Anthem FINAL DRAFT – LOGO TO BE INSERTED UPON FINAL PRODUCTION DATE

Medical Policy

Subject:	Allogeneic, Xenographic, Synthetic, and Composite Products for Wound Healing and Soft Tissue Grafting		
Document #:	SURG.00011	**Publish Date:**	12/18/2019~~10/01/2019~~
Status:	Revised	**Last Review Date:**	~~06~~11/0~~6~~7/2019

Description/Scope

This document addresses the use of soft tissue (e.g., skin, ligament, cartilage, etc.) substitutes in wound healing and surgical procedures. There is a wide array of uses for such products, including use as a cover for wounds related to disease processes (e.g., diabetes, peripheral artery and venous disease, recessive dystrophic epidermolysis bullosa), coverage or support of surgical and other wounds (e.g., complex abdominal wall repair, breast, and other types of reconstructive procedures), use as a surgical reconstructive material during surgical procedures (e.g., ligament augmentation or substitution, slings for internal organs, trauma, fistula repair, congenital defects), structural support of soft tissues (e.g., injection laryngoplasty, cosmetic augmentation), treatment for dermal and other burns, use in nerve grafting procedures, and many others. Tissue-engineered skin is a significant advance in the field of wound healing and was developed due to limitations associated with the use of autografts.

For the purposes of this document the following terms are defined as below:

- *Autologous:* A product derived from the individual's own body or body products.
- *Allogeneic:* A product derived from humans, other than the individuals themselves.
- *Xenographic:* A product derived from non-human organisms (e.g., cows, pigs, horses, etc.).
- *Synthetic:* A product derived from man-made materials.
- *Composite:* A product derived from a mix of materials of various origins.

Note: The use of fresh, unfrozen, unprocessed allogeneic cadaver-derived skin grafts is not addressed in this document.

Note: This document does not address the use of meshes or patches of non-biologic origin when used for standard hernia repair procedures.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Note: This document does not address products used to treat osteochondral defects.

Note: For additional information please see:
- ANC.00007 Cosmetic and Reconstructive Services: Skin Related
- ANC.00008 Cosmetic and Reconstructive Services of the Head and Neck
- MED.00110 Growth Factors, Silver-based Products and Autologous Tissues for Wound Treatment and Soft Tissue Grafting
- SURG.00023 Breast Procedures; including Reconstructive Surgery, Implants and Other Breast Procedures
- TRANS.00035 Mesenchymal Stem Cell Therapy for the Treatment of Joint and Ligament Disorders, Autoimmune, Inflammatory and Degenerative Diseases

Position Statement

Medically Necessary:

The use of allogeneic amniotic membrane-derived grafts or wound coverings, including AmbioDisk™, AmnioGraft®, Artacent® Ocular, and Prokera® ~~and AmnioGraft®~~, is considered **medically necessary** for reconstruction of large conjunctival resections, treatment of corneal injuries and as an adjunct to surgical procedures involving the cornea.

AlloDerm® Regenerative Tissue Matrix, also known as AlloDerm RTM, and AlloDerm® RTU, also known as AlloDerm Ready to Use, are considered **medically necessary** for either of the following uses:
- Surgical repair of complex abdominal wall wounds (for example, due to infection, fascial defect, etc.); **or**
- Breast reconstruction surgery.

The sheet or membrane form of AmnioBand is considered **medically necessary** when used for the treatment of diabetic foot ulcers that have not healed with standard conservative therapy (such as surgical debridement, complete off-loading, and standard dressing changes) attempted for at least 1 month but not greater than 52 weeks.

Apligraf® is considered **medically necessary** for a total of five (5) applications for either of the following indications:

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- Venous insufficiency skin ulcers with all the following characteristics:
  - Chronic, non-infected, partial- or full-thickness ulcers due to venous insufficiency; **and**
  - Standard therapeutic compression also in use; **and**
  - At least 1 month of conventional ulcer therapy (such as standard dressing changes, and standard therapeutic compression) has been ineffective; **or**
- Diabetic foot ulcers with all the following characteristics:
  - Full-thickness neuropathic diabetic foot ulcers; **and**
  - Extends through the dermis but without tendon, muscle, joint capsule, or bone exposure; **and**
  - At least 3 weeks of conventional ulcer therapy (such as surgical debridement, complete off-loading and standard dressing changes) has been ineffective.

Biobrane® is considered **medically necessary** when used for the treatment of full-thickness or deep partial-thickness burns.

DermACELL™ is considered **medically necessary** when used for the following indications:
- Breast reconstruction surgery; **or**
- Full-thickness diabetic foot ulcers of greater than 6 weeks duration that extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure.

Dermagraft® is considered **medically necessary** when used for either of the following indications:
- The treatment of full-thickness diabetic foot ulcers of greater than 6 weeks duration that extend through the dermis, but without tendon, muscle, joint capsule, or bone exposure; **or**
- When used on wounds with dystrophic epidermolysis bullosa.

DermaMatrix® is considered **medically necessary** for breast reconstruction surgery.

EpiCord is considered **medically necessary** when used for the treatment of diabetic foot ulcers that have not healed with standard conservative therapy (such as surgical debridement, complete off-loading, and standard dressing changes) attempted for at least 1 month but not greater than 52 weeks.

The sheet or membrane form of EpiFix™ is considered **medically necessary** when used for either of the following indications:

- The treatment of diabetic foot ulcers that have not healed with standard conservative therapy (such as surgical debridement, complete off-loading, and standard dressing changes) attempted for at least 1 month but not greater than 52 weeks; **or**
- The treatment of chronic venous stasis ulcers when the wound has been present for at least 1 month and has been unsuccessfully treated with compression therapy for at least 14 days.

EZ Derm™ is considered **medically necessary** when used for the treatment of full-thickness or deep partial-thickness burns.

FlexHD® is considered **medically necessary** for breast reconstruction surgery.

Fresh frozen unprocessed allograft skin products (for example, AlloSkin™*, TheraSkin®) are considered **medically necessary** for the treatment of full-thickness or deep partial-thickness burns when the following criteria have been met:

- Fresh, *unfrozen* allograft is not readily available; **or**
- In the opinion of the treating provider, the use of fresh, *unfrozen* allograft poses significant risk of disease transmission.

- ***Note:** "AlloSkin," "AlloSkin RT™" and "Alloskin™ AC" are different products. AlloSkin is a fresh-frozen product, AlloSkin RT is a fresh irradiated product (not frozen) and Alloskin AC is an acellular dermal matrix product.

Grafix® PRIME is considered **medically necessary** when used for the treatment of diabetic foot ulcers that have not healed with standard conservative therapy (such as surgical debridement, complete off-loading, and standard dressing changes) attempted for at least 1 month but not greater than 52 weeks.

The sheet or membrane form of GraftJacket™ is considered **medically necessary** for the treatment of lower extremity dermal wounds that have not healed with standard conservative therapy (such as surgical debridement, complete off-loading, standard dressing changes, and compression therapy) attempted for at least 1 month but not greater than 52 weeks.

Integra™ Bilayer Matrix Wound Dressing, an artificial skin substitute, is considered **medically necessary** in the post-excisional treatment of full-thickness or deep partial-thickness burns.

Oasis™ is considered **medically necessary** for the treatment of lower extremity dermal wounds that have not healed with standard conservative therapy (such as surgical debridement, complete off-loading, standard dressing changes, and compression therapy) attempted for at least 1 month but not greater than 52 weeks.

OrCel™ is considered **medically necessary** in children with recessive dystrophic epidermolysis bullosa who are undergoing reconstructive hand surgery.

PriMatrix™ is considered **medically necessary** for the treatment of lower extremity dermal wounds that have not healed with standard conservative therapy (such as surgical debridement, complete off-loading, standard dressing changes, and compression therapy) attempted for at least 1 month but not greater than 52 weeks.

Strattice™ is considered **medically necessary** when used for the following indications:

- Surgical repair of complex abdominal wall wounds (for example, due to infection, fascial defect, etc.); **or**
- Breast reconstruction surgery.

Investigational and Not Medically Necessary:

The following products are considered **investigational and not medically necessary** when criteria above are not met and for any use not listed above:

- AlloDerm Regenerative Tissue Matrix
- Allogeneic amniotic membrane-derived grafts or wound coverings
- AlloDerm Ready To Use
- AlloSkin
- AmbioDisk
- AmnioBand, sheet or membrane form
- AmnioGraft
- Apligraf
- Artacent Ocular
- Biobrane

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- DermACELL
- Dermagraft
- DermaMatrix
- EpiCord
- EpiFix, sheet or membrane form
- EZ Derm
- FlexHD
- Fresh frozen unprocessed allograft skin products (for example, AlloSkin*, TheraSkin)
- Grafix PRIME
- GraftJacket, sheet or membrane form
- Integra Bilayer Matrix Wound Dressing
- Oasis
- OrCel
- PriMatrix
- Prokera
- Strattice

The use of **all** other allogeneic, xenographic, synthetic, and composite products for wound healing or soft tissue grafting, including but not limited to the following products, is considered **investigational and not medically necessary** for all uses:

- Actishield™
- ActiveBarrier®
- ActiveMatrix®
- Affinity™
- AlloGen-LI™
- AlloGen™
- AlloMax™
- AlloMend™
- Allopatch HD™
- AlloPatch® Pliable
- Alloskin AC

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- AlloSkin RT
- AlloWrap®
- AlloWrap™ Dry
- AlloWrap™ DS
- Alphaplex™ with MariGen Omega3™
- Ambio5®
- ~~AmbioDisk™~~
- Amnio wound
- AmnioArmor
- AmnioBand, particulate or injectable form
- AmnioCare®
- AmnioClear®
- AmnioCord®
- AMNIOEXCEL™
- Amniofill®
- AmnioFix™
- Amnioflex™
- AmnioHeal®
- AmnioMatrix™
- AmnioMTM™
- Amniopro™
- AmnioShield®
- Amniostrip™
- Amniovo™ (Solo, Dual, and Matrix)
- Amniovo™ Max
- Amniowrap2™
- Aongen™ Collagen Matrix
- Architect Extracellular Matrix™
- Artacent® AC Powder
- Artacent® cord
- Artacent® Flex

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- Artacent® Wound
- Artelon®
- ArthroFlex™
- Ascent®
- Atlas Wound Matrix
- Avance® Nerve Graft
- Avaulta Plus™
- Avive®
- Axograft™
- AxoGuard® nerve connector
- AxoGuard® nerve protector
- Axolotl Ambient™
- Axolotl Cryo™
- Axolotl DualGraft™
- Axolotl Graft™
- Axolotl Shot™
- BellaCell HD
- Belladerm®
- BellaGen™
- Bio-ConneKt®
- BioDDryFlex® Resorbable Adhesion Barrier
- BioDExCel™
- BioDFactor™
- BioDFence™
- BioDOptix™
- BioFiber™
- BioVance®
- BioWound
- BioWound plus
- BioWound Xplus
- CardioCel®

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- CardioGRAFT®
- CellerateRX®
- Cellesta amnion granulate
- Cellesta amniotic membrane
- Cellesta cord
- Cellesta flowable amnion
- Cellesta™ Amniotic Membrane
- CG CryoDerm™
- CLARIX™ 100 Quick-Peel Wound Matrix
- CLARIX™ 1k
- CLARIX™ FLO
- CollaFilm®
- CollaFix™
- CollaGUARD®
- CollaMend™
- COLLARX®
- CollaSorb™
- CollaWound™
- Coll-e-Derm™
- Collexa®
- Collieva®
- Conexa™
- Coreleader Colla-Pad
- CorMatrix®
- Cortiva™ Allograft Dermis
- C-QUR™
- CRXa™
- CryoMatrix®
- CryoSkin®
- Cuffpatch™
- CYGNUS Matrix™

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- CYGNUS Max™
- CYGNUS Solo™
- Cymetra®
- Cytal® Burn Matrix (formerly MatriStem)
- Cytal® Multilayer Matrix (formerly MatriStem)
- Cytal® Wound Matrix (formerly MatriStem)
- Cytoflex®
- Cytoplast™
- DeNovo® NT Graft
- DermADAPT™ Wound Dressing
- DermaPure™
- DermaSpan™
- Dermavest 2™
- Dermavest™
- DressSkin™
- DuraForm™
- Duragen® XS
- Duragen™ Plus
- DuraMatrix™
- Durepair® Regeneration Matrix
- Endobon® Xenograft Granules
- Endoform™
- ENDURAgen™
- EpiBurn
- Epicel®
- EpiDex®
- EpiFix™, particulate or injectable form
- Excellagen®
- Fibro-Gide®
- FloGraft™
- FlowerDerm™

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- FlowerFlo™ (FlowerAmnioFlo)
- FlowerPatch™ (FlowerAMINOPatch)
- Fluid flow™
- Fluid GF™
- FortaDerm™ Wound Dressing (see PuraPly™)
- Fortiva™ Porcine Dermis
- GalaFLEX®
- GalaFORM®
- GalaSHAPE® 3D
- Gammagraft™
- Genesis amniotic membrane
- Gentrix® Surgical Matrix
- GENTRIX™
- GORE BIO-A® Fistula Plug
- Gore® Acuseal Cardiovascular Patch
- Grafix® CORE
- GrafixPL PRIME
- Graftjacket™ Xpress injectable
- GraftJacket™, injectable form
- GraftRope™
- HA Absorbent Wound Dressing
- Helicoll
- HeliMEND
- hMatrix®
- Hyalomatrix®
- Inforce®
- Integra® Dermal Regeneration Template (also see Omnigraft)
- Integra® Flow
- InteguPly™
- Interfyl
- Jaloskin®

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- Keramatrix®
- Kerasorb®
- KeraSys™
- Kerecis™ Omega3 (formerly MariGen Omega3)
- Keroxx Flowable Wound Matrix
- LiquidGen™
- Lyoplant® (See Tutopatch)
- MariGen Omega3 (see Karecis Omega3)
- MatrACELL®
- MatriDerm®
- MatriStem®
- Matrix HD™
- MatrixDerm™ (see Cytal)
- Medeor™
- MediHoney®
- Mediskin®
- Membrane Patch™
- Memoderm™
- Menaflex™ Collagen Meniscus Implant
- Meso BioMatrix™
- MIRODERM™
- Miromatrix Biological Mesh
- Nanofactor™ Flow
- Nanofactor™ Membrane
- Neoform Dermis™
- NEOX® 100 Quick-Peel Wound Matrix
- NEOX® 1k Wound Matrix
- NEOX® FLO
- Neuragen®
- NeuraWrap™
- Neuroflex™

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- NeuroMatrix™
- NeuroMend™
- NEVELIA® bi-layer matrix
- Novachor
- Novafix™
- NuCel®
- NuShield®
- Omnigraft (also see Integra Dermal Regeneration Template)
- OrthADAPT™
- Orthoflow
- OsseoGuard®
- Ovation®
- Ovitex™
- PalinGen Flow™
- PalinGen SportFlow™
- PalinGen® Xplus Hydromembrane
- PalinGen® Xplus Membrane
- Pelvicol®
- PelviSoft®
- Peri-Guard® Repair Patch
- Peri-Strips Dry®
- Permacol™
- Phasix Mesh™
- Plurivest®
- Preclude® Pericardial Membrane
- Preclude® Vessel Guard
- Progenamatrix™
- ProLayer
- ProMatrX ACF
- Promogran™
- PTFE felt

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- Puracol®
- PuraPly™ (see Fortaderm)
- Puros® Dermis
- PX50® and X50® Plus
- RegenePro™
- RENÚ® Gel
- RENÚ® Voice
- Repliform®
- Repriza™
- Restore® Orthobiologic Soft Tissue Implant
- Restorigin
- Revita®
- Revitalon™
- Rx Flow
- Rx Membrane
- Seamguard®
- SERI® Surgical Scaffold
- SIS Wound Dressing II
- SJM™ Pericardial Patch
- SportMatrix
- SportMesh™
- SS Matrix™
- SteriGraft™
- SteriMatrix™
- SteriSheild™
- Stimulen™ Collagen
- StrataGraft®
- Stravix™
- Suprathel®
- SureDerm
- SurgiCord™

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- surgiGRAFT™
- surgiGRAFT™
- surgiGRAFT™ nano
- surgiGRAFT™-Dual
- SurgiMend®
- Surgisis® (including Surgisis® AFP™ Anal Fistula Plug, Surgisis® Gold™ Hernia Repair Grafts, and Surgisis® Biodesign™)
- Surgraft
- Talymed™
- tarSys™
- TenoGlide™
- TenSIX™
- TheraForm™ Standard/Sheet
- TissueMend®
- Tornier® BioFiber Absorbable Biological Scaffold
- TranzGraft®
- TruSkin™
- Tutomesh™ Fenestrated Bovine Pericardium
- Tutopatch™ Bovine Pericardium
- Unite™
- Vascu-Guard®
- Veritas® Collagen Matrix
- VersaShield™
- Viaflow
- WoundEx®
- Woundfix Plus
- Woundfix Xplus
- Woundfix,
- Xceed™
- XCM Biologic™
- Xelma®

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

- XenMatrix™ Surgical Graft
- XenoSure® Biolog
- X-Repair
- Xwrap™ (Hydro, DRY, and ECM)

Rationale

General considerations

There are currently a wide variety of products available for soft tissue grafting and wound treatment. These products differ in species source (e.g., human cadaveric, synthetic, bovine, porcine, equine, a combination of several types, etc.), tissue source (e.g., dermis, pericardium, intestinal mucosa, etc.), bioburden reduction (e.g., nonsterile, sterile), additives (e.g., antibiotics, surfactants), delivery formats (e.g., wet packaged, freeze-dried), and preparation requirements (e.g., multiple rinses, rehydration). Additionally, they are procured, produced, manufactured or processed in sufficiently different manners that they cannot be addressed and evaluated as equivalent products. This is made evident not only in the wide range of shelf-life recommendations for these types of products, but also in the descriptions of their physical properties. Additionally, there are a limited number of comparative studies available addressing the clinical outcomes for allographic, xenographic, and composite products, and the results are heterogeneous. What comparative data that is available demonstrates a wide range of outcomes, with some studies reporting no differences and others indicating significant differences in the rate of healing, incidence of seroma and infection, surgical failure and other outcomes. Therefore, each product is assessed on the basis of the available scientific evidence specific to that product rather than considering groups of products as belonging to a class (for example, acellular dermal matrix products) and then evaluating all members of that class as though they were therapeutically equivalent. While this approach has certain merits, within each possible class that could be constructed there are products that have no full-text, peer-reviewed, published studies available to evaluate the safety and efficacy or draw a conclusion as to whether that particular product is therapeutically equivalent to another similar but studied product. Products for which there is a lack of quality published and peer-reviewed evidence to consider are considered investigational and not medically necessary. For other products, there may be one or more published studies of varying quality. The use of blinding in studies for these types of products may pose a challenge due to the nature of the products compared to standard therapies, as well as other factors. However, investigators should strive to design and apply rigorous study methodologies to minimize possible sources of bias within their trials.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Below, we summarize the findings of the most recent or most rigorous studies available. Please note that the discussion below is not meant to be an exhaustive review of the evidence available, but to address the most significant studies available for each product. Many studies have been omitted because they were considered poorly designed or too small to adequately demonstrate efficacy for a more general population.

Non-Product Specific Acellular Dermal Matrix (ADM) Studies, Meta-analyses, and Systematic Reviews

The use of ADM products of various origins has been proposed for both immediate and two-stage breast reconstruction surgeries and has become widely used and accepted. However, the current evidence of these techniques has been understudied and the data that has been made available is not from rigorously designed and conducted randomized controlled trials (RCTs).

