter **(Effective 01/01/18)**

Previous Coding:

Q4119 MatriStem wound matrix, per sq cm **(Deleted 12/31/16)**
Q4120 MatriStem burn matrix, per sq cm **(Deleted 12/31/16)**
Q4129 Unite Biomatrix, per sq cm **(Deleted 12/31/16)**

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Policy History:

Medical Policy Panel, January 2013
Medical Policy Group, April 2013 **(2):** New Policy
Medical Policy Administration Committee, August 2013
Available for comment August 22 through October 5, 2013
Medical Policy Group, December 2013 **(3)**: 2014 Coding Update – added new codes Q4137, Q4138, Q4139, Q4140, Q4141, Q4142, Q4143, Q4145, Q4146, Q4147, Q4148, Q4149 (effective 01/01/2014)
Medical Policy Panel, January 2014
Medical Policy Group, January 2014 **(3):** Updates to Policy statements, Key Points, Governing Bodies, Key Words, & References; added coverage statement for treatment of upper and lower eyelid retraction or conjunctival contraction requiring soft tissue spacer or replacement with AlloDerm®; added graft names under breast reconstructive surgery and updated list of grafts considered investigational.
Medical Policy Administration Committee, March 2014
Available for comment February 26 through April 11, 2014
Medical Policy Group, November 2014: 2015 Annual Coding Update – Updated code Q4147 with 'architect px, or architect fx' and added HCPCS codes Q4150, Q4150, Q4153-Q4157, Q4159 and Q4160.
Medical Policy Panel, January 2015
Medical Policy Group, April 2015 **(3):** Updates to Description, Key Points, Approved Governing Bodies, Key Words, & References. Thirteen new skin and soft tissue substitutes were added to the list considered investigational. No change to policy intent.
Medical Policy Group, November 2015: 2016 Annual Coding Update. Added new HCPCS codes Q4161, Q4164, and Q4165 to current coding. Revised HCPCS code Q4153 to add Plurivest
Medical Policy Group, May 2016 **(3)**: Removed information related to "ocular burns" from Key Points (literature review & summary) & References (removed Clare et al 2012) and transferred to new medical policy #624; no other changes made to current policy
Medical Policy Panel, June 2016
Medical Policy Group, June 2016 **(3):** 2016 Updates to Description, Key Points, Governing Bodies, Key Words, Coding & References; policy statements updated to reflect addition of Integra® Dermal Regeneration Template and Amniotic membrane Graft* (including Biovance®, Epifix®, Grafix™) to coverage criteria for the treatment of chronic, noninfected, full-thickness diabetic lower extremity ulcers; removed these from noncovered list; updated noncovered list with additional products not considered to meet medical criteria for coverage
Medical Policy Administration Committee, August 2016
Available for comment August 1 through September 14, 2016
Medical Policy Group, December 2016: 2017 Annual Coding Update. Added new CPT codes Q4166 – Q4175 to current coding. Created Previous Coding section and moved deleted codes Q4119, Q4120, and Q4129 to this section. Updated verbiage for revised codes Q4105 and Q4131.

Medical Policy Panel, January 2017
Medical Policy Group, May 2017 **(3):** 2017 Updates to Key Points, Key Words, Approved by Governing Bodies, Current Coding & Reference sections; removed all information related to **amniotic products** and relocated those to medical policy #597; removed policy section statements for dates of service prior to January 1, 2014; Policy section also updated by adding coverage criteria for AlloPatch and Allomax; added multiple products to ones considered investigational.
Medical Policy Administration Committee, June 2017
Available for comment May 31 through July 14, 2017
Medical Policy Panel, June 2017
Medical Policy Group, July 2017 **(3)**: added Cortiva™ to IV list; removed Cellerate® from IV list; no change in other policy statements; no change in comment period
Medical Policy Panel ad hoc product update, August 2017
Medical Policy Group, August 2017 **(3)**: Clarified policy statement regarding Integra® Dermal Regeneration Template and Integra® Omnigraft Dermal Regeneration Matrix (Omnigraft®)
Medical Policy Group, December 2017: Annual Coding Update 2018. Added new HCPCS codes Q4176 and Q4182 to the Current Coding section.
Medical Policy Panel, February 2018
Medical Policy Group, March 2018 **(3)**: 2018 Updates to Description, Key Points, Governing Bodies, Key Words, & References; Policy statements updated to include coverage criteria for DermACELL, FlexHD Pliable and Integra Flowable Wound Matrix as indicated
Available for comment March 14 through April 27, 2018