To properly address the question of both safety and efficacy, the MultiCentre Canadian Acellular Dermal Matrix trial (MCCAT) has begun recruitment in a two-arm parallel superiority trial that will compare one-stage ADM facilitated implant breast reconstruction with two-stage tissue expander and implant breast reconstruction (Zhong, 2013). The results addressing this pressing issue are eagerly anticipated.

In 2012, two well-designed meta-analysis studies were published that evaluated the available peer-reviewed published evidence addressing the use of ADMs for use in breast reconstruction procedures. Ho and colleagues conducted their meta-analysis using 16 studies that met their inclusion criteria. They noted that analysis of complication rates was limited by the small number of studies and the small sample size of study participants. Additionally, they commented that the overall quality of the evidence was low. Five studies were included that had data for both subjects who received ADM and those who did not. Overall, they found that the ADM group had significantly higher complication rates for seroma, infection, and reconstructive failure when compared with the non-ADM group. ADM-assisted breast reconstructions were found to be almost 4 times as likely to be complicated by seroma, nearly 3 times as likely to become infected, and 3 times as likely to have a reconstructive failure as breast reconstructions performed without the use of ADM. After exclusion of outlier data, they found that the pooled odds ratio (OR) of developing skin flap necrosis in ADM reconstructions was three-fold higher than non-ADM reconstructions.

Kim and others conducted a meta-analysis on 44 studies that met their inclusion criteria. The results found that there was an increased rate of total complications with ADM use when compared to non-ADM reconstructions

(15.4% vs. 14.0%). For specific complications, this finding continued to apply; specifically for seroma (4.8% vs. 3.5%), infections (5.3% vs. 4.7%), and flap necrosis (6.9% vs. 4.9%). However, the rate of hematoma was greater in the control cohort (1.5% vs. 1.0%). The rate of reconstructive failure was very similar in both cohorts, 3.8% vs. 3.8%. When looking at the studies that provided comparative data between ADM and non-ADM groups in the same study, the authors noted that there was an increase in the risk of total complications (relative risk [RR], 2.05; 95% confidence interval [CI], 1.55 to 2.70), seroma (RR, 2.73; 95% CI, 1.67 to 4.46), infection (RR, 2.47; 95% CI, 1.71 to 3.57), and reconstructive failure (RR, 2.80; 95% CI, 1.76 to 4.45) in the ADM group vs. the non-ADM group. These findings call into question the practice of using ADM for breast reconstruction surgery.

A systematic review of ADM use for abdominal wall reconstruction was published by Zhong and others (2011). They report on a total of 30 articles that met inclusion criteria, specifically mentioning that they did not identify any level I or II studies addressing this issue. They included 4 level III and 26 level IV studies. Among their findings they report wide variation in indications for ADM use and poorly defined terminology used to define subject populations (e.g., abdominal wall reconstruction, high-risk/recurrent/complex/large ventral hernia and high-risk/contaminated wound). The incidence of postoperative hernia varied widely, with some studies reporting 0% and others reporting 80%. Out of the 30 studies reviewed, three used porcine ADM, one a synthetic composite mesh, and one a bovine-derived ADM. No separate data was provided for these studies. The remainder of the studies used allogeneic ADMs. Within the literature, there was significant variation with regard to placement of ADMs within the surgical field, with ADM used as underlay/inlay, interposition, overlay/onlay or sandwiched (underlay and overlay) repairs. The type of fascial repair (bridged vs. reinforced) also had significant impact on outcomes. They state that in cases where fascial re-approximation was achieved, ADM used in a reinforced repair with fascial re-approximation was significantly better than that used in a bridged repair without fascial re-approximation. With the significant variation in selection criteria, ADM types, and surgical techniques, this pool of evidence should not be used to evaluate the use of ADM for abdominal reconstructions in a global manner, and each study should be weighed on its own merits.

Ibrahim and colleagues (2013) conducted a large retrospective study using data from the American College of Surgeon's (ACS) National Surgical Quality Improvement Program (NSQP) database. The study investigated 30 day outcomes in 19,100 cases that involved tissue expander implant-based breast reconstruction surgeries. A subset of 3301 (17.3%) cases involved the use of ADMs as part of the surgical procedure. It was reported that, overall, the rate of complications was not statistically different between cases that used ADMs (n=175, 5.3%) and those that did not (n=776, 4.9%) (p=0.396). This rate is much lower than the rate of complications reported in previous studies. It should be noted that there are several major limitations of this study, including the fact that the data was derived

retrospectively from a large database with no randomization, no blinding, and no concurrent comparison groups. Additionally, the ACS does not use a standardized definition for the term "complications." This presents a major problem, considering that there may be significant heterogeneity in the major study endpoint data. Also of import is that the data in the NQSP database is derived from academic medical centers, and no data from community hospitals and private clinics is included. It is unclear whether or not this had an impact on complication rates. Finally, there were significant differences between groups at baseline with regard to age, race, and type of reconstruction, which may have introduced significant bias into the analysis.

In 2017, Lee and others published a meta-analysis investigating the use of ADMs for implant-based breast reconstruction. A total of 17 studies were included, with only one being a prospective RCT and the others having retrospective nonrandomized designs. There were 12 studies available involving comparisons with FlexHD, DermaMatrix, and AlloDerm RTM or AlloDerm RTU. In the meta-analysis comparing FlexHD and AlloDerm RTM, involving a total of six studies, both products showed similar pooled risks for all complications. For comparisons between DermaMatrix and AlloDerm RTM, the results from four studies likewise found no differences between the pooled risks of complications. Finally, the meta-analysis of four studies comparing AlloDerm RTM or AlloDerm RTU demonstrated that the pooled risks for the complications did not differ. The authors concluded that these products have similar risks of complications compared to AlloDerm RTM.

Sorkin (2017) reported the results of a retrospective controlled study involving 1297 subjects who underwent expander/implant based breast reconstruction procedures with either ADM (n=655) or no ADM (n=642). At 2 years post-procedure, no significant differences were seen between groups with regard to overall complications (OR, 1.21; p=0.263), major complications (OR, 1.43; p=0.052), wound infections (OR, 1.49; p=0.118), or reconstructive failures (OR, 1.55; p=0.089). No significant differences were reported in patient-reported outcome scores, including satisfaction with breasts, psychosocial well-being, sexual well-being, physical well-being, and postoperative pain.

Products addressed in the Medically Necessary statement

Allogeneic amniotic membrane-derived grafts or wound coverings used for ophthalmologic indications.

Allogeneic amniotic membrane-derived products have a history of longstanding use for the management of select ophthalmologic wounds and reconstruction of large conjunctival resections where there is limited access to autologous tissue for transplant, or when allogeneic transplant is not appropriate. These types of products come in a wide array of forms, including cryopreserved, fresh-frozen, lyophilized, irradiated, stored in mineral oil, and others.

Most products used are obtained directly from tissue banks and not marked by any particular manufacturer. However, several products are commercially marketed, including AnmioGraft and Prokera.

Reconstruction of large conjunctival resections

The treatment of large conjunctival resections, commonly needed for the surgical treatment of cancerous lesions of the eye, is a challenge due to the finite amount of conjunctival tissue available for local conjunctivoplasty or rotational flaps. In such cases, the use of amniotic membrane-derived products have become the standard-of-care option to provide adequate grafting materials to successfully complete these types of procedures, and multiple small case series studies have been published to support this use (Asoklis, 2011; Dalla Pozza, 2005; Gündüz, 2006; Hanada, 2017; Paridaens, 2001; Tanaka, 2016, Tseng, 1997).

Bullous keratopathy in individuals who are not candidates for curative endothelial or penetrating keratoplasty

Amniotic membrane-derived products are one of several modalities used for treatment of bullous keratopathy due to corneal endothelial dysfunction. Given that amniotic membrane-derived products do not address the underlying endothelial disease, their role in treating bullous keratopathy is palliative rather than curative; for this reason, it is a reasonable alternative for individuals who are not candidates for curative endothelial or penetrating keratoplasty. Supporting evidence includes a prospective RCT of 40 subjects treated with amniotic membrane transplantation or anterior stromal puncture (Paris F dos S, 2013). At 90 and 180 days post-procedure, the presence of a regular epithelial surface was higher in the amnion group than in the control group (60% vs. 16.7% at 90 days, p=0.006; and 50% vs. 6. 3% at 180 days, p=0.008). At 180 days follow-up there was no statistical difference between the two groups in pain severity (p=0.391) or duration (p=0.715). Georgiadis (2008) published the results of a prospective case series study involving 81 subjects with bullous keratopathy treated with cryopreserved amniotic grafts. They reported that 71 (87.6%) eyes became asymptomatic with healed epithelium at a mean of 21 months follow-up. Repeated amniotic transplantation was needed for 7 subjects and 3 underwent penetrating keratoplasty. Visual acuity improved in 64 (79%) subjects and remained unchanged in 14. No complications were recorded.Multiple other small case series studies describe positive results from the use of amniotic graft products for bullous keratopathy (Chansanti O, 2005; Espana EM, 2003; Pires RT, 1999; Siu, 2015; Srinivas, 2007; Stefaniu, 2014).

Acute chemical burns of the ocular surface

Acute chemical burns of the ocular surface can be challenging to treat due to the lack of transplantable or resectionable autologous tissue. Use of amniotic membrane-derived products has been shown to reduce inflammation and promote healing. The use of this type of graft has been described in two prospective RCTs. The first involved subjects (44 eyes) with acute moderate grade ocular burns treated with amniotic graft (n=20) or standard medical care (n=24) (Tamhane, 2005). Standard medical care involved the use of topical prednisolone acetate (1%), ofloxacin, sodium ascorbate (10%), sodium citrate (10%), preservative-free lubricants, homatropine (2%), oral vitamin C (500 mg) and antiglaucoma therapy including timolol maleate 0.5% drops and/or oral acetazolamide if required. The authors reported that the log mean percentage reduction in size of epithelial defect by day 7 was 7.43 ± 0.89 after amnion treatment vs. 6.23 ± 1.10 with control treatment (p=0.01). However, there was no difference between the two groups in eyes with severe burns. Additionally, no difference between groups was noted in the final visual acuity, symblepharon formation, corneal vascularization, and tear function tests at 3 months. The second RCT involved 100 subjects with moderate to severe ocular burns treated with amniotic graft (n=50) or standard medical care (n=50) (Tandon, 2011). The rate of epithelial healing was reported to have been significantly better in the amnion group vs. controls (p=0.0004). No other differences between groups was reported with regard to final visual outcome, symblepharon formation, corneal clarity and vascularization with or without amniotic membrane transplantation. In addition to these RCTS, multiple small to medium sized case series studies have been reported demonstrating beneficial results with amniotic grafts for ocular chemical burns (Arora, 2005; Kheirkhah, 2008; Prabhasawat. 2007; Tejwani, 2007; Uçakhan, 2002; Westekemper, 2000).

Persistent corneal epithelial defects that do not respond to conservative therapy

The prompt treatment of persistent corneal epithelial defects that do not respond to conservative therapy is critical due to the risk of the development of corneal ulcers, corneal melt, and perforation. While first-line treatment of corneal defects include topical lubricants, antibiotics, therapeutic contact lenses and patching, when these methods fail, the use of amniotic membrane-derived products has become the standard of care. In severe cases, the option of corneal transplantation is available, but that procedure entails its own significant risks, and less invasive methods are often tried first. One prospective RCT evaluated 19 subjects with corneal thinning treated with amnion (n=9) or allograft cornea (n=10) (de Farias, 2016). All subjects showed significant increase in final thickness in the area of thinning at 180 days postoperatively, but those who received corneal transplant had a slight but significantly higher final thickness (p=0.48). Regardless of the surgical technique, all subjects showed epithelialization. No difference between groups was noted for post-op corneal opacity. Subjects undergoing amnion grafting showed an 89% decrease in neovascularization, whereas none was reported in the corneal transplant group. Final corrected distance visual acuity was better in subjects submitted to AMT. In addition to this study, additional small case series studies

have been published demonstrating beneficial outcomes (Dekaris, 2010; Gris, 2002; Lee, 1997; Letko, 2001; Prabhasawat, 2001; Seitz, 2009).

Corneal perforation when corneal tissue is not immediately available or as adjunct to corneal transplantation in individuals with active inflammation

As noted above, the use of corneal transplant is the preferred method of treatment for corneal perforation. However, the temporary use of amniotic membrane-derived products has been a standard temporary option when transplant tissue is not immediately available or if there is ongoing active inflammation. Multiple small case series studies have described the successful use of amnion-derived grafting products for this purpose (Hick, 2005; Prabhasawat, 2001; Rodríguez-Ares, 2004; Solomon, 2002).

Corneal ulcers or corneal melts that do not respond to conservative therapy

Similar to the treatment of persistent corneal epithelial defects, treatment of corneal ulcers or corneal melts (also known as keratolysis) that do not respond to conservative therapy is critical to avoid the development of corneal perforation. While corneal ulcers and corneal melts may result from a wide range of etiologies, a common characteristic is underlying inflammation. The use of amniotic membrane-derived products is accepted as an adjunctive treatment along with treatment of the primary cause of the condition when use of topical lubricants, antibiotics, or therapeutic contact lenses fails. Multiple small case series studies have been published supporting this approach (Chen, 2006; Hanada, 2001; Kruse, 1999; Prabhasawat, 2001; Sheha, 2009; Solomon, 2002; Tok, 2015).

Neurotrophic keratitis that does not respond to conservative therapy

Neurotrophic keratitis, similar to persistent corneal epithelial defects, corneal ulcers, and corneal melts, presents a significant risk of corneal perforation when unresponsive to conservative therapy such as topical lubricants, antibiotics, therapeutic contact lenses and patching. As with those other conditions, treatment of refractory neurotrophic keratitis with amniotic membrane-derived products has become widely accepted as standard of care and described in several small to moderate sized case series studies (Chen, 2000; Iveković, 2002; Khokhar, 2005; Suri, 2013; Uhlig, 2015).

Partial limbal stem cell deficiency in conjunction with superficial keratectomy

Limbal stem cell deficiency is characterized by a loss or deficiency of the stem cells in the limbus that are vital for re-population of the corneal epithelium. Total limbal stem cell deficiency is commonly treated with limbal cell transplantation; partial limbal stem cell deficiency is commonly treated with an approach which includes grafting with amniotic membrane-derived products in conjunction with superficial keratectomy to remove the diseased tissue (Kheirkhah, 2008; Sangwan, 2004).

Extensive, double, or recurrent pterygium in which there is insufficient healthy tissue to create a conjunctival autograft

A pterygium is a triangular, fleshy fold of tissue that extends from the conjunctiva and encroaches onto the cornea. The size and growth rate of pterygia vary, and when vision is affected, surgery is often indicated. Treatment of pterygium is most commonly done with autograft or bare scleral techniques. Multiple RCTs have demonstrated that for both primary and recurrent pterygium, treatment with autograft was superior to treatment with amniotic membrane-derived products (Küçükerdönmez, 2007; Luanratanakorn, 2006; Prabhasawat, 1997; Tananuvat, 2004). This is supported by the American Academy of Ophthalmology in their 2013 report tited Options and Adjuvants in Surgery for Pterygium (Kaufma, 2013), as well as Cochrane review (Clearfield, 2016). However, when there is extensive, double, or recurrent pterygium in individuals who have insufficient healthy tissue to create a conjunctival autograft, the amniotic membrane-derived products may be used.

Moderate or severe Stevens-Johnson syndrome involving the cornea and/or conjunctiva

For moderate or severe Stevens-Johnson syndrome (SJS), there are few treatment options, and the use of amniotic membrane-derived products has been widely accepted as the standard of care. A prospective RCT published by Sharma (2016) involved 50 subjects with acute SJS who were assigned to treatment with either amnion (n=25) or medical therapy (n=25). The authors reported that best-corrected visual acuity at 6 months was significantly better in the amnion group vs. controls (p=0.042). Mean tear film breakup time and Schirmer test results were also significantly better in the amnion group vs. controls (p=0.015 and p=0.001, respectively). Conjunctival congestion persisted in 44% of control subjects vs. 4% in the amnion group at 6 months (p=0.03). Corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications were not reported in the amnion group, but the control group experienced corneal haze (44%, p=0.001), corneal vascularization and conjunctivalization (24%, p=0.03), symblepharon (16% , p=0.12), ankyloblepharon (4%, p=1.00), ectropion and entropion (8%, p=0.47), and trichiasis and metaplastic lashes (24%, p=0.03). Several small case series studies have

also demonstrated favorable outcomes (Gregory, 2011; Honavar, 2000; John, 2002; Shammas, 2010; Tomlins, 2013).

Other conditions

Amniotic membrane-derived products have been investigated for the treatment of other conditions, including glaucoma and dry eye. The treatment of glaucoma has been studied in two controlled trials. The first, published by Mahdy (2010), was a nonrandomized controlled trial involving 30 pediatric subjects with glaucoma treated with either trabeculectomy with mitomycin C or trabeculectomy with mitomycin C plus lyophilized amniotic membrane. The authors reported that operative success occurred in 80% of amnion group subjects and 60% of control subjects. Mean postoperative intraocular pressure was significantly decreased in both groups. However, the intraocular pressure gradually increased throughout the follow-up visits, with significantly higher intraocular pressure in the amnion group vs. controls up to 18 months ($p<0.05$). Complications such as inflammation, choroidal detachment, or toxic keratopathy were not noted in the amnion group but were noted in the control group. The authors concluded that trabeculectomy with amniotic membrane transplantation and mitomycin C can effectively control the elevated intraocular pressure in pediatric patients with glaucoma without significant postoperative complications. The other study by Sheha and others (2008) was a prospective RCT of 37 eyes with glaucoma undergoing trabeculectomy with mitomycin C and amnion (n=19 eyes) or trabeculectomy with mitomycin C alone (n=18). Complete success, defined as intraocular pressure < 22 mm Hg without glaucoma medications, was reported in 93.7% of amnion-treated eyes and 60% control eyes at 6 months ($p=0.03$), and 80% and 40% at 12 months ($p=0.03$). Intraocular pressure decreased significantly in both groups at 12 months ($p<0.0001$). Early postoperative hypotony developed in 16.7% of control eyes owing to excessive filtration but none of the amnion group eyes ($p=0.1$). Encapsulated bleb occurred in 38.9% of control eyes but in 5.3% of amnion-treated eyes ($p=0.02$). While these studies have demonstrated significant benefits, the use of amniotic membrane-derived products has not yet become widely accepted as standard practice. A wide array of other less invasive treatment options are currently available which provide significant relief to this population.

Short term treatment of dry eye has also been a proposed use for amniotic membrane-derived products. One small RCT has been published addressing this treatment option (John, 2017). The small prospective RCT involved 17 subjects with dry eye disease treated with either cryopreserved amnion (n=8) or standard care (n=9). The authors stated that pain and visual disturbances decreased significantly in the amnion group but not in the control group (no p values provided). No differences between groups were reported for visual acuity. Dry Eye Work Shop (DEWS) measures were significantly improved vs. controls (no p values provided). No differences between groups were

reported for corneal topography measures. Central corneal nerve density, dendritiform cell density and corneal sensitivity was greater in the amnion group (no p values provided). While these reported findings seem beneficial, the small sample size and lack of proper statistical data do not allow reliable conclusions. Two case series studies have also demonstrated beneficial outcomes (Cheng, 2016; McDonald, 2018, described below). Use of amniotic membrane-derived products also limits visual acuity. However, this treatment has not been widely accepted as a standard treatment approach in the clinical setting. Many effective less invasive treatments are available for dry eye.

Several branded amniotic-membrane derived products have been the subject of published peer-reviewed studies. These are described below:

Prokera

Prokera is a composite product consisting of amniotic membrane tissue in between two rings of clear, flexible material. It was cleared through the FDA's 510K process and is intended for use in eyes in which the ocular surface cells have been damaged, or underlying stroma is inflamed and scarred. The device is inserted between the eyeball and the eyelid to maintain space in the orbital cavity and to prevent closure or adhesions.

To date, the largest study published addressing the use of Prokera was a retrospective case series study involving 97 eyes of 84 subjects with severe dry eye refractory to maximal medical management (McDonald, 2018). Subjects had superficial punctate keratitis (86%), filamentary keratitis (13%), exposure keratitis (19%), neurotrophic keratitis (2%), and corneal epithelial defect (7%). After treatment with Prokera for a mean of 5.4 days, 74 (88%) of subjects demonstrated an improved ocular surface. Dry eye workshop score (DEWS) was reduced significantly from 3.25 at baseline to 1.44 at 1 week, 1.45 at 1 month, and 1.47 at 3 months ($p<0.001$ for all). A total of 10 eyes (10%) required repeated treatment to complete healing. Apart from discomfort during CAM placement, there were no adverse events.

Another smaller retrospective case series study involved placement of Prokera in 58 subjects undergoing penetrating keratoplasties (PKP) in high-risk recipients (Nguyen, 2014). Twelve subjects underwent their first PKP and 46 had repeat PKP. The authors reported that risk factors for graft failure included repeat PKP (79.3%), corneal neovascularization (51.7%), preexisting glaucoma (46.6%), and presence of anterior synechiae (37.9%). Both first and repeat PKP groups had similar survival rates until 6 months (75% vs 74%, OR, 1.06, p=1.00). At 12 months,

the first PKP group showed a better survival rate (67% vs 43%, OR, 2.60, p=0.20). Eyes with > 3 risk factors had a higher graft failure rate (OR, 5.81, p=0.003).

Vlasov (2016) reported on the use of Prokera in 80 subjects undergoing photorefractive keratectomy. Subjects were treated with either Prokera (n=40) or high-oxygen-transmissible bandage contact lens (Acuvue Oasys, n=40). No significant differences between groups were reported with regard to visual outcomes, corneal clarity, and optical quality of the cornea. The Prokera group experienced 1 case of spontaneous extrusion, 1 case of delayed epithelial healing, 2 cases of persistent defect, 4 cases of corneal infiltrates, and 1 case of nongranulomatous uveitis. Four cases of corneal infiltrates were reported in the control group. The authors concluded that the use of Prokera for post- photorefractive keratectomy wound healing remains speculative.

AlloDerm Regenerative Tissue Matrix (RTM)

AlloDerm Regenerative Tissue Matrix, also known as AlloDerm RTM, is a human-derived decellularized grafting product which is regulated through the U.S. Food and Drug Administration (FDA) Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) process as human tissue for transplantation. There are over a dozen small case series studies and nonrandomized controlled trials published in the peer-reviewed medical literature describing the use of AlloDerm RTM to partially or completely enclose an implanted breast prosthesis during post-mastectomy breast reconstruction (Becker, 2009; Bindingnavele, 2007; Breuing, 2005, 2007; Gamboa-Bobadilla, 2006; Preminger, 2008; Salzberg, 2006, 2011; Spear, 2008; Woo, 2017). The goal of using AlloDerm RTM for this type of procedure is to reduce complications related to contracture, periprosthetic atrophy, and development of thin capsules. The results provided in these case series studies indicate good symmetry, increased soft tissue padding, and decreased rippling and implant visibility. While the available data is limited regarding the long-term benefits and outcomes of this procedure, it has become a widely used and accepted method of breast reconstruction. Expert opinion of breast surgeons supports the use of AlloDerm RTM for this indication.

However, care must be taken when selecting AlloDerm RTM for use in breast reconstruction. A retrospective, nonrandomized controlled study by Weichman and others published in 2012 found significant complication rates with its use. In their study, 407 consecutive subjects underwent 628 immediate 2-stage breast reconstructions either with AlloDerm RTM (n=442, 70.3%) or without AlloDerm RTM (n=186, 29.6%). The authors reported that major complications were significantly increased in the AlloDerm RTM group (15.3% vs. 5.4%, p=0.001). Complications included infection requiring intravenous antibiotics (8.6% vs. 2.7%, p=0.001), flap necrosis requiring excision (6.7% vs. 2.7%, p=0.015), and explantation of the tissue expander (7.7% vs. 2.7%, p=0.004).

The treatment of infected or contaminated abdominal wall wounds and defects is difficult. Standard fascial prostheses such as polypropylene and polyester mesh, which are routinely used for non-complex cases, may exacerbate wound infection, fistula and adhesion formation, and erosion, leaving few real options for such individuals. The use of AlloDerm RTM for the treatment of complex abdominal wall wounds has been reported in over 30 peer-reviewed journal articles (Espinosa-de-los-Monteros 2007; Glasberg, 2006; Lee, 2009; Lin, 2009; Maurice, 2009; Patton, 2007; Vertrees, 2009). These studies demonstrate a high rate of successful wound healing with relatively low numbers of complications. As with the use of AlloDerm RTM for breast reconstruction, AlloDerm RTM for complex abdominal wall wounds has been widely used and is an accepted treatment method, although data is limited regarding the long-term benefits and outcomes of this use. Expert opinion of surgeons who routinely treat these types of wounds supports the use of AlloDerm RTM for this indication.

At this time, there is limited data addressing the use of AlloDerm RTM in treating chronic wounds. There is very limited evidence available regarding the use of AlloDerm RTM in the treatment of burns or for surgical reconstruction procedures such as in the treatment of lid retraction in individuals with Graves' disease or in the prevention of Frey's Syndrome. Additionally, AlloDerm RTM has been proposed for use in a wide variety of other surgical applications.

The use of AlloDerm RTM has been proposed for the treatment of various nasal and oral surgeries, including palatal fistula. At this time, there are only a limited number of small studies addressing this use in clinical trials (Helling, 2006; Steele, 2006). These studies show promising results, but are small and use weak study designs. Additional studies are needed to demonstrate the efficacy of this use of AlloDerm RTM.

In the one available clinical trial of AlloDerm RTM in people with lid retraction due to Graves' disease, only 14 participants were studied in a non-blinded fashion (Sullivan, 2003). While the findings of this study were promising, further controlled studies with larger numbers of participants are needed to confirm the efficacy of this procedure.

There are currently two studies available in the peer-reviewed literature addressing the use of AlloDerm RTM for treatment of burns. The first study involved 19 participants randomized to AlloDerm RTM with an *autograft* overgraft vs. AlloDerm RTM with an *allograft* overgraft which was replaced with an autograft overgraft after 1 week (Munster, 2001). Graft uptake was not different between groups. Immediate use of AlloDerm RTM with thin autograft was associated with more healing than spilt thickness grafts. The second study involved 52

nonrandomized participants all of whom received AlloDerm RTM covering to radial arm free flap donor sites (Sinha, 2003). The results of this study indicated that there were minimal contractures or restrictions to the healed graft. While these studies suggest some benefit from the use of AlloDerm RTM for burns, larger randomized trials are needed to confirm efficacy of this procedure.

At this time, there are two available studies in the peer-reviewed literature regarding the use of AlloDerm RTM to treat Frey's syndrome. The first involved 64 participants randomly assigned to the use of AlloDerm RTM placement in the parotid bed following removal of the parotid gland vs. no AlloDerm RTM (Govindaraj, 2001). While the rate of gustatory sweating in the AlloDerm RTM group was found to be statistically lower than the control group, the AlloDerm RTM group also had an almost three-fold increase in complications, including both a higher frequency of seroma as well as one wound infection. In a second study, 30 participants were randomized into 3 groups; (1) superficial parotidectomy with placement of AlloDerm RTM, (2) superficial parotidectomy without placement, and (3) deep-plane rhytidectomy (Sinha, 2003). The incidence of both subjective and objective Frey's syndrome was significantly higher in group 2 when compared to both groups 1 and 3. However, given the small numbers of subjects in each group, the results of this study do not allow strong conclusions to be drawn as to the effectiveness of this procedure.

AlloDerm Ready To Use (RTU)

LifeCell, Inc. has introduced another product, AlloDerm RTM Ready To Use (also referred to as AlloDerm Ready To Use or AlloDerm RTU) that is sterile and reportedly easier to use. This product is similar to their AlloDerm RTM product in origin and processing and is treated as human tissue for transplantation under the FDA's HCT/P process. Both products are derived from donated cadaveric dermis and undergo the same aseptic tissue processing. However, AlloDerm RTM is supplied as an aseptic product. The AlloDerm RTU product undergoes additional sterilizing with electron beam radiation. Additionally, whereas AlloDerm RTM is freeze-dried prior to packaging and requires rehydration prior to use, AlloDerm RTU is not freeze-dried and requires no rehydration.

Weichman (2013) conducted a nonrandomized controlled, consecutive series study of subjects undergoing either immediate breast reconstruction with tissue expander or permanent implants. For the first year of the study, all subjects requiring reconstruction with acellular dermal matrix received AlloDerm RTM (n=58; 90 breasts). At the 1 year point, subjects meeting the same criteria were all treated with AlloDerm RTU (n=64; 105 breasts). Concurrently, the investigators followed all individuals undergoing breast reconstruction without the need for acellular dermal matrix, and who underwent submuscular coverage (n=223; 351 breasts). For the most part, the two

AlloDerm groups were equivalent with the exception that the RTM group was noted to have statistically significantly larger mean specimen weight and higher body mass index (BMI) vs. the RTU group (p=0.0485 and p=0.0376, respectively). The RTU group also had a higher incidence of nipple-sparing surgeries (p=0.0021). With regard to complications, the RTU group had significantly fewer overall infections vs. the RTM group (8.5% vs. 20%, p=0.0088). However, there were no significant differences between AlloDerm groups with regard to explantations (RTU=2 vs. RTM=6, p=0.147) or major infections requiring antibiotics (RTU=4.7% vs. RTM=12.2%, p=0.069). The incidence of seroma, hematoma, and skin flap necrosis were not different between AlloDerm groups. When comparing the RTU group vs. the submuscular coverage group, the RTU group had significantly higher incidence of immediate permanent implantations (p=0.0001) and nipple-sparing surgeries (p=0.0012), as well as greater tissue expander size, initial tissue expander fill and percentage tissue expander fill. Both groups were found to have similar outcomes with regard to skin flap necrosis, overall infection, need for explantation and the incidence of seroma and hematoma. Univariate analysis found that risk factors for increased infectious complications included breast with flap necrosis (p=0.0003), those in which RTM was used (p=0.0004), and those with seroma (p=0.0012). In addition, diabetes was an independent risk factor, and individuals with diabetes were 2.9 times more likely to suffer complications (p=0.037). The authors identified the differences between the RTU and tissue expander groups to be possible confounding factors in this study. The authors conclude that the use of AlloDerm RTU is acceptable and mitigates the risk of infectious complications compared to aseptic AlloDerm RTM.

In 2015, Lewis and others published the results of a retrospective case series study of subjects receiving AlloDerm RTM (n=93) or AlloDerm RTU (n=74) as part of either breast reconstruction or breast augmentation procedures to investigate the incidence of complications and "red breast syndrome" (RBS). While the decrease in individual complications, including seroma, necrosis, and RBS were not significant between AlloDerm groups, the overall complication rate was significantly in favor of the RTU group (p=0.046). Based on aggregate complication rate on a per-breast basis, the absolute risk reduction with RTU was reported to be 14.9%. The authors concluded that the use of the sterile AlloDerm RTU product resulted in fewer complications when compared to aseptic AlloDerm RTM.

Parikh (2018) reported the results of a retrospective cohort study involving 1285 consecutive subjects undergoing 2039 immediate prosthetic breast reconstructions. Subjects underwent treatment with either AlloDerm RTM (n=612, 910 breasts) or with AlloDerm RTU (n=673, 1129 breasts). The authors reported that the RTM group experienced a significantly higher rate of explantation compared to the RTU group (18.0% vs. 12.0%, p=0.0036). No significant differences were reported with regard to the between-group rates of surgical site infection, wound

dehiscence, mastectomy flap necrosis, seroma, or hematoma. Multivariate regression analysis indicated that subjects in the RTM group did have higher odds of explantation vs. the RTU group (OR, 1.570, p=0.0161).

The results of these studies, in conjunction with the previously reported evidence from AlloDerm RTM, have demonstrated a significant outcome benefit of the AlloDerm RTU product. This product is accepted as substantially equivalent to the AlloDerm RTM product. These products are sourced and processed in an identical manner, with the addition of a sterilization process in the case of the RTU product. This addition has not been demonstrated to have any negative impact on the performance of the product, and there is building evidence that there is some benefit derived from its sterilized nature.

AlloDerm RTU has also been studied for other conditions, including insufficient conjunctiva (Park, 2017), however, the level of evidence is weak and warrants further evaluation.

AmnioBand

AmnioBand is a dehydrated human placental membrane comprised of amnion and chorion. It is treated as human tissue for transplantation under the FDA's HCT/P process. This product is available in both sheet or membrane form and particulate or injectable form.

There are currently a few small studies published on the use of the sheet/membrane from in human subjects. DiDomenico (2016) described an RCT involving 40 subjects with chronic nonhealing DFUs assigned to receive continued standard of care or treatment with AmnioBand plus standard care. Subjects were followed until wound closure or 12 weeks, whichever came first. The authors reported that at 6 weeks, 70% (14/20) of the AmnioBand group was completely healed vs. 15% (3/20) of the controls. At 12 weeks, 85% (17/20) of the AmnioBand group were completely healed vs. 25% (5/20) of controls (mean time to healing 36 days vs. 70 days, respectively). Only one adverse event and one serious adverse event were reported in the AmnioBand group, although neither was deemed graft related by the authors.

This same group published a retrospective crossover study to evaluate the effectiveness of AmnioBand in subjects that failed to respond to the standard care treatment in the above mentioned RCT (DiDomenico, 2017). This report involved 11 subjects, and 9 (82%) wounds healed with AmnioBand. The mean wound area decreased from 1.7 cm^2 to 0.2 cm^2 (p=0.0005), with a corresponding mean percentage area reduction of 92%. Of the 2 wounds that failed to meet the definition of healed in this study, 1 DFU decreased in area by 91% and the other by 26%.

An evaluator-blinded RCT was published involving 80 subjects with DFUs assigned to treatment with AmnioBand (n=40) vs. continued standard care (n=40) (DiDomenico, 2018). Subjects failed a minimum of 4 weeks of standard care prior to entry into the study. At 6 weeks, 12 subjects in the control group (30%) and 2 from the AmnioBand group (5%) were withdrawn from the study due to failure to have their wounds decrease at least 50%. These subjects were considered treatment failures. Complete wound healing at 6 weeks, the primary endpoint, was reported in 68% of the AmnioBand group vs. 20% of the control group subjects ($p<0.0001$). At 12 weeks, complete healing was reported in 85% of AmnioBand subjects vs. 33% of control subjects ($p<0.0001$). Mean time to heal at 6 weeks was 29.2 days vs. 39.5 days, respectively ($p<0.0001$). At 12 weeks, mean time to heal was 37 days vs. 67.3 days ($p<0.0001$), respectively. The HR for treatment with AmnioBand vs. standard care was 4.25. There were 11 adverse events (AEs) reported, with 3 in the AmnioBand group and 8 in the control group. All involved localized pedal infections initially treated with antibiotics. A total of 4 serious adverse events were also reported, with 1 in the AmnioBand group and 3 in the control group. All were related to foot infections requiring hospitalization, with the majority progressing to osteomyelitis and IV antibiotic treatment and debridement as necessary. No adverse events were found to be graft related.

The results of these three studies demonstrate that DFUs failing standard care subsequently treated with AmnioBand have significantly better results with regard to complete wound closure and time to heal when compared to standard care. The use of AmnioBand for other conditions has yet to be sufficiently investigated.

At this time there are no studies available addressing the use of the particulate or injectable form of AmnioBand. Further investigation is needed to assess the safety and efficacy of this form of the product.

Apligraf

Apligraf is a composite grafting product composed of agarose, L-glutamine, hydrocortisone/bovine serum albumin, bovine insulin, human transferrin, triiodothyronine, ethanolamine, O-phosphoryl-ethanolamine, adenine, selenious acid, DMEM powder, and HAM's F-12 powder. It has been approved through the FDA's Premarket Approval (PMA) process. It has been considered for a wide variety of uses, but primarily for treatment of diabetic ulcers and burn wounds.

Veves and others published the results of a RCT addressing the use of Apligraf for the treatment of neuropathic diabetic ulcers (2001). In this trial, 208 subjects were randomly assigned to be treated with either Apligraf (n=112)

or standard care (n=96). At the 12 week follow-up, 63 (56%) subjects in the Apligraf group achieved complete wound healing vs. 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, with the exception of individuals with osteomyelitis or lower-limb amputations, both of which were less frequent in the Apligraf group. Steinberg and colleagues conducted an RCT following the methodology used by Veves et al (2010). This study involved 72 subjects, 33 of whom received treatment with Apligraf and 39 control subjects who received standard care. However, this study was discontinued early, due to non-safety-related reasons. The authors do not elaborate on this further. Because this study was stopped before full enrollment, results from this study are underpowered for demonstrating statistically significant differences. However, even though the study was halted prematurely, the results are similar to those reported by Veves; in particular, the Steinberg study showed significant (p=0.049) superiority of Apligraf to achieve complete healing at 12 weeks follow-up in comparison to the control group. These results, taken together, support the use of Apligraf for the treatment of foot ulcers.

Apligraf has been investigated for the treatment of burns in only one peer-reviewed published study (Waymack, 2000). In this randomized controlled trial, 40 subjects with burn injuries were treated with either meshed autograft covered by meshed allograft or meshed autograft covered by Apligraf. There was no difference in take rate or the median days to 75% graft take. The unblinded investigators rated 22 (58%) of the Apligraf sites as superior to controls, 10 (26%) equivalent to controls, and 6 (16%) worse than controls (p=0.0037). Pigmentation of the Apligraf sites was also rated as superior to control sites at 2 years (p=0.0005), and normal vascularity was seen in 18 (47%) of Apligraf sites vs. 6 (16%) of controls for the same time period (p value not provided). Further study is needed to fully evaluate the use of Apligraf for the treatment of burns.

Biobrane

Biobrane, a synthetic product composed of a silicone film bonded to a nylon fabric base, has been approved through the FDA's PMA process. Data regarding the use of synthetic Silicone/Nylon Membrane wound dressing (e.g., Biobrane) has been described in four separate randomized controlled trials (RCTs) in peer-reviewed published medical journals (Barret, 2000; Feldman, 1991; Gerding, 1990; Lal, 2000). All of these studies found that in comparison to their various control groups the use of Biobrane significantly improved pain scores and healing times.

Additionally, the use of Biobrane has been reported in a small case series study of 18 subjects with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS-TEN) (Rogers, 2017). The authors reported that there were no complications, infections, premature removals, or Biobrane-associated sepsis in 24/25 applications (96%). Time to healing was 13 (12-16) days, and mean burn center length of stay was 34 days. This small study demonstrates promising data regarding the safety and efficacy of Biobrane for SJS and other conditions.

Based on clinical practice standards, relevant expert opinions, the above mentioned evidence, and the overall clinical experience with Biobrane, an acceptable level of safety and efficacy has been established for the use of this product in the treatment of burns and Stevens-Johnson Syndrome. The evidence for use of this product for other indications is still unclear and further investigation is warranted.

DermACELL

DermACELL, a product composed of acellular human dermis, has been studied for a limited number of indications, including chronic lower extremity wounds in individuals with diabetes and breast reconstruction. It is treated as human tissue for transplantation under the FDA's HCT/P process.

The most rigorous study to date was a prospective non-blind RCT involving 168 subjects with DFUs assigned in a 2:2:1 fashion to treatment with DermACELL (n=71), conventional care (n=69), or Graftjacket (n=28) (Walters, 2016). At 16 weeks post intimal treatment, subjects in the DermACELL group were reported to have a significantly higher proportion of completely healed ulcers vs. the conventional care group (67.9% vs 48.1%; p=0.0385) but no significant differences vs. the Graftjacket group (67.9% vs 47.8%; p=0.1149). The DermACELL group also did not exhibit a greater average percent reduction in wound area vs. either comparison group (conventional care=91.4% vs 80.3%; p=0.0791; Graftjacket group=91.4% vs 73.5%; p=0.0762). No differences between groups were reported with regard to severe adverse events ($p \geq 0.05$).

Another large study was a retrospective consecutive case series study involving 140 subjects undergoing breast reconstruction treated with either AlloDerm RTU or DermACELL (n=70, each group) (Zenn, 2016). Subjects were selected on either side of the time point when the investigators switched from using AlloDerm RTU to DermACELL. No statistical differences were reported between groups with regard to complications, including the incidence of seroma, infection, implant loss, and unplanned return to the operating room.

Pittman and others (2017) published the results of a retrospective review of 58 subjects who underwent breast reconstruction with either DermACELL (n=30) or AlloDerm RTU (n=28). The authors reported that 74% of the AlloDerm RTU subjects underwent immediate reconstruction with tissue expanders vs. 56% of the DermACELL group. Mean initial expansion volumes were 193 ml and 188 ml, respectively. In those subjects having direct-to-implant procedures, the mean implant size was 463 cc and 443 cc, respectively. Unfortunately, no p-values were provided for these comparisons, but the authors stated that no statistical differences were found. Likewise, no differences between groups were noted with regard to unilateral vs. bilateral reconstruction and breast irradiation. The DermACELL group had significantly shorter time to drain removal (15.8 vs. 20.6 days, p=0.017). A significantly higher rate of "red breast", defined as self-limiting erythema in the absence of skin edema or induration in an otherwise asymptomatic subject isolated to the lower pole of the breast in the distribution of the acellular matrix graft, was reported in the AlloDerm RTU group (13 vs. 0, p=0.0001). No differences between groups was noted with regard to hematoma, seroma, flap necrosis, or cellulitis requiring oral antibiotics. Delayed wound healing was reported as occurring more frequently in the AlloDerm RTU group (20% vs. 8%); however, the significance of this is unclear as no p-values were provided. While these findings are promising, the small size, retrospective and unblinded nature of the methodology impairs the strength of this study.

Cazzell (2017) conducted an RCT involving 132 subjects with chronic DFUs undergoing treatment in a 2:2:1 fashion with either DermACELL (n=53), conventional care (n=56), or GraftJacket (n=23). Subjects were followed through 24 weeks, with endpoint measurement at 12, 16, and 24 weeks. A single application of DermACELL resulted in significantly greater wound closure rates vs. conventional care at all three endpoints (p=0.0123, p=0.0003, and p=0.0008, respectively), and significantly higher healing rate vs. conventional care at week 16 and week 24 (p=0.028 and p=0.489, respectively). GraftJacket did not show a significantly greater healing rate over conventional care at any of these time points, but small numbers of subjects may have impacted that finding. Closed ulcers in the DermACELL group remained healed at a significantly greater rate vs. the conventional care arm at 4 weeks post study termination (100% vs. 86.7%; p=0.0435). No significant difference was noted between the GraftJacket group vs. the conventional care group for healed wounds remaining closed. Again, small numbers of subjects introduces significant potential bias into this observation.

Chang (2017) reported a retrospective comparative series study of 47 subjects who underwent breast reconstruction using FlexHD Pliable (n=18), AlloDerm RTM (n=15), or DermACELL (n=14). The authors reported that there were no differences in the rates of seroma, infection, or skin flap necrosis. Additionally, there were no cases of red breast, expander explanation, or failed reconstruction in any group. Time to drain removal was significantly shorter

in FlexHD and DermACELL subjects compared to AlloDerm RTM (20 days vs. 15 days vs. 26 days, respectively; p=0.01).

Other smaller non comparative studies have also been published describing significant benefits due to DermACELL (Bullocks, 2014; Ortiz, 2017; Yonehiro, 2013).

While relatively new to the market, DermACELL has been subject to multiple published clinical trials, including several RCTs and reasonably sized case series studies. The clinical experience with this product had demonstrated an acceptable level of safety and efficacy for use in the treatment of diabetic foot ulcers and during breast reconstruction procedures. The evidence for use of this product in other procedures or for other indications is still unclear and further investigation is warranted.

Use of DermACELL for the treatment of large, complex diabetic foot ulcers (DFUs) with exposed probed tendon or bone was described by Cazzell (2019). This case series study involved 61 subjects with Wagner grade 3 or 4 DFUs between 4 to 52 weeks in duration. The authors reported that the entire per-protocol population (n=47) achieved 100% granulation with a mean time to 100% granulation of 4.0 weeks. The mean percent wound area reduction was 80.3% at 16 weeks. DFUs 15 cm or smaller were substantially more likely to close compared to DFUs larger than 29 cm (p=0.0008) over a 16-week duration. No complications related to the use of DermACELL were reported. These findings are promising, but the small population and poor study methodology make it difficult to generalize these findings to a wider population.

DermACELL AWM and DermACELL AWM Porous are two products also available on the market. They are not substantially different from the original DermACELL product, having the same tissue origin and processing. They are just different formats of the original DermACELL, and are considered equivalent for the purposes of this document.

Dermagraft

Dermagraft is a composite grafting product composed of cryopreserved human fibroblastin and allograft collagen scaffold that has been approved through the FDA's PMA process. The use of Dermagraft has been described in several peer-reviewed studies (Gentzkow, 1996; Marston, 2003; Warriner, 2011). The largest and most rigorous of these was a RCT involving 355 subjects with venous stasis ulcers (VLUs) randomized to receive compression therapy plus Dermagraft (n=186) vs. compression therapy alone (n=180) (Harding, 2013). The endpoint was the

proportion of subjects healed by 12 weeks. No differences were found between groups, with 34% (64/186) of subjects in the Dermagraft group experiencing healing by week 12 vs. 31% (56/180) in the control group (p=0.235). However, a significant difference was reported for subjects with ulcers ≤ 12 months duration, with 52% (49/94) of the subjects in the Dermagraft group healed at 12 weeks vs. 37% (36 /97) of the control subjects (p=0.029). For ulcers ≤ 10 cm^2, no differences were identified in complete healing at week 12 (p=0.223). The most common adverse events (AEs) were wound infection, cellulitis and skin ulcer. The frequency of AEs did not markedly differ between the treatment and control groups.

The results of another RCT were reported by Marston and colleagues (2003). This study involved 314 subjects with diabetic foot ulcers (DFUs) present for at least 2 weeks; 245 of these were considered chronic ulcers (> 6 weeks). Of the 245 chronic ulcer subjects, 19% (46) did not complete the 12 week study period. All participants were randomized to receive treatment with Dermagraft (n=130) or standard care (n=115). The final analysis showed that among subjects with chronic ulcers, the Dermagraft group healed significantly better at 12 weeks than standard care (30% vs. 18%, p=0.023). Additionally, for subjects with forefoot or toe ulcers, 29.5% of the Dermagraft-treated ulcers were closed compared to 19.6% of the controls (p=0.065). Similar findings were reported for heel ulcers, with 33% vs. 8% of ulcers healed, respectively (p=0.01). Dermagraft-treated subjects were significantly faster to heal (p=0.04), and at 12 weeks, the median percent with closure was 91% for the Dermagraft group compared to 78% for the control group (p=0.044).

Another RCT using Dermagraft was published by Gentzkow et al (1996). This study involved 50 subjects with DFUs randomized to receive treatment with either standard of care (n=13) or one of three Dermagraft regimens plus standard care: (1) one piece of Dermagraft applied weekly for a total of 8 pieces and 8 applications (n=12); (2) two pieces of Dermagraft applied every 2 weeks for a total of 8 pieces and 4 applications (n=14); and (3) one piece of Dermagraft applied every 2 weeks for a total of 4 pieces and 4 applications (n=11). At 12 weeks, the percentage of subjects who achieved complete wound closure was significantly higher in the high frequency Dermagraft (Group 1) than in the control group (50.0% vs. 7.7%, p=0.03), and the percentage that achieved at least 50% closure was 75% in Group 1 vs. 23.1% in controls. No recurrences were reported at the 14 month follow-up period.

Label warnings and precautions indicate that Dermagraft is contraindicated for use in ulcers that have signs of clinical infection or in ulcers with sinus tracts.

Dermagraft was granted an FDA Humanitarian Device Exemption (HDE) (2002) for the treatment of dystrophic epidermolysis bullosa. Additional clinical trials are needed to investigate the safety and effectiveness of this product for other applications.

DermaMatrix

DermaMatrix, a product composed of acellular human dermis, has been studied for a variety of indications. It is treated as human tissue for transplantation under the FDA's HCT/P process. Below are discussions of several of the most recent controlled studies.

The use of DermaMatrix was evaluated in a retrospective, nonrandomized controlled trial involving 50 subjects who were assigned to undergo breast reconstruction with DermaMatrix (n=25) or AlloDerm RTM (n=25) (Becker, 2009). The authors reported that there were no significant differences between groups with regard to complication rates. Both groups exhibited good incorporation, with evidence of neovascularization. A larger retrospective non-controlled study was done which involved 173 subjects receiving breast reconstruction and implantation of either AlloDerm RTM (n=49), DermaMatrix (n=110), FlexHD (n=62), or no implantation (n=64) (Brooke, 2012). The authors reported no significant differences between groups with regard to overall complication rates between the implanted and control groups (p=0.48) or between implant groups (p=0.47).

Athavale and colleagues published the results of a retrospective, non-controlled study of the complication rate for parotid reconstruction surgery involving 100 subjects who received treatment with either AlloDerm RTM (n=69) or DermaMatrix (n=31) (2012). Sixty-nine AlloDerm implants were associated with a total of 5 complications (7%), whereas 31 DermaMatrix implants were associated with a total of 8 complications (26%) (p=0.0107). Subgroup analyses found that for subtotal parotidectomies, the incidence of complications was found to be 8% for the AlloDerm RTM group and 37% for the DermaMatrix group (p=0.004). The authors conclude that:

> …this study suggests that DermaMatrix was associated with increased postoperative complications compared with AlloDerm when used for reconstruction of parotidectomy defects. To better define the complication profile of AlloDerm versus DermaMatrix in the postoperative parotid bed, a prospective study should be considered to determine implant performance following parotidectomy reconstruction.

This study does not support the use of DermaMatrix for parotid reconstruction surgery. Additional studies are warranted to determine the safety and efficacy of this product for this indication.

Michelotti (2013) conducted a retrospective, nonrandomized controlled study of 73 subjects with breast cancer who underwent 284 tissue expander reconstructions. Subjects had received treatment with no ADM use (n=64 reconstructions), or with the use of AlloDerm RTM (n=49 reconstructions), DermaMatrix (n=110 reconstructions), or FlexHD (n=64 reconstructions). Overall, there were 18 (6.3%) seromas reported in all 284 reconstructions. In the subjects who received treatment with ADMs (n=220 reconstructions), there were 17 (7.7%) seromas reported; 2 in the AlloDerm RTM group, (11.76%), 6 in the DermaMatrix group (35.29%), and 9 in the FlexHD group (52.94%) (p=0.016). Within the limited scope of this small nonrandomized or blinded study, the results of this study demonstrate that the use of DermaMatrix appears to be similar to AlloDerm RTM with regard to the occurrence of postoperative seromas, and significantly better than FlexHD. This study highlights that there are significant differences in the clinical performance of different ADMs, and further investigation into this issue is warranted.

The design and methods of a moderately sized RCT were reported by Argarwal in early 2015. This trial, known as the BREASTrial, was designed to compare AlloDerm RTM to DermaMatrix for immediate breast reconstruction procedures. The planned follow-up time was 2.5 years. Argarwal and others randomized 128 subjects to undergo reconstruction with either AlloDerm RTM (n=64, 101 breasts) or DermaMatrix (n=64, 98 breasts) at the beginning of the study. The protocol describes three phases of the study. Phase I is from time of mastectomy and tissue expander placement to the definitive reconstruction procedure. Phase II is from definitive reconstruction to 3 months postoperatively. Finally, Phase III is from 3 months to 2 years postoperative. The primary outcome is the incidence of complications and secondary outcomes include: expander dynamics; degree of biointegration; impact of radiation therapy, chemotherapy, smoking, obesity and diabetes; duration of drains; and patient satisfaction. While the surgeons and subjects were aware of group assignment, the pathologist who evaluated the implant for biointegration was blinded to assignment. Results from Phase I of the BREASTrial have been reported by Mendenhall (2015). In the AlloDerm RTM group, 5 subjects lost their tissue expander vs. 11 losses in the DermaMatrix group (p=0.11). The overall complication rate was 36.2%; for the AlloDerm RTM group it was 33.6% vs. 38.8% in the DermaMatrix group (p=0.52). The only complications that were significantly different between groups were early loss of the implant defined as less than 45 days (1.0% for AlloDerm RTM vs. 6.1% for DermaMatrix; p=0.049) and loss due to skin necrosis (1.0% for AlloDerm RTM vs. 47.1% for DermaMatrix; p=0.027). The authors also reported that less time was needed in the AlloDerm RTM group for complete expansion vs. DermaMatrix (42 days vs. 70 days; p<0.001). The results of Phase II, from the time of definitive reconstruction to 3 months post-operative were published in 2017 by Mendenhall and colleagues. The authors reported an overall complication rate of 16.6%, with under half of them (7.5%) being classified as “major” complications requiring inpatient or operative management. The most common complications were infection (4.6%), wound dehiscence

(3.5%), skin necrosis (2.9%), and hematoma (0.6%). Overall implant loss rate was 2.9%. No differences were reported between the AlloDerm RTM and DermaMatrix groups with regard to complications. Only obesity was reported as an independent predictor of complications. The results from Phase III are pending.

Finally, as mentioned above, Lee and colleagues (2017) published a meta-analysis investigating the use of ADMs for implant-based breast reconstruction. A total of 17 studies were included, with only one being a prospective RCT and the others having retrospective non-randomized designs. There were 12 studies available involving a comparisons with FlexHD, DermaMatrix, and AlloDerm RTM or AlloDerm RTU. For comparisons between DermaMatrix and AlloDerm RTM, the results from four studies likewise found no differences between the pooled risks of complications. Finally, the meta-analysis of four studies comparing AlloDerm RTM or AlloDerm RTU demonstrated that the pooled risks for the complications did not differ. The authors concluded that these products have similar risks of complications compared to AlloDerm RTM.

Based on clinical practice standards, relevant expert opinions, the above mentioned studies, and the overall clinical experience with DermaMatrix, an acceptable level of safety and efficacy has been established for the use of this product in breast reconstruction procedures. The evidence for use of this product in other procedures is still unclear and further investigation is warranted.

EpiCord

EpiCord, a dehydrated umbilical cord allograft, is treated as human tissue for transplantation under the FDA's HCT/P process. A double-blind RCT published by Tettelbach (2018) addressed the safety and efficacy of the EpiCord product and involved 155 subjects with DFUs assigned in a 2:1 fashion to treatment with either EpiCord (n=101) or standard care with alginate wound covering (n=54). The per-protocol analysis included 134 subjects who completed the 12-week study period (n=86 EpiCord [85%], n=48 controls [89%]). All subjects had type 1 or 2 diabetes-related foot ulcers 1-15 cm^2 present for at least 30 days and non-healing despite 2 weeks of optimal conservative therapy. The ITT analysis showed that the EpiCord group was more likely to heal within 12 weeks vs. control subjects (70% vs. 48%, p=0.0089). This finding was upheld in the per-protocol analysis, with healing rates at 12 weeks being 81% in the EpiCord group and 54% in the control group (p=0.0013). Additionally, of those wounds that were deemed to have had adequate debridement (n=107, ITT population), 96% of the EpiCord-treated wounds healed completely within 12 weeks, vs. 65% of the control treated wounds (p<0.0001). At the 16 week follow-up, 73% of the EpiCord and 54% of the control subjects had complete healing (p=0.0199). In the per-protocol population, 85% vs. 60% of wounds were healed, respectively (no p-values provided). Of the wounds

healed in the 12-week trial period, 96% of EpiCord-treated wounds and 85% of the control-treated wounds remained healed at 16 weeks (no p-values provided). Adverse events were recorded in 75 subjects, with a total of 160 adverse events recorded, however none were attributed to the treatment dressings.

Based on clinical practice standards, relevant expert opinions, the above mentioned studies, and the overall clinical experience with EpiCord, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of DFUs. The evidence for use of this product for other indications is still unclear and further investigation is warranted.

EpiFix

EpiFix is a product composed of allographic amniotic membrane and is regulated by the FDA's HCT/P process as human tissue for transplantation. The use of EpiFix has been proposed for the treatment of various conditions including burns and corneal injuries. There are several peer-reviewed published studies available describing the use of materials derived from allographic amniotic membrane. However, the available evidence addressing EpiFix has been very limited. Three small case series studies describing the use of EpiFix have been published (Forbes, 2012; Sheik, 2013; Zelen, 2013a). These studies involved very small numbers of subjects; 5, 4, and 11, respectively. Such evidence provides limited data demonstrating the safety and efficacy of this product.

A smaller non-blinded RCT involving 25 subjects with DFUs assigned to either standard care (n=12) or treatment with EpiFix (n=13) was reported by Zelen and others (2013c). The authors report significantly reduced ulcer surface area at both week 4 and at week 6 ($p<0.001$). The mean reduction in ulcer size was most marked at the end of week 1, when the mean reduction in wound size was noted to be 20% for the control group and over 80% in the EpiFix group. At 4 weeks, none of the subjects from the control group (0%) were healed, whereas 10 of the 13 subjects in the EpiFix group (77%) had wounds that had completely epithelialized ($p<0.01$). At 6 weeks, 1 of the 12 subjects from the control group (8%) was healed and 12 of the 13 subjects in the EpiFix group (92%) were healed ($p<0.001$). For those subjects that healed, mean time to complete healing was 5 weeks in the control group (n=1) versus 2.5 ± 1.9 weeks in the EpiFix group (n=12). At the 6 week evaluation, 12 of the 13 subjects in the EpiFix group had healed completely. In early 2014, follow-up data from this trial was published (Zelen, 2014a). The authors reported that 11 of the 12 subjects from the initial RCT control group who had failed treatment were subsequently treated with EpiFix. The report included data from 18 of the total 24 subjects treated with EpiFix from both cohorts who had complete follow-up data to 12 months. The authors reported that 17 of the 18 subjects (94.4%) continued to have fully healed wounds at 12 months of follow-up.

Serena (2014) reported the results of an unblinded RCT involving 84 subjects with VLUs assigned to receive treatment with either EpiFix plus multi-layer compression therapy (n=53) or multi-layer compression therapy alone (n=31). The primary study outcome was the proportion of subjects achieving 40% wound closure at 4 weeks. The authors reported that 62% in the Epifix group vs. 32% in the control group met the primary endpoint (p=0.005). Furthermore, after 4 weeks, in wounds treated with Epifix, the mean size of the wound decreased 48.1% vs. 19.0% for controls.

Zelen (2014b) published the interim results of a second unblinded RCT involving 60 subjects with DFUs randomized in a 1:1:1 fashion to receive treatment with either EpiFix, Apligraf, or standard wound care (n=20 per group). At the 4 and 6 week endpoints, the proportion of EpiFix subjects achieving complete wound closure was 85% and 95%, significantly higher (all adjusted p-values ≤ 0.003) than for the subjects receiving Apligraf (35% and 45%) or control treatment (30% and 35%). After 1 week, wounds treated with EpiFix had reduced in area by 83.5% vs. 53.1% for Apligraf subjects. The median time to healing was significantly faster (all adjusted p-values ≤ 0.001) with EpiFix (13 days) vs. 49 days for the Apligraf group and 49 days for control subjects. A follow-up publication to that study with a total of 100 subjects was published in 2015 (Zelen, 2015). The final subject distribution for this study was 35 subjects in the EpiFix group, 33 subjects in the Apligraf group, and 35 subjects in the standard wound care group. The reported 12 week compete closure rate was reported to be 97%, 73% and 51%, respectively (p=0.00019). Compared to standard care, subjects treated with EpiFix had a significantly higher probability of healing (HR=5.66, adjusted $p=1.3x10^{-7}$), while no difference in probability was reported between the Apligraf and standard care groups. Subjects treated with Apligraf were less likely to heal than those treated with EpiFix [HR=0.30, unadjusted $p=5.8x10^{-5}$]. The mean time-to-heal within 12 weeks was 23.6 days in the EpiFix group, 47.9 days in the Apligraf group, and 57.4 days in the standard care group (adjusted $p=3.2x10^{-7}$). The results of this additional paper confirm the findings originally reported, that EpiFix provides significant healing benefits for individuals with diabetic foot ulcers.

Another RCT involved 109 subjects with VLUs who were treated with either EpiFix combined with multilayer compression dressing (n=52) or multilayer compression dressings alone (n=57) (Bianchi, 2017). The investigators reported that subjects receiving weekly application of EpiFix and compression were significantly more likely to experience complete wound healing than those receiving control treatment (60% vs. 35% at 12 weeks, p=0.0128, and 71% vs. 44% at 16 weeks, p=0.0065). Both the time-to-heal and higher probability of complete healing within 12 weeks were significantly improved in the EpiFix group vs. controls (p=0.0110 and p=0.01, respectively).

Based on this evidence, specifically the data provided in the Bianchi (2017), Serena (2014) and Zelen (2014b) studies, the use of EpiFix appears to provide significant clinical benefit when compared to standard compression therapy alone in the treatment of VLUs and DFUs. Furthermore, the criteria presented in the medically necessary statement for EpiFix in the Position Statement section above is based on the subject inclusion criteria of these two studies.

Tettelbach (2018) reported the results of an RCT involving 110 subjects with DFUs treated with either EpiFix (n=54) or standard care (n=56). Of these, 98 subjects successfully completed the study, 47 in the EpiFix group and 51 in the control group. The authors reported that both the intent-to-treat (ITT) and per-protocol analysis revealed that EpiFix subjects were significantly more likely to have complete healing vs. control subjects (ITT: 70% vs. 50%, p=0.0338, per-protocol: 81% vs. 55%, p=0.0093). A Kaplan-Meier analysis comparing time-to-heal demonstrated significantly improved time to heal in the EpiFix group vs. controls (log-rank p<0.0187). Additionally, Cox regression analysis showed that EpiFix subjects were more than twice as likely to heal completely within 12 weeks vs. control subjects (HR, 2.15; p=0.003). At the final follow-up at 16 weeks, 95% of EpiFix-healed ulcers and 86% of control group healed ulcers remained closed. The authors concluded that their results confirmed that EpiFix is an efficacious treatment for lower extremity ulcers in a heterogeneous patient population.

In 2015, Patel and others published the first study to address the use of EpiFix as a protective measure for the prostatic neurovascular bundle during nerve-sparing robot-assisted prostatectomy. This prospective study involved 58 potent and continent subjects who underwent the procedure compared to 58 propensity-matched subjects who underwent the same procedure without the use of EpiFix. It was reported that continence at 8 weeks returned in 81.0% of the EpiFix subjects vs 74.1% of the control subjects (p=0.373). Mean time to continence was enhanced in the EpiFix subjects vs. controls (1.21 months vs. 1.83 months; p=0.033). Potency at 8 weeks returned in 65.5% of the EpiFix subjects vs. 51.7% of the controls (p=0.132). Mean time to potency was enhanced in the EpiFix group vs. controls (1.34 months vs. 3.39 months; p=0.007). The authors concluded that the use of EpiFix appeared to hasten the early return of continence and potency in subjects following nerve-sparing robot-assisted prostatectomy. However, the results of this small unblinded nonrandomized study need to be further investigated and a large well-controlled blinded trial is warranted.

EZ Derm

EZ Derm is a product composed of porcine acellular dermis and cleared through the FDA's 510K process. The available evidence addressing the use of the EZ Derm brand porcine-derived decellularized fetal skin is limited. Data from two moderately-sized retrospective case series studies have been published. The first involved 157 subjects with partial-thickness burns treated with EZ Derm (Troy, 2014). The authors reported 19 complications, including premature separation of graft (n=9, 16%), infection (n=4, 3%), and need for excision (n=6, 4.5%). The other study involved 164 subjects, also with burns (Burkey, 2016). The authors reported a significant decrease in average narcotic dose following treatment ($p<0.001$) and fewer dressing changes needed ($p<0.001$). Only 4 (2.4%) subjects developed infections, although only one of these infections was at the site of the study graft.

Additionally, two small trials from over a decade ago addressing the use of EZ Derm for the treatment of burns have been published (Healy, 1989; Vanstraelen, 1992). The Vanstraelen study concluded that hypertrophic scarring occurred in 25% of xenograft-dressed sites, but none was seen in the comparison group. Several allergic reactions were reported to the porcine xenograft. The conclusions of the Healy study found, in comparison to burned participants treated with Jelonet®, individuals treated with EZ Derm did not vary significantly in terms of bacterial colonization rate, need for surgical treatment, time for spontaneous healing, analgesic requirements or frequency of dressing changes.

Based on clinical practice standards, relevant expert opinions, the above mentioned studies, and the overall clinical experience with DermaMatrix, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of burns. The evidence for use of this product for other indications is still unclear and further investigation is warranted.

FlexHD

FlexHD is an acellular hydrated dermis product and is treated as human tissue for transplantation under the FDA's HCT/P process. For the most part, the data addressing the use of FlexHD is from retrospective, nonrandomized controlled studies. The largest of these was published by Palaia and colleagues in 2015. This study involved 450 subjects undergoing immediate two-stage implant breast reconstructions who received treatment with either AlloDerm (n=134) or FlexHD (n=316). Demographics between the two groups were similar, with the exception that the FlexHD group had a significantly greater mean expander fill volume ($p=0.0134$). The authors reported no significant differences between groups with regard to seroma formation, incidence of infection, or explantation. There was a significant difference between groups with regard to rate of extrusion, with 6.2% reported for the AlloDerm group vs. 1.9% for the FlexHD group ($p=0.0062$). Another large retrospective nonrandomized controlled

study involved 417 subjects (592 breasts) who received breast reconstruction following radiation therapy for breast cancer (Seth, 2012). In this study, 137 subjects received reconstruction with FlexHD and 280 underwent standard reconstruction without implantation. The authors noted significant differences in the baseline characteristics between groups, with the FlexHD group having a larger body mass (p=0.0001) and more nipple-sparing mastectomies (p=0.04). Postoperatively, the FlexHD group was noted to have received larger intraoperative fill volumes (p<0.0001). No significant differences were noted between groups with relation to complications (p=0.19). However, it was reported that when stratified for radiation exposure, the FlexHD group had a lower risk of complications (p=0.003). The control group was seen to have a higher rate of extrusion (p=0.01) and pain and tightness (p=0.0005). Liu (2014) reported the results of a retrospective, nonrandomized controlled study of 382 subjects (547 reconstructions) who underwent immediate implant-based breast reconstruction with the use of FlexHD (n=97), AlloDerm RTM (n=165), or either immediate or two-stage reconstruction with no ADM (n=120). The authors reported that subjects who received treatment with ADMs were significantly more likely to have delayed healing (20.2% vs. 10.3%, p=0.009). Furthermore, a multivariate analysis identified that FlexHD posed a significantly greater risk of implant failure compared to AlloDerm RTM (p=0.042). This study provides more data demonstrating that not all ADMs are equivalent, and that significant differences in clinical results may be seen between products. Another large retrospective case series involved 255 subjects (369 breasts) who underwent breast reconstruction (Seth, 2013). This study compared the use of FlexHD (n=159; 233 breasts) to AlloDerm RTM (n=96; 136 breasts). This study found no significant differences between groups with regard to total complication rate including flap necrosis (p=0.849), IV antibiotic use (p=0.09), hematoma (p=0.431), seroma (p=1.0), and dehiscence (p=1.0). In 2016, Sobti described a study involving 233 subjects undergoing breast reconstruction with FlexHD (n=101) or AlloDerm (n=132). The study involved the use of either AlloDerm RTM or AlloDerm RTU (31.1% vs. 68.9%) as well as a mix of FlexHD Pliable/Perforated, FlexHD Pliable, or FlexHD Structural (80.2%, 18.8%, and 0.9%, respectively). No significant differences were reported with regard to infection rate (p=0.92), rates of seroma (p=0.25), hematoma (p=0.96), explantation (p=0.38), or delayed wound healing (p=0.70). Another retrospective non-controlled study, also discussed in the DermaMatrix section below, involved 173 subjects receiving breast reconstruction and implantation with AlloDerm RTM (n=49), DermaMatrix (n=110), FlexHD (n=62), or no implantation (n=64) (Brooke, 2012). The authors reported no significant differences between groups with regard to overall complication rates between the implanted and control groups (p=0.48) or between implant groups (p=0.47). Finally, Rawlani and others (2011) conducted a large case series study describing the use of FlexHD during tissue expander breast reconstruction. During a mean follow-up time of 44 weeks, 121 subjects underwent several expansions prior to expander-to-implant exchange. Complications occurred in 20 (16.5%) of the subjects including nine soft tissue infections, eight partial flap necroses, and two seromas. Eleven subjects

ultimately required explantation. Subjects undergoing radiation therapy (n=26) were significantly more likely to have complications (30.8% vs. 13.7%).

Michelotti (2013) conducted a retrospective, nonrandomized controlled study of 73 subjects with breast cancer who underwent 284 tissue expander reconstructions. Subjects had received treatment with no ADM use (n=64 reconstructions), or with the use of AlloDerm RTM (n=49 reconstructions), DermaMatrix (n=110 reconstructions), or FlexHD (n=64 reconstructions). Overall, there were 18 (6.3%) seromas reported in all 284 reconstructions. In the subjects who received treatment with ADMs (n=220 reconstructions), there were 17 (7.7%) seromas reported; 2 in the AlloDerm RTM group, (11.76%), 6 in the DermaMatrix group (35.29%), and 9 in the FlexHD group (52.94%) (p=0.016). Within the limited scope of this small nonrandomized or blinded study, the results of this study demonstrate that the use of FlexHD appears to be inferior to AlloDerm RTM or DermaMatrix with regard to the occurrence of postoperative seromas. This study highlights that there are significant differences in the clinical performance of different ADMs, and further investigation into this issue is warranted.

In 2013, Bochicchio and colleagues published the results of a prospective, consecutive case series study involving subjects undergoing complicated hernia surgery. Between January 2005 and December 2007, 55 consecutive subjects were treated with AlloDerm RTM. From February 2008 to January 2010, 40 subjects received treatment with FlexHD. The authors reported that at 1 year follow-up, all (100%) of the AlloDerm RTM subjects and 11 (31%) FlexHD subjects were diagnosed with a recurrence requiring surgical revision. This difference is quite startling, but is mitigated by the fact that, as the authors point out, there were significant differences between groups in the operative technique used. As such, the results reported are of little use in helping to understand the differences between FlexHD and AlloDerm RTM with regard to safety and efficacy since there is significant bias in the study design.

Cahan and colleagues (2011), evaluated a new surgical approach to breast reconstruction. This study involved 98 subjects undergoing 159 mastectomies using either FlexHD or AlloDerm RTM. The authors report that successful reconstruction was achieved in 93% of cases. Complications were seen in 23% of subjects, including dehiscence, seroma, full-thickness necrosis and infection. Removal of the implant was needed in 5 cases as a result of persistent infection (5%). Unfortunately, no data was provided enumerating the number of subjects receiving each product nor was any data provided comparing outcomes between product groups. The relative performance of FlexHD in this setting is unclear.

Finally, a small case series study involving the use of FlexHD for post-mastectomy breast reconstruction was published by Vu (2015). This prospective study reported on the outcomes of 41 subjects who underwent 72 procedures conducted by a single surgeon. The surgical complication rate was 12.5% (9 of 72 breasts), and included hematoma (n=2) and skin flap necrosis (n=7). Resolution of six of these complications occurred with surgical interventions. The seventh subject experienced complete failure of reconstruction. The authors noted a complete lack of infections or seromas in this study. Responses to the self-administered BREAST-Q questionnaire were received from 97.6% of subjects, and demonstrated satisfaction with breasts and psychosocial and sexual well-being had all returned to baseline values at 6 months postoperatively (p=0.903, p=0.321, p=0.479, respectively). Interestingly subjects who underwent postoperative radiation therapy reported lower satisfaction with their breasts as well as lower sexual satisfaction (p=0.004 and 0.006, respectively). These results are interesting, especially the lack of seroma and infections.

The body of evidence addressing the use of FlexHD is predominantly retrospective nonrandomized controlled studies, with a few case series also available. While this methodology is not particularly robust, the data from studies are consistent in identifying lower or equivalent complication rates when compared to AlloDerm RTM and other ADMs. Based on this evidence, expert opinion supports the use of FlexHD as an adjunct to breast reconstruction surgical procedures, and such use has become the standard of care alongside the AlloDerm products.

Fresh Frozen Unprocessed Allograft Skin (including AlloSkin and TheraSkin)

The use of fresh, unfrozen, unprocessed skin allograft has been used as a treatment of serious burn injuries since the First World War and it has become an accepted standard therapy. The current process for the collection and preparation of these allografts involves several steps, starting with the harvesting of the skin sample from carefully selected cadaver donors. Following harvesting, initial serological and microbial testing takes place to screen for communicable diseases, including HIV and hepatitis. Next, the sample is bathed in a solution of various chemicals, including antibiotics, for several hours to several days to kill or inactivate possible pathogens. The tissue is then packaged aseptically for shipping and clinical use. The shelf life of this type of product is approximately 3 days from the time of harvesting, and it must be used within this time. One complexity in the use of this type of product is that, in urgent clinical situations, the results of final, definitive pathological tests are not usually available until approximately 10-14 days after harvesting. This means that, in urgent clinical situations, the clinician using the product is expected to use it prior to being assured of absolute clearance of pathogens. This concern, as well as other issues such as shelf life, etc., has led to the use of fresh frozen (cryopreserved) skin allograft as an acceptable alternative product for the treatment of burns for over 40 years. This product is processed in a similar manner to the

fresh unfrozen products, but it is frozen once the initial screening is completed, and it is not released for use until after the definitive pathology reports have been completed. This additional step of freezing also allows for a shelf life of up to 5 years, which makes it more easily accessible for use in urgent medical situations. However, there is some evidence that indicates that this type of product loses some degree of viability due to the cryopreservation process, which may have an impact on its clinical effectiveness. However, this issue has not been well studied.

There are several brands of fresh, frozen, unprocessed allograft, including AlloSkin and Theraskin. These products are treated as human tissue for transplantation under the FDA's HCT/P process.

A small number of studies have been published in the peer-reviewed literature addressing the use of Theraskin. Landsman and colleagues (2010) conducted a single-center, retrospective, uncontrolled case series study of 188 subjects with VLUs and diabetic foot ulcers. The authors used historical controls for comparison, many of which were derived from previously published RCTs. The follow-up time was 20 weeks. The authors reported that at the 12 week follow-up, 60.4% of diabetic ulcers and 60.7% of venous ulcers were closed. At 20 weeks, those numbers increased to 74.1% and 74.6%, respectively. Neither of these differences was statistically significant. The authors conclude that Theraskin is "highly effective" for the treatment of both VLUs and diabetic foot ulcers. No superiority was found, and in the absence of the desired outcome, the authors proffer that Theraskin is equivalent to the control treatment. However, such conclusions reflect an inappropriate interpretation of the data from this effectiveness trial, which was not initially designed to test for equivalency, but superiority. To answer the question of equivalency, the authors would have had to have used an equivalency or non-inferiority study design, which would have utilized a different initial hypothesis and different set of assumptions.

DiDomenico and others (2011) conducted a non-controlled comparative trial of Theraskin compared to Apligraf involving 28 subjects with diabetic foot ulcers, 16 of whom received Theraskin and 12 received Apligraf. At 12 weeks, 66.7% of the Theraskin subjects and 41.3% of the Apligraf subjects had closed wounds. These numbers changed only slightly at 20 weeks, to 66.7% and 47.14% respectively. The authors concluded that Theraskin was more efficacious in healing diabetic foot ulcers. However, it should be noted that randomization problems in this study resulted in uneven blocks of subject enrollment in the two cohorts, and the small sample size was not sufficiently powered to conclude whether Theraskin was more effective than Apligraf.

Sanders (2014) reported the results of a small RCT involving 23 subjects with DFUs randomized to receive treatment with either Dermagraft (n=12) or Theraskin (n=11). At 12 weeks follow-up, 7 (63.6%) subjects in the Theraskin group and 4 (33.3%) in the Dermagraft group were healed (p=0.0498). At the end of the 20 week

evaluation period, 90.91% of Theraskin subjects vs. 66.67% of the Dermagraft subjects were healed (p=0.4282). Time to healing in the Theraskin group was significantly shorter (8.9 weeks) than in the Dermagraft group (12.5 weeks) (log-rank test, p=0.0323). The authors noted that the results of this study are similar to previous outcomes reported using these treatment modalities (see above studies) and suggest that, after 12 weeks of care, DFUs managed with Theraskin are approximately twice as likely to heal as DFUs managed with Dermagraft, with approximately half the number of grafts required. However, they are careful to comment that, "Research confirming these results with a larger sample size and in individuals with different types of wounds is warranted."

Towler (2018) reported the results of a prospective RCT comparing Apligraf (n=12) to Theraskin (n=15) for the treatment of VLUs. The authors reported no statistical differences between groups with regard to time to complete healing at 12 or 20 weeks (p=0.294 and p=0.569, respectively). Additionally, no differences were noted between groups with regard to the number of grafts needed (p=0.119). No adverse events were reported for either group. The authors concluded that both products are safe and effective to treat VLUs. However, the study was limited by small sample size, lack of blinding and other methodological issues.

In 2018, Choi reported on the use of cadaver allograft (n=698) vs. conventional treatment (n=584) in subjects with burns involving > 30% body surface area. In both unmatched and propensity-matched subject groups, 90-day in-hospital mortality was significantly better in the allograft group vs. controls (31.7 vs. 39.7% for unmatched comparisons and 37.8 vs. 47.3% for propensity matched comparisons). Logistic regression analyses showed a significant association between cadaver skin allograft and lower 90-day in-hospital mortality in the propensity-matched groups (OR, 0.42).

The use of fresh, unfrozen, unprocessed skin allograft products has been a part of standard medical practice for the treatment of burns for almost a century. However, concerns regarding the risk of disease transmission and shelf life continue to be an issue, and other products have been proposed as an alternative. One of the most commonly used alternative products is fresh frozen skin allograft. Unfortunately, the current level of evidence addressing the safety and efficacy of fresh frozen skin allograft is weak. No solid conclusions can be made regarding the superiority, equivalency, or inferiority of these types of products in relation to other treatment options. However, despite this lack of evidence, a decades-long anecdotal track record for these products, easy access and availability, and a higher degree of certainty that the product is free from communicable pathogens has led to their acceptance as the standard of care in the burn treatment community.

Grafix PRIME

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Grafix PRIME is a grafting product derived from allogeneic amniotic membrane. It is treated as human tissue for transplantation under the FDA's HCT/P process.

Lavery and others (2014) conducted an RCT involving 97 subjects with DFUs who were randomized to receive treatment with either Grafix PRIME (n=50) or standard care (n=47). The proportion of subjects achieving complete wound closure was reported to be significantly higher in the Grafix group (62%) vs. the control group (21%, p=0.0001). Median time to healing was 42 days in the Grafix group vs. 69.5 days in the control group (p=0.019). Fewer Grafix-treated subjects experienced adverse events (44% vs. 66%, p=0.031) and wound-related infections (18% vs. 36.2%, p=0.044). Among the study subjects that healed, ulcers remained closed in 23 of 28 subjects (82.1%) in the Grafix group vs. 7 of 10 subjects (70%) in the control group (p=0.419). The authors concluded that treatment with Grafix significantly improved DFU healing compared with standard wound therapy and reduced DFU-related complications.

In 2018, a follow-up study was published by this group reporting on the results of 24 subjects who had failed treatment in the control group and crossed over to treatment with Grafix Prime (Lavery, 2018). The authors reported a 65.4% complete healing rate at a median of 34 days of treatment. These subjects also experienced fewer adverse events and wound-related infections than subjects followed in the initial study period reported above (adverse events, p=0.019; infections, p=0.116).

In 2016, Johnson and others published a report of a retrospective nonrandomized study comparing the outcomes from two separate cohort studies involving Grafix PRIME (n=40) or Epifix (n=39) for the treatment of a variety of wounds including VLUs, surgical wounds, DFUs, arterial ulcers, pressure ulcers, and 'other' wounds. The authors reported that the proportion of wounds achieving complete wound closure was 63.0% (29/46) for the Grafix group and 18.2% (10/55) for the Epifix group (OR=7.5, p<0.0001) for all treated wounds combined. When analyzed by wound type, the results indicated that treatment with Grafix group had a significantly higher rate of completely closed VLUs (70% vs. 7%, p=0.0024) and surgical wounds (81.9 vs. 18.2%, p=0.009). The small number of subjects, and retrospective, non-random, and unblinded methodology used in this study impair the generalizability of the results.

Another published case series study addressed the use of Grafix PRIME and included 67 wounds in 66 subjects with either DFUs (n=27), VLUs (n=34), or other chronic wounds (n=6) (Regulski, 2013). At 12 weeks, 51 of 67 wounds (76.1%) were healed. By wound type, 23 of 34 (67.6%) VLUs and 23 of 27 (85.2%) DFUs were healed at

12 weeks. The average time to closure in these wounds was 5.8 (± 2.5) weeks. No significant differences were reported between the two wound type groups, and no adverse events or recurrences were reported.

Raspovic (2018) reported a retrospective case series analysis of 360 subjects with 441 DFUs treated with Grafix PRIME or Grafix CORE using data from Net Health's Wound Expert electronic health records database. The mean size of the index wound was 5.1 cm^2 with 3.9 mm depth. Mean wound duration prior to study treatment was 102 days. The mean duration of treatment with a Grafix product was 89.3 days (median 56.0). Complete wound closure at the end of treatment occurred in 59.4% of subjects. Median time to closure was 42.0 days with a median of 4 graft applications. The proportion of closure decreased as wound size increased, with 72.3% of wounds between 0.25 cm^2 to 2 cm^2 having complete healing at a median of 21 days and 4 applications. For wounds larger than 25 cm^2, only 27.8% achieved complete healing at a median of 105 days and 11 applications. The authors did not provide any data regarding the percentage of subjects receiving treatment with Grafix PRIME vs. those receiving Grafix CORE.

Ananian (2018) reported the results of a single-blind non-inferiority RCT comparing Grafix PRIME vs. Dermagraft in 62 subjects (31 in each group) with chronic DFUs. At the end of the 9-week study period, 100% reepithelialization occurred in 48.7% of Grafix subjects and 38.7% of Dermagraft subjects, meeting the endpoint of non-inferiority, defined for this study as a treatment effect difference of 20% (p=NS). At 28 days post-initial study application, a 50% or greater reduction in wound area was reported in 70.8% of Grafix subjects and 67.7% of Dermagraft subjects. The percent average reduction in wound size at the end of the study period was 86.3% in the Grafix group vs. 78.1% for the Dermagraft group (p=NS). The Grafix group had a mean of 5.3 applications vs. 4.4 applications to achieve 100% reepithelialization (p=NS).

Based on clinical practice standards, relevant expert opinion, the above mentioned studies, and the overall clinical experience with Grafix PRIME, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of DFUs. The evidence for use of this product for other indications is still unclear and further investigation is warranted.

GraftJacket

GraftJacket is an acellularized human skin-derived product and is treated as human tissue for transplantation under the FDA's HCT/P process.

One randomized controlled trial compared the use of standard surgical debridement followed by GraftJacket placement vs. standard surgical debridement alone (20 participants in each group) (Brigido, 2004). The findings of the study demonstrated significant differences between the two groups, with the experimental group demonstrating much faster healing progression. While the results of this study are promising, the small sample size, as well as its single-blind design, limits its utility. The same authors conducted a second RCT with 28 subjects with chronic DFUs who were assigned to receive either GraftJacket (n=14) or standard care (n=14) (Brigido, 2006). At 16 weeks, 12 of 14 (85.7%) of the GraftJacket subjects demonstrated complete wound closure, compared with 4 of 14 (28.6%) in the control group (p value not provided). Subjects treated with GraftJacket demonstrated a statistically significant higher percentage of wound healing with respect to wound area, and clinically significant differences in wound depth and wound volume ($p<0.001$).

Reyzelman (2009) reported the results of an RCT involving 85 subjects with diabetic foot ulcers assigned to receive treatment with either GraftJacket (n=46) or standard care (n=39). The authors reported significantly better complete and mean healing times in the GraftJacket group (69.6% and 5.7 weeks) compared to the controls (46.2% and 6.8 weeks) who received standard care ($p=0.029$). Furthermore, there was a significantly higher non-healing rate for the control group (53.9%) compared with the study group (30.4%) at 12 weeks ($p=0.015$). Neither the subjects nor the investigators were blind to group assignment.

A prospective non-blind RCT involving 168 subjects with DFUs assigned in a 2:2:1 fashion to treatment with DermACELL (n=71), conventional care (n=69), or Graftjacket (n=28) (Walters, 2016). At 16 weeks post intimal treatment, no significant differences in the proportion of completely healed ulcers vs. the conventional care group was found (67.9% vs 47.8%; $p=0.1149$). No differences between groups were reported with regard to severe adverse events ($p\geq0.05$).

Cazzell (2017) conducted an RCT involving 132 subjects with chronic DFUs undergoing treatment in 2:2:1 fashion with either DermACELL (n=53), conventional care (n=56), or GraftJacket (n=23). Subjects were followed through 24 weeks, with endpoint measurement at 12, 16, and 24 weeks. GraftJacket did not show a significantly greater healing rate over conventional care at any of these time points. No significant difference were noted between the GraftJacket group vs. the conventional care group for healed wounds remaining closed. However, as noted above, the results of this comparison for GraftJacket are significantly hampered by small numbers of subjects, and the results should be viewed with that in mind.

GraftJacket has also been proposed for use in shoulder surgery to repair soft tissue injuries. Barber and colleagues (2012) reported on an RCT involving 42 subjects with rotator cuff injuries randomized to undergo repair with GraftJacket (n=20) or standard surgical procedures (n=22). At the 2-year follow-up period, significant benefits were noted on several scales, including the American Shoulder and Elbow Surgeons (ASES) (p=0.035) and Constant (p=0.008) assessment tools. No significant difference was seen on the University of California, Los Angeles (UCLA) tool (p=0.43). Imaging studies found that at 2 years, 85% of the GraftJacket group had intact grafts, compared to only 40% in the standard care group (p<0.01). A prospective case series study by Gupta and others (2012) involved 24 subjects with rotator cuff tears treated with GraftJacket and followed for 3 years postoperatively. The authors report significant improvements with regard to pain, (p=0.002), mean active forward flexion and external rotation (p=0.002), mean shoulder abduction (p=0.0001), supraspinus strength (p=0.0003), and ASES scores (p=0.0003). Ultrasonography showed 76% of repairs were fully intact, with the remainder of subjects with partially intact repairs.

Marks and colleagues (2017) reported on a study involving the use of GraftJacket for the treatment of 60 subjects with osteoarthritis at the first carpometacarpal (CMC I) joint who underwent treatment with either trapeziectomy with suspension-interposition arthroplasty using the flexor carpi radialis (FCR) tendon (n=29) vs. GraftJacket (n=31). They reported that baseline Michigan Hand Outcomes Questionnaire (MHQ) total scores significantly increased from 51 to 83 in the FCR group and 53 to 76 in the GraftJacket group by 12 months (p<0.05 for both). No differences between groups were reported (p>0.05). Complications were reported in 5 FCR-related subjects, and 10 in the GraftJacket group (p=0.24). Revision surgery was required for 1 allograft subject. They concluded that the use of the FCR tendon or GraftJacket for trapeziectomy with suspension-interposition arthroplasty leads to similar outcomes, but with more complications, mainly tendon irritations, associated with GraftJacket. They noted that they "only use the allograft in cases of severe instability requiring a larger amount of suspension-interposition material or for revision procedures after failed suspension-interposition with the FCR tendon."

Based on clinical practice standards, relevant expert opinions, the above mentioned studies, and the overall clinical experience with GraftJacket, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of lower extremitydermal wounds. The evidence for use of this product for other indications is still unclear and further investigation is warranted.

Integra Bilayer Matrix Wound Dressing

Integra Bilayer Matrix Wound Dressing is a composite grafting material made from cross-linked bovine tendon collagen and glycosaminoglycan and a semi-permeable polysiloxane (silicone) layer. It has been cleared through the FDA's 510K Premarket Notification process. The use of this product has been found to be efficacious in the post-excisional treatment of full-thickness or deep partial-thickness burns when autografting is not feasible. This conclusion is supported by well-designed randomized studies (Branski, 2007; Heimbach, 2003). However, efficacy has not been demonstrated in the literature for other uses.

Oasis

Oasis is a grafting product composed of decellularized intestinal mucosa of porcine origin and has been cleared through the FDA's 510K process.

The first study addressing Oasis was published by Mostow and colleagues in 2005. They described a randomized controlled trial (RCT) involving 62 participants who received Oasis and compression therapy for venous stasis leg ulcers vs. a control group of 58 participants who received compression therapy alone. The authors reported significantly better healing rate in the Oasis group over the control group at 12 weeks. Another publication described a RCT involving individuals with DFUs (Neizgoda, 2005). The experimental group included 37 participants who were treated with the Oasis graft and 36 who were treated with Regranex gel. As with the previously described trial, the authors reported significantly improved results with the Oasis graft.

Romanelli and colleagues describe a study comparing Oasis against a product not currently available in the U.S., Hyaloskin (2007). The result of this trial, while favorable to Oasis, is not particularly useful in the evaluation of Oasis. This is due to the fact that the comparison product is unknown here in the U.S. and there is no currently available scientific literature addressing its use in the clinical setting.

The same group published a second RCT involving 50 subjects with either mixed venous/arterial ulcers (n=25) or venous ulcers (n=25) (Romanelli, 2010). Participants were randomized to receive treatment with either Oasis or standard petrolatum impregnated gauze and followed for 8 weeks. At the completion of the study, the authors reported that for all measures the Oasis group was significantly superior compared to the control group, including average healing (5.4 weeks vs. 8.3 weeks, $p=0.02$) and complete wound closure (80% vs. 65%, $p<0.05$). Granulation of tissues increased from 50% to 65% in the Oasis group and decreased in the control group ($p<0.02$). The Oasis group also required fewer dressing changes, more than doubling the time between dressing changes.

Cazzell (2015) reported the results of an unblinded RCT involving 82 subjects with neuropathic ulcers treated with either Oasis (n=41) or standard care (n=41). Subjects were followed for 12 weeks or complete ulcer closure. The Oasis group had a significantly greater proportion of wounds closed by 12 weeks vs. controls at all measurement times (54% vs. 32%, p=0.021). The time to closure for ulcers that achieved closure was 2 weeks earlier in the Oasis group vs. controls (9 vs. 11 weeks, respectively). The probability of wound closure at 12 weeks was 62% for the Oasis group vs. 40% for controls. Median reduction in ulcer area was significantly greater for Oasis at each weekly visit ($p<0.05$ for all). The most important predictor of wound closure in regression analysis was group assignment (HR, 2.005; p=0.049). No significant differences between groups with regard to adverse events were reported.

Based on clinical practice standards, relevant expert opinions, the above mentioned studies, and the overall clinical experience with Oasis, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of lower extremity dermal wounds. The evidence for use of this product for other indications is still unclear and further investigation is warranted.

OrCel

OrCel is a living skin equivalent (composite cultured skin) composed of human allogeneic skin cells cultured in layers of Type I bovine collagen that has been approved through the FDA's PMA process. This product was granted an FDA HDE in 2001 for use in children with recessive dystrophic epidermolysis bullosa (RDEB), who are undergoing reconstructive hand surgery. However, there is still little clinical data to support the use of OrCel for other applications.

PriMatrix

Primatrix is a product derived from acellular bovine dermis and has been cleared through the FDA's 510K process. To date, there are only a limited number of small studies addressing its use in humans. One retrospective, nonrandomized controlled series involved 68 subjects with either diabetic foot wounds (n=40) or venous stasis ulcers (n=28) who received treatment with either Apligraf (n=34) or PriMatrix (n=34) (Karr, 2011). The number of subjects with each type of wound receiving treatment with Apligraf or PriMatrix was equal, with 20 diabetic foot wounds and 14 venous stasis wounds in each group. For diabetic foot ulcers, the Apligraf-treated group's time to complete healing was 87 days, the PriMatrix was 37 days. The average number of graft applications was 2 in the Apligraf group and 1.5 in the PriMatrix group. For venous stasis ulcers, the time to complete healing was 63 days in

the Apligraf group and 32 days in the PriMatrix group. The Apligraf group had 1.7 graft applications compared to 1.3 in the PriMatrix group.

Another retrospective, nonrandomized controlled series involved 20 subjects with Charcot neuropathy and chronic non-healing ulceration treated with either PriMatrix (n=12) or standard wound care (n=8) (Kavros, 2012). The mean time to healing in the PriMatrix group (116 days) was significantly shorter than in the control group (180 days) ($p<0.0001$). A significantly faster rate of healing was observed with PriMatrix (87.9 mm^3/wk) compared with control (59.0 mm^3/wk) ($p<0.0001$). The authors conclude that, "The significantly faster rate of healing and steeper slope of volume reduction in the PriMatrix group warrants further investigation into its effects on healing of neuropathic ulcerations and potential limb salvage."

Based on clinical practice standards, relevant expert opinions, the above mentioned studies, and the overall clinical experience with PriMatrix, an acceptable level of safety and efficacy has been established for the use of this product for the treatment of lower extremity dermal wounds. The evidence for use of this product for other indications is still unclear and further investigation is warranted.

StrataGraft

StrataGraft is a allograft product derived from human dermis with a layer composed of neonatal immortalized keratinocytes (NIKS) and is treated as human tissue for transplantation under the FDA's HCT/P process. A small phase I/II comparative trial of StrataGraft to cryopreserved cadaver skin was conducted by Schurr (2009) to assess autograft take in 15 subjects 2 weeks after coverage. At the 2-week time point the authors reported that the StrataGraft subjects exhibited a fully stratified epidermis with multilamellar lipid sheets and barrier function as well as robust human β defensin-3 mRNA levels. Analysis revealed no differences in autograft take between wound sites pretreated with StrataGraft skin substitute or cadaver allograft. No StrataGraft-related adverse events or serious adverse events were observed.

Holmes (2019) reported on the results of an open-label, controlled, randomized study of StrataGraft vs. autograft for the treatment of deep partial-thickness burns (3%-43% total body surface area) in 30 subjects who were assigned to treatment with ≤ 220 cm^2 autograft; ≤ 440 cm^2 of autograft; or ≤ 440 cm^2 of StrataGraft. Two comparable wounds on each subject were randomized to receive StrataGraft tissue or autograft. By Day 28, the authors reported that no StrataGraft tissue treatment sites had undergone additional autografting. At 3 months, 93%

and 100% of the StrataGraft tissue and autograft treatment sites achieved complete wound closure, respectively. The most common adverse event was pruritus (17%).

Additional data from larger, well-designed trials is needed to fully understand the safety and efficacy of StrataGraft.

Strattice

Strattice is an acellular dermal collagen product of porcine origin and has been cleared under the FDA's 510k process. In 2012, three studies evaluating the use of Strattice were published. The largest was a retrospective, controlled study looking at the use of Strattice (n=96) vs. AlloDerm RTM (n=90) for tissue expander breast reconstruction (Glasberg, 2012). The authors reported a significantly higher complication rate in the AlloDerm RTM group (21.4% vs. 6.3%; p=0.0003), caused by the incidence of seromas (12.7% vs. 1.4%; p=0.0003). No other significant differences were reported, including capsule formation (2.4% for AlloDerm RTM and 2.8% for Strattice). This study was not prospective, randomized, or blinded.

The second trial involved the use of Strattice for complex abdominal reconstruction (Itani, 2012). This case series study involved 80 subjects undergoing contaminated ventral hernia repair that were prospectively enrolled and treated with Strattice. Sixty subjects continued through the final 24 month follow-up (25% loss to follow-up). The authors reported that midline restoration was achieved with primary closure in 64 subjects with defects bridged in 16 subjects. At 24 months, 53 subjects (66%) experienced 95 wound events including seroma (n=23, 29%), infection (n=28, 35%), dehiscence (n=14, 18%), hematoma (n=7, 9%), and abscess (n=7, 9%). No grafts required complete excision. Hernia recurrence was reported in 22 subjects (28%) by month 24. There was no correlation between infection-related events and hernia recurrence.

The third study, by Patel and colleagues, was a retrospective case study also evaluating the use of Strattice for complex abdominal reconstruction (2012). This study involved 41 subjects with complex ventral hernias undergoing component separation with Strattice underlayment. Concomitant panniculectomy was conducted in 9 subjects (22%). The complication rate was 24.4% (10/41), with the majority of early complications being skin necrosis (n=9), but also included Strattice exposure (n=5). These subjects required intervention in the operating room (OR). Wound dehiscence and seroma were noted in 3 subjects respectively. One subject required skin grafting for wound closure.

Rosen (2013) published a study investigating the use of acellular matrix for the reconstruction of infected and contaminated abdominal wall defects. The study involved 128 subjects who received treatment with Strattice (n=102), AlloDerm RTM (n=16), Biodesign (n=4), Xenmatrix (n=4), and BioA (n=4). Postoperative wound complications were identified in 61 (47.7%) subjects. The report indicated that predictors of wound complications included American Society of Anesthesiologists (ASA) score, diabetes, smoking, number of previous abdominal surgeries or hernia repairs, hernia defect size, and operative time. Hernia recurrence was identified in 40 (31.3%) subjects at a mean follow-up time of 21.7 months. The majority of recurrent hernias were asymptomatic and 7 subjects underwent repair.

Use of Strattice was reported in a study of 41 subjects with complex abdominal wall defects at increased risk for perioperative complications (Patel, 2013). Reported comorbidities included coronary artery disease (63.4%), diabetes mellitus (36.6%), and chronic obstructive pulmonary disease (17.1%). The authors reported that fascial closure was achieved in 40 subjects (97.6%). Recurrent/complex hernia was present in 78% subjects. The overall complication rate was 22.0%, and included seroma (7.3%), wound dehiscence with Strattice exposure (4.9%), cellulitis (2.4%), and hematoma (2.4%). All subjects achieved abdominal wall closure with no recurrent hernias or need for Strattice removal.

Maxwell and Gabriel (2014) reported the results of a case series study of 106 subjects undergoing revision breast surgery with the use of Strattice. The mean follow-up time was 3.1 years, with 1 subject experiencing a complication, yielding an overall complication rate of 0.9%. All subjects' presenting complaints resolved after revision surgery, with no recurrence of the presenting complaint during the follow-up period.

A retrospective case-control study of 80 subjects undergoing ventral hernia repair with either Strattice (n=40) or conventional open repair (n=40) was reported by Richmond (2014). Mean follow-up was 33.1 months. The authors reported that the defect size was greater in the Strattice group (mean, 372.5 vs. 283.7 cm^2, p=0.01) as was the percentage Ventral Hernia Working Group Grade III/IV hernias (65.0% vs. 30.0%, p=0.03). Despite this, the number of recurrences were lower in the Strattice group (13.2% vs. 37.5%, p=0.02), and infection rates were lower as well (0% vs. 23%, respectively, p=0.002). Finally, the indications for reoperation, including recurrence or complications requiring reoperation, were also lower in the Strattice group (17.5% vs. 52.5%, p=0.002).

Huntington (2016) published the results of a retrospective nonrandomized comparative study involving 223 subjects who underwent open ventral hernia repair with AlloDerm (n=40), AlloMax (n=23), FlexHD (n=70), Strattice (n=68), or Xenmatrix (n=22). The mean follow-up was 18.2 months. The authors reported the hernia

recurrence rate varied significantly by product, with 35% for AlloDerm, 34.5% for AlloMax, 37.1% for FlexHD, 14.7% for Strattice, and 59.1% for Xenmatrix (p=0.001). After multivariate analysis with Strattice as the comparator, AlloMax had a 3.4 higher OR for recurrence, FlexHD a 2.9 OR, and Xenmatrix a 7.8 OR. They concluded that the choice of biologic mesh affects long-term postoperative outcomes in ventral hernia repair, and Strattice had significantly lower odds of hernia recurrence compared with AlloMax, FlexHD, and Xenmatrix.

In 2016, Dikmans and colleagues published the results of a retrospective case series study involving the use of Strattice during single-stage breast reconstruction procedures in 88 subjects. Unilateral procedures were done in 60 subjects and bilateral in 25 (n=110 breasts). Minor complications reported included seroma (20.9%), skin necrosis (20.0%), wound dehiscence (11.8%), erythema/inflammation (14.5%) and infection (11.8%). The authors observed that the total complication rate was very high (78%), and although most complications were minor, reoperation was performed in 22.7%, with explantation of the implant in 11.8% of breasts. They concluded, "The use of a Strattice sheet in single-stage implant-based breast reconstruction may be a promising technique, but more evidence from prospective, randomized studies is necessary to justify its use."

A retrospective review involving 41 subjects who underwent 52 breast reconstructions using ADMs was reported by Paprottka (2017). Subjects received treatment with either EpiFlex (n=15), Strattice (n=21), or Tutomesh (n=16). Follow-up was 36 months (range 12-54). Overall complication rate was 17%, with 7% for the EpiFlex group, 14% for the Strattice group, and 31% for the Tutomesh group. Capsular contracture occurred in 6%, more frequently in this study compared to the current literature. The authors recommended the use of human derived grafting materials (EpiFlex) over those from porcine of bovine sources.

Lohmander (2019) conducted a non-blinded RCT involving 135 subjects undergoing immediate breast reconstructions assigned to treatment with either Strattice (n=64) or with no ADM (n=65). Overall, the outcomes were similar between groups, but 4 subjects (6%) in each group had reconstructive failure with implant loss. However, the group treated with Strattice exhibited a trend of more overall complications and reoperations (p=0.070) and with higher risk of wound healing problems (p=0.013). The authors noted, "Further investigation of risk factors and patient selection in a long-term follow-up is warranted."

Also see Clemens, 2013 and Mazari, 2018 in the SurgiMend section below for an additional study involving Strattice.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

The use for the treatment of other indications is still under investigation. Based on clinical practice standards, relevant expert opinions, the above mentioned studies, and the overall clinical experience with Strattice, an acceptable level of safety and efficacy has been established for the use of this product for the surgical repair of complex abdominal wall wounds and breast reconstruction surgery. The evidence for use of this product for other indications is still unclear and further investigation is warranted.

Products addressed in the Investigational and Not Medically Necessary statement

AlloMax

AlloMax is an acellular, non-cross-linked allograft dermis product and is treated as human tissue for transplantation under the FDA's HCT/P process. The currently available evidence in the peer-reviewed published literature addressing the use of AlloMax is sparse. A case series study involving 65 subjects undergoing tissue expander breast reconstruction was described by Venturi (2013). The results of this study are limited, but include a complication rate of 4.6% (3 subjects). These included one case of cellulitis and two cases of partial mastectomy flap necrosis requiring debridement. No seromas or explantations were reported. Histological verification of full graft incorporation was demonstrated in the first 20 biopsies. A second retrospective case series involving 203 subjects (348 breasts) undergoing mastectomy with immediate breast reconstruction was reported by Rundell in 2014. The authors reported that infection occurred in 6.6% of subjects, with 3.7% being major infections requiring intravenous antibiotics and 2.9% being minor infections requiring oral antibiotics only. Seromas occurred in 3.4% of cases and reconstruction failure occurred in 0.6% of cases. The authors stated that the analysis suggested that the complication prevalence was significantly higher in individuals with a BMI > 30 (p=0.03).

AlloPatch

AlloPatch is a product composed of acellular human dermis treated as human tissue for transplantation under the FDA's HCT/P process.

At this time, there is limited evidence published in the peer-reviewed literature addressing the use of this product. The most rigorous study to date involved 45 subject with chronic refractory DFUs (Zelen, 2016b). A total of 40 subjects in this investigator-blinded RCT were assigned in a 1:1 fashion to either standard care alone (n=20) or AlloPatch plus standard care (n=20). AlloPatch grafts were applied weekly for up to 12 weeks. Initial ulcer size at baseline was greater in the AlloPatch group vs, controls (4.7 cm^2 vs. 2.7 cm^2). At 6 weeks, the authors reported that

65% of the AlloPatch group subjects were completely healed (13/20) vs. 5% in the control group (1/20). At 12 weeks, the proportions of DFUs healed were 80% and 20%, respectively. The mean time to heal within 12 weeks was 40 days in the AlloPatch group vs. 77 days for controls. No differences between groups was reported with regard to adverse or serious adverse events. The authors reported that, "Weekly application of HR-ADM is an effective intervention for promoting closure of non-healing DFUs."

This group published a continuation study with an additional 40 subjects (n=20 per group) and results of the total 80 subject population were reported by Zelen in 2018. In the continuation population, the AlloPatch group had more smokers (7 vs. 1, p=0.044) and the control group was older (67 years vs. 55 years, p=0.008). At 6 weeks, 85% of the AlloPatch group vs. 15% of the controls were completely healed ($p=2.7 \times 10^{-6}$). The mean percent area reduction in wounds was greater in the AlloPatch group (62% vs. 50%, $p=2.7 \times 10^{-6}$). Mean time to healing at the 6-week time point was 27 days for the AlloPatch group vs. 41 days for controls ($p=9.9 \times 10^{-7}$). At 6 weeks, 2 AlloPatch subjects (5%) and 19 control subjects (48%) were withdrawn from the study due to failure to have a 50% reduction in wound area. At 12 weeks, 80% of AlloPatch subjects and 30% of the control subjects had complete wound healing ($p=8.4 \times 10^{-6}$). At 12 weeks, mean time to heal was 38 days in the AlloPatch group vs. 72 days in the control group ($p=3.9 \times 10^{-7}$). After adjusting for age and baseline wound area, the HR for the AlloPatch vs. the control group was 8 ($p=3.7 \times 10^{-7}$). No adverse events related to the study treatment were reported.

Further investigation is warranted to fully evaluate the safety and efficacy of AlloPatch treatment for DFUs.

AMNIOEXCEL

AMNIOEXCEL is a dehydrated human amnion-derived tissue allograft and is treated as human tissue for transplantation under the FDA's HCT/P process. There is currently only one available study published on its use in human subjects. Snyder (2016) reported on the results of a prospective, open-label, randomized, parallel group trial involving 29 adults with type 1 or type 2 diabetes mellitus who have one or more ulcers presenting for more than 1 month with no signs of infection/osteomyelitis. Subjects were randomized in a 1:1 fashion to receive treatment with either standard care (SOC, n=14) or AMNIOEXCEL+SOC (n=15) until wound closure or 6 weeks. The authors reported that 35% of subjects in the experimental group achieved complete wound closure at or before week 6 vs. 0% in the SOC group (p=0.017). They observed that there was a more robust response noted in the per protocol population, with 45.5% of subjects in the experimental group achieving complete wound closure, while 0% of SOC alone subjects achieved complete closure (p=0.0083).

Amniofix

Amniofix is a product that consists of an injectable form of processed allogeneic amniotic tissue and is treated as human tissue for transplantation under the FDA's HCT/P process. Only one RCT regarding its use has been published in the peer-reviewed published literature. Zelen and colleagues (2013b) report on 45 subjects with plantar fasciitis randomized in a single-blind fashion to receive one of three treatments: (1) standard care plus injection with 1.25 cc of sterile 0.9% saline (control group); (2) standard care plus injection with 0.5 cc Amniofix (0.5 cc group), and (3) standard care plus injection with 1.25 cc Amniofix (1.25 cc group). All subjects also received injection with 2 cc of 0.5% Marcaine plain, and the use of tramadol for pain was allowed as needed throughout the study. There were 15 subjects in each group. A total of 41 subjects (91.1%) completed the 8 week follow-up period. All 4 subjects who failed to complete the study were in the control group. The authors report that significant benefits were seen in all groups throughout the study compared to baseline on the American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot Scale ($p<0.01$). Additionally, the AOFAS scale outcomes were significantly higher for both Amniofix groups vs. controls ($p<0.001$). No differences were noted between the two Amniofix groups. At the end of week 1, the median reduction in pain was 3 points for controls and 6 points and 5 points for those receiving 0.5 cc and 1.25 cc of Amniofix, respectively ($p<0.001$; $p=0.004$). Using the Wong–Baker FACES Pain Rating Scale, a visual analog pain scale (VAS), controls reported moderate to severe pain throughout the 8 week study period. Both Amniofix groups reported a significant reduction of pain from very severe at baseline to within the mild to moderate range at 1 week, and reported continuing reduction in pain over the study period ($p<0.001$), with no statistically significant difference between groups. Based upon the physical and mental scales on the SF-36v2 quality of life tool, it was reported that both Amniofix groups had significant improvements from baseline compared to controls. No difference between Amniofix groups was reported. At the end of the first follow-up week, significantly more subjects in both Amniofix groups vs. controls needed additional treatment with tramadol (57.1% of controls, 73.3% of the 0.5 cc group, and 100% of the 1.25 cc group). This was not significant for the 0.5 cc group vs. controls, but was for the 1.25 cc group vs. controls ($p=0.004$) as well as the 1.25 cc group vs. the 0.5 cc group ($p=0.032$). At the second follow-up visit, rates of tramadol use were significantly lower in all groups ($p>0.05$ for all groups). No adverse events related to treatment were observed in any study subjects. This small study indicates some benefit from the use of Amniofix for individuals with plantar fasciitis. However, due to the small study population and lack of investigator blinding, further research is warranted to fully understand the efficacy of this treatment method.

Amniotic Allografts – Not specified

There is an increasing body of evidence in the available peer-reviewed published literature addressing the use of allogeneic amniotic tissues for the treatment of a variety of uses, including ophthalmologic, obstetric, and burn conditions. A small number of these publications address branded products, which are addressed elsewhere in this document. However, the vast majority of the published studies involve the use of amniotic-derived products that are: (1) not specified by the authors, (2) branded products not commercially available in the U.S, or (3) materials that are locally sourced. Many of these studies are randomized controlled trials, but with small study populations (Abdulhalim, 2015; Amer, 2010; Andonovska, 2008; de Farias, 2016; Harvinder, 2005; Küçükerdönmez, 2007; Luanratanakorn, 2006; Paris, 2013; Sharma, 2016; Sheha, 2008; Tamhane, 2005; Tandon, 2011). These studies are heterogenous with regard to the type of amniotic graft used, including lyophilized, cryopreserved and glycerin preserved products. Furthermore, there is a wide array of indications addressed across these studies, with a critical mass of evidence not established for any particular one. Finally, , due to the differences in the harvesting and processing procedures these materials undergo that may impact the physical properties of the materials, the findings of such studies cannot be used to support the use of amniotic-derived products as a group.

Artelon (Including CMC and TMC)

Artelon is a synthetic grafting material made from degradable polyurethaneurea cleared through the FDA's 510K process. The only currently available study addressing this product is a RCT consisting of 109 subjects with osteoarthritis of the carpometacarpal joint of the thumb (Nilsson, 2010). In this study, 72 subjects were treated with Artelon and 37 were treated with standard tendon interposition arthroplasty. There was a significant loss to follow-up, with less than 50% of subjects having available data at the 1 year follow-up time point. The authors report that swelling and pain were more common in the Artelon group and 6 implants were removed because of such symptoms. Interestingly, 5 of these subjects did not receive antibiotics preoperatively according to the study protocol. In the intention-to-treat analysis but not in the per-protocol analysis, significantly better pain relief (VAS) was obtained in the control group. Self-perceived disability evaluated by the DASH (disability of arm-shoulder-hand) questionnaire improved in both groups. However, these findings are not particularly useful, given the significant loss to follow-up reported.

At this time, the available peer-reviewed published articles addressing Artelon TMC are very small case series studies involving 13 and 15 subjects each (Jörheim, 2009; Nilsson, 2005; respectively). This level of evidence is inadequate to fully evaluate the safety and efficacy of this product. Further investigation is warranted.

Avance Nerve Graft

Avance nerve graft is a decellularized allogeneic product derived from donated peripheral nerve tissue and is treated as human tissue for transplantation under the FDA's HCT/P process. The currently available evidence addressing the clinical use of Avance was published by Brooks and others (2011). This case series study involved 108 subjects with nerve injuries. Outcomes were only available for 59 subjects (56%). The authors report "meaningful recovery" in 87% of subjects available for evaluation. A post hoc subgroup analysis demonstrated no significant differences with regard to nerve type, gap length, subject age, time to repair, age of injury, or mechanism of injury ($p>0.05$). No graft related adverse experiences were reported and a 5% revision rate was observed. The data presented is insufficient to allow full assessment of the safety and efficacy of the Avance nerve graft.

Avaulta

Avaulta is a composite product composed of polypropylene mesh with acellular cross-linked collagen of bovine origin and has been cleared through the FDA's 510K process. The use of Avaulta Plus and Avaulta Biosynthetic Support System for the treatment of vaginal prolapse has been described in one prospective case series study involving 40 subjects (Bondili, 2012). Subjects were followed for up to 3 years (median 27 months (range 20-36).The primary outcome was quality of life (QoL) and patient satisfaction as measured by the International Consultation on Incontinence Modular Questionnaire–Vaginal Symptoms (ICIQ-VS) tool. Twelve subjects (30%) were undergoing a second procedure to address prolapse. Of the 40 subjects, 19 (47%) underwent anterior repair, 20 (5%) posterior repair, and 1 (2.5%) underwent both anterior and posterior procedures. Vaginal laxness improved significantly, with 67.25% of subjects reporting preoperative laxness which improved to 5% of subjects with laxness at follow-up ($p<0.0001$). Decreased vaginal sensation also improved, from 30% to 7.5% ($p<0.01$). Sexual activity was reported to improve from only 32% to 100% postoperatively. The authors report that 1 subject continued to have prolapse symptoms (2.5%), resulting in a 97.5% success rate ($p<0.0025$). Only 2 subjects (5%) needed to digitate the vagina to vacate their bowels, a significant decrease from 12 (57%) preoperatively ($p<0.001$). Vaginal pain decreased from 55% preoperatively to 2.5% postoperatively ($p<0.0001$). No surgical complications were mentioned. The results of this small uncontrolled case series are promising. Further data from more rigorously designed and executed studies is warranted.

Belladerm

BellaDerm is a product composed of acellular human dermis and is treated as human tissue for transplantation under the FDA's HCT/P process.

Solomon and others (2013) published the results of a retrospective case series study involving 47 subjects who underwent penis girth enhancement utilizing circumferential grafting with allograft material. The subjects received either AlloDerm RTM (n=9), Belladerm (n=20), and Repriza (n=21). Mean follow-up was 11.25 months (range 1 to 120 months). The rate of infection, which the authors defined as an open wound with graft exposure, occurred in 20 (42%) of 47 subjects. Of these, 17 (36%) subjects had graft exposure only and 3 (6%) subjects sustained graft exposure and total graft loss. Graft exposure or loss occurred in 3 AlloDerm RTM subjects, 9 Belladerm subjects, and 8 Repriza subjects. No AlloDerm RTM subjects sustained graft loss, whereas 2 with Belladerm and 1 with Repriza did. No statistical differences between groups with regard to infection or graft loss was reported.

This study is too small and the methodology too weak to sufficiently assess the safety or efficacy of any of these products for this procedure.

Biodesign

Please see 'Surgisis' section below.

Cardiocel

CardioCel is a product produced from bovine pericardial tissue and has been cleared through the FDA's 510K process. At this time, the available published in the peer-reviewed literature addressing this product is limited. ~~The only large study currently published~~Pavy (2017) published the results of~~is~~ a retrospective series of 102 subjects who underwent procedures addressing variety of congenital heart diseases, including septal defects to pulmonary outflow disorders ~~(Pavy, 2017)~~. No infections, intraoperative implantation difficulties or postoperative mortality were reported to be associated with CardioCel. Graft failure reoperations occurred in 5 subjects (5%), 4 of whom had the patch implanted for aortic angioplasty (2 in the ascending aorta and 2 in the aortic arch), and 1 subject had a monocusp replacement. The median time between the first and the second operation for graft failure was 245 (range 5-480) days. The authors concluded that, "Our experience shows that the patch is well tolerated in the septal, valvar and pulmonary artery positions. However, we experienced graft failures in infants in the aortic position."

Bell and colleagues (2019) reported on the results of another series study involving 377 subjects with congenital heart defects who received surgical treatment with 501 Cardiocel patches. Median follow-up was 31 months (1-60 months), and 11 deaths (2.9%) were reported, with 1 reportedly related to Cardiocel. The authors reported no echocardiographic or radiological evidence of patch calcification in any subject. The overall freedom from reintervention at 3 and 5 years post-implantation was 96%. A total of 14 (2.8%) implants required 18 reinterventions (3.6%) at the site of implantation. No differences in performance of Cardiocel in neonates (0-28 days), infants (29-365 days) or children older than 1 year (p=0.22) were reported.

These results are promising, but data from larger, well-designed studies is needed to fully understand the safety and efficacy of Cardiocel use in the repair of congenital heart diseases.

Clarix

Clarix is a product composed of cryopreserved acellular human amniotic membrane and umbilical cord and is treated as human tissue for transplantation under the FDA's HCT/P process.

Bemenderfer (2019) provided the only currently available published peer-reviewed study on this product. The unblinded non-randomized study involved 104 subjects undergoing total ankle arthroplasty who received skin closure with either Clarix (n=54) or standard care (n=50). The authors reported that use of Clarix significantly decreased the overall time to skin healing (28.5 days vs. 40 days; p=0.03). No differences between groups were reported with regard to reoperations, skin dehiscence, local wound care, or antibiotic prescriptions. These results are promising, but additional data from larger controlled studies is needed to understand the safety and efficacy of this product.

Conexa

Conexa is a product produced from acellular porcine dermis and has been cleared through the FDA's 510K process. At this time, the only comparative trial published in the peer reviewed literature addressing the use of this product was reported by Maillot and others in 2018. This prospective non-randomized trial involved 32 consecutive subjects with large-to-massive rotator cuff tears assigned to treatment with 1) arthroscopic complete repair (repair group), 2) open repair and xenograft patch augmentation (patch group), or 3) arthroscopic debridement and tenotomy of the long head of the biceps (debridement group). Subjects were evaluated preoperatively and postoperatively at 3, 6, 12 and 24 months. The authors reported that the mean improvement in the Constant-Murley

score was +29.1, significant for all groups at the final follow-up examination ($p<0.01$ for all). No differences were reported between the repair and patch groups. However, comparison between the debridement group and the patch group at 12 months and the final follow-up was significant ($p<0.001$), as was the comparison between the debridement group and the repair group ($p<0.002$). Complications occurred in 5 of 11 subjects in the patch group and only 1 in the repair group and none in the debridement group. The authors concluded that "the use of porcine dermis patches to augment repairs of massive and irreparable rotator cuff tears is not recommended because there is no benefit compared with repair without augmentation and patches result in more complications."

CorMatrix

CorMatrix is a product produced from acellular porcine small intestinal submucosa and has been cleared through the FDA's 510K process. At this time, there is very limited peer-reviewed published evidence addressing the use of CorMatrix. The data that is available addresses its use in cardiovascular surgical procedures. The largest of these studies is a retrospective, nonrandomized control study involving 111 subjects undergoing coronary artery bypass surgery (CABG) who had pericardial reconstruction with CorMatrix, compared to 111 control subjects who underwent a standard CABG procedure without pericardial reconstruction (Boyd, 2010). The authors reported that postoperative atrial fibrillation occurred in 39% of controls vs. 18% of CorMatrix subjects. No other results were significantly different. The safety and value of CorMatrix is difficult to interpret in this study, as it is the pericardial reconstruction procedure that seems to be the significant variable. Another publication by Quarti and colleagues (2011) describes the use of CorMatrix in a wide variety of cardiovascular surgeries, with no comparison groups provided. While the authors report no significant complications due to the use of CorMatrix, this study provides little in the way of helpful data to determine the safety and efficacy of this product. Similarly, Kelley and others (2017) reported the results of a retrospective case series study of 25 subjects who underwent anterior leaflet augmentation. They reported a 32% recurrence rate of mitral regurgitation and concluded that further research is needed. Finally, Ashfaq (2017) reported good results from the use of CorMatrix in a small case series of 15 pediatric subjects undergoing atrioventricular (AV) septal defect repair. They reported 12 (80%) subjects either improved or had stable left AV valve performance remaining at "mild" or less insufficiency, two (13%) declined from "none" to mild, and one (7%) from declined from mild to "severe," No residual shunting or left ventricular outflow tract (LVOT) obstruction was noted at follow-up. Only one (7%) reoperation was performed after 3 years due to left AV valve zone of apposition dehiscence. No permanent pacemakers were needed, and no deaths were reported.

Overall, the data regarding the safety and efficacy of CorMatrix is incomplete and conflicting. Further investigation with larger well-designed trials is needed.

Cortiva

Cortiva allograft dermis is a product composed of acellular human dermis and is treated as human tissue for transplantation under the FDA's HCT/P process.

Keifer and colleagues (2016) described a retrospective comparative trial involving 166 subjects who underwent 198 breast reconstruction procedures with either AlloDerm RTM (n=98, 174 breasts) or Cortiva (n=68, 124 breasts). Follow-up data was limited to 60 days post-procedure. The authors noted that subjects in the Cortiva group were significantly older (p=0.002), heavier (p=0.008) and had a higher rate of hypertension (p=0.01). The results indicated that the Cortiva group had a significantly higher rate of mastectomy flap necrosis (p=0.02). However, a multiple linear regression model analysis did not identify matrix type as a predictive factor in developing mastectomy flap necrosis. Only BMI was identified as a predictive factor (p=0.036). The authors addressed the limitations of this study, noting the retrospective, unblinded methodology, limited geographical scope of the study, and short follow-up period. They concluded by stating further work should involve larger sample sizes, wider geographical scope, and longer follow-up time.

Parikh (2018) published the interim results from an ongoing prospective single-blind RCT comparing Cortiva vs. AlloDerm RTU for submuscular breast reconstruction. The report involved data from 59 breasts (Cortiva, n=31; AlloDerm, n=28). The authors reported no statistically significant differences with respect to time to drain removal, complications, fill volumes, patient-reported outcomes, or narcotic consumption. These results are promising, but the final analysis from this trial will provide a more complete picture of the safety and efficacy of Cortiva.

Cymetra

Cymetra, an injectable micronized particulate form of AlloDerm RTM (decellularized human dermis), has been proposed as a minimally invasive tissue graft product. It is treated as human tissue for transplantation under the FDA's HCT/P process. At this time, there are only three peer-reviewed published articles addressing the use of this product. All of these studies involve participants with vocal cord paralysis. One study by Morgan and colleagues (2007) was a retrospective, nonrandomized controlled trial involving 19 participants undergoing injection laryngoplasty with Cymetra or medialization laryngoplasty. The authors reported no significant difference between

groups at 3 months follow-up. No long-term comparison data was provided. Another report of a retrospective case series study involving 10 participants who all received injection laryngoplasty was reported by Milstein et al (2005). The authors of this study reported significant improvement in voice quality, glottal closure, and vocal fold bowing. Of the study population, only 8 participants (40%) were found to have lasting benefit. Finally, Karpenko and others (2003) reported the results of a small (n=10) case series study. The results indicated that there were no significant quantitative or subjective voice quality improvements. They also stated that significant improvements were identified in maximum phonation time, relative glottal area, and subjective judgment of glottal competency. However, these results were not maintained at the 3 month study interval.

Enduragen

Enduragen is a product composed of porcine acellular dermal matrix and has been cleared through the FDA's 510K process. McCord and others (2008) have published the only available study addressing the use of Enduragen. Their retrospective case series involved 69 subjects who underwent 192 reconstructive or cosmetic eyelid procedures with Enduragen grafts. Eight procedures were for spacers in the upper lid, 104 were for spacers in the lower lid, and 17 were for lateral canthal reinforcement. There were 13 eyelid complications, for a complication rate of 10%. Nine cases required surgical revision, and there were four cases of infection, all of which were successfully treated with oral and topical antibiotics. The results of this study are insufficient to adequately evaluate the safety and efficacy of Enduragen. Further research is needed.

Barmettler (2018) published the results of a prospective, randomized clinical trial involving 39 subjects (42 eyelids) undergoing lower eyelid retraction repair with spacer graft. Subjects were assigned to undergo their procedure with autologous auricular cartilage (n=19 eyelids), SurgiMend (n=11 eyelids), or Enduragen (n=12 eyelids). The authors reported no significant differences between groups with regard to 6-month measures including MRD2, conjunctival injection, tearing, discomfort, itching, corneal abrasions, or repeat procedures.

Fortiva

Fortiva is a product composed of porcine acellular dermal matrix and has been cleared through the FDA's 510K process. The only currently available published peer-reviewed study addressing its use in a clinical setting was published by Maxwell in 2019, who reported on the results of a retrospective non-randomized controlled study investigating the use of Fortiva (n=72) compared to Strattice (n=98) and Alloderm (n=59) in 229 subjects undergoing abdominal wall reconstruction. The incidence of recurrence of abdominal wall defect was significantly

higher in the Alloderm group (20.3%) compared with the Fortiva (10.2%) and Strattice groups (6.9%) (p=0.040). The 1-, 3-, and 5-year survival rates for the repair with Fortiva were 1.4% and 6.9%, and 0%. For Strattice, the results were 5.1%, 9.2%, and 10.2%, and for Alloderm, 6.8%, 18.5%, and 20.3%. Although subjects in the Alloderm group had the longest median hernia-free interval, 26.8 months (2-60 months), this was not found to be significantly different from Fortiva and Strattice (data not provided). The most common complication was surgical site infection (26.2%), followed by delayed healing (24.0%). Seroma formation was reported to have been significantly lower in the Fortiva group vs. the Strattice and Alloderm groups (1.4% vs 13.3% vs 11.9%; p=0.021). This study indicates promising results; however, this data is limited and not methodologically robust. Additional investigation into the safety and efficacy of Fortiva is needed.

GalaFLEX

GalaFLEX is a synthetic bioabsorbable product composed of poly-4-hydroxybutyrate and was cleared through the FDA's 510K process. The only currently available published peer-reviewed study addressing its use in a clinical setting was published in 2018 by Adams. This study was a case series report involving 62 subjects undergoing mastopexy procedures. The authors reported that 89.7% of subjects had successful ptosis correction and maintenance at 1 year. Both subject and surgeon satisfaction for breast shape, droop/sag of the breast, and maintenance of results at 1 year was reported as high. Adverse events deemed to be related to the device occurred in 5 subjects (8.0%), including nerve pain, breast swelling, ptosis, and 2 instances of asymmetry. It is not clear how the safety and efficacy of this product compares to other products, including those considered the standard of care for breast procedures. Additional comparative trials are warranted.

Gentrix

Gentrix is a product composed of porcine acellular urinary bladder and has been cleared through the FDA's 510K process. The only currently available published peer-reviewed study addressing its use in a clinical setting was published by Wang and others in 2018. They reported on a small unrandomized controlled trial involving 65 subjects who underwent paraesophageal hernia (PEH) repair with (n=32) or without (n=33) reinforcement with Gentrix. There was no difference reported between groups with regard to recurrence rates, size of recurrence, postoperative symptomatic or quality of life improvement. The authors noted that subjects in the unreinforced group who suffered recurrence had more severe symptoms and a higher rate of dissatisfaction. Of the 3 subjects with recurrences after Gentrix placement, reoperation demonstrated anterior failure where no reinforcement had occurred because of the posteriorly placed U-shaped graft. It is not clear how the safety and efficacy of this product

compares to other products, including those considered the standard of care. Additional comparative trials are warranted.

Gore BioA

Gore BioA is a completely synthetic, bioabsorbable product composed of 67% polyglycolic acid and 33% trimethyl chitosan and was cleared through the FDA's 510K process. Ommer and others published the results of a case series study involving 50 subjects with trans-sphincteric (n=28) or supra-sphincteric (n=12) anal fistula who were treated with Gore BioA (2012). Postoperatively, 1 subject developed an abscess which had to be managed surgically. In 2 subjects, the plug had fallen out within 2 weeks after surgery. Six months after surgery, the fistula had been healed in 20 subjects (50.0%). Three additional fistulas healed after an additional 7 to 12 months. The authors reported that the overall healing rate was 57.5% (23/40). However, they noted that healing rates differ significantly between the surgeons (from 0 to 75%), and also varied depending on the number of previous interventions. In individuals having had only drainage of the abscess, success occurred in 63.6% (14/22) whereas, in those having had one or more flap fistula reconstructions, the healing rate decreased slightly to 50% (9/18). Further study is warranted to better understand the impact of surgeon experience as well as optimal selection criteria for individuals requiring treatment for anal fistulas. Heydari (2013) described the results of a retrospective case series study involving 48 subjects with 49 anal fistulas treated with the Gore BioA. The overall healing rate was reported to be 69.3% (34/49 fistulas, 33/48 subjects). Eight subjects (24.2%) had complete healing by 3 months after surgery, 21 subjects (63.6%) had healed by 6 months, and 4 subjects (12.1%) had healed by 12 months. At 3 months, there were no reports of perineal pain or fecal incontinence. The authors reported no incidents of dislodged devices, anal stenosis, bleeding, or local infection.

In 2018 Jordan and others published the results of a retrospective comparative study involving 87 subjects undergoing breast reconstruction with mesh underlay reinforcement at 123 sites with either polypropelene mesh (n=58) or Gore BioA (n=65). The overall incidence of bulge or hernia was 11.4%. The Gore BioA group experienced significantly more bulges/hernias than the polypropylene mesh group (20% vs. 1.7%). They concluded that use of Gore BioA was associated with a 13.3-fold risk of bulge/hernia (p=0.016) and was not appropriate for anterior rectus fascia reinforcement following abdominal tissue transfer.

While these reports are promising, the lack of larger comparative trials impedes a full assessment of the efficacy of the GORE BioA device. Further investigation is warranted.

In 2017, the American Society of Colon and Rectal surgeons published a new Practice guideline for the management of anal fissures (Stewart, 2017). Their recommendations do not mention the use of grafts or plugs of any kind.

Gore® Acuseal Cardiovascular Patch

Gore® Acuseal Cardiovascular Patch is an expanded polytetrafluoroethylene (ePTFE) separated by an elastomeric layer and may be available both with and without covalently bound bioactive heparin. It has been cleared through the FDA's 510K process. Stone (2014) published the results of a prospective randomized study comparing clinical outcomes of Acuseal vs. bovine pericardium patching (Vascu-Guard) when used for primary closure for carotid endarterectomy. This study involved 200 subjects assigned in a 1:1 fashion and the mean follow-up period was 15 months. They reported that mean hemostasis time was 4.90 min for Acuseal vs. 3.09 min for Vascu-Guard (p=0.027). The mean operative times were similar for both groups (2.09 hr vs. 2.16 hr, p=0.669). The incidence of reexploration for neck hematoma was higher in the Vascu-Guard group; 6.12% vs. 1.03% (p=0.1183). The incidence of perioperative ipsilateral neurologic events was 3.09% for Acuseal patching vs. 1.02% for Vascu-Guard patching (p=0.368). The respective freedom from ≥ 70% carotid restenosis at 1, 2, and 3 years were 100%, 100%, and 100% for ACUSEAL patching vs. 100%, 98%, and 98% for Vascu-Guard patching (p=0.2478).

Grafix CORE

Grafix CORE is a grafting product derived from allogeneic chorion membrane. It is treated as human tissue for transplantation under the FDA's HCT/P process.

Frykberg (2016) reported the results of a prospective case series study involving subjects with complex DFUs ≤ 15 cm in their longest dimension and extending through the dermis with exposed muscle, tendon, fascia, bone or joint capsule. All were treated with weekly applications of Grafix CORE. The intent-to-treat (ITT) population included 31 subjects and the per-protocol population included 27 subjects. The ITT subject population had significant co-morbidities, with 80% having hypertension, 60% current or former smokers, 55% having heart disease, and 45% having a previous partial foot amputation. Prior advanced treatment (for example, negative pressure wound therapy) for the index wound had occurred in 67.7% of subjects. At 16 weeks, 96.3% of the per-protocol group had 100% granulation of the index wound and complete closure occurred in 59.3%. The mean area reduction of the index wound at day 28 was 54.3% and 72.8% at 8 weeks. At the end of the 16-week study period the mean wound area reduction was 92.3%. No Grafix-related adverse events were reported. This study demonstrated the use of

Grafix CORE in the healing of complex DFUs. However, the small study population and lack of controls hampers the generalizability of these results.

Raspovic (2018) reported a retrospective case series analysis of 360 subjects with 441 DFUs treated with Grafix PRIME or Grafix CORE using data from Net Health's Wound Expert electronic health records database. The mean size of the index wound was 5.1 cm^2 with 3.9 mm depth. Mean wound duration prior to study treatment was 102 days. The mean duration of treatment with a Grafix product was 89.3 days (median 56.0). Complete wound closure at the end of treatment occurred in 59.4% of subjects. Median time to closure was 42.0 days with a median of 4 graft applications. The proportion of closure decreased as wound size increased, with 72.3% of wounds between 0.25 cm^2 to 2 cm^2 having complete healing at a median of 21 days and 4 applications. For wounds larger than 25 cm^2, only 27.8% achieved complete healing at a median of 105 days and 11 applications. The authors did not provide any data regarding the percentage of subjects receiving treatment with Grafix PRIME vs. those receiving Grafix CORE.

At this time the safety and efficacy of Grafix CORE, is uncertain. Additional well designed and conducted trials are warranted.

Hyalomatrix

Hyalomatrix is a synthetic wound covering product composed of a benzyl ester of hyaluronic acid. This product has been approved through the FDA's PMA process. The currently available evidence addressing the use of Hyalomatrix is limited mostly to small, uncontrolled, unblinded case series studies. Only one RCT has been published to date involving 16 subjects with VLUs, 9 of which were treated with Hylaomartix and 7 treated with standard wound care (Alvarez, 2017). The authors reported that the incidence of wound healing at 12 weeks was 66.6% for the Hyalomatrix group vs. 14.2% for controls (p=0.066). At 16 weeks, the incidence of wound healing was 87.5% of subjects in the Hyalomatrix group vs. 42.8% in the control group (p=0.059). The mean time to healing in the Hyalomatrix group was 41 days compared with 104 days in the control (p=0.029). The largest studies available involve 300, 262, 79, and 57 subjects (Gravante, 2007; Caravaggi, 2003 and 2011; Gravante 2010, respectively). The Carravaggi study addresses chronic wounds while the Gravante studies address burns. The rest of the studies published involve significantly fewer than 30 subjects and encompass a variety of indications including various surgically created wounds (Faga, 2013; Landi, 2014; Onesti, 2014), traumatic wounds (Onesti, 2014; Vaienti, 2013), and chronic ulcers (Motolese, 2013). In summary, the body of literature addressing Hyalomatrix is limited to predominantly small case series studies involving a heterogeneous collection of indications. While most

of these studies demonstrate promising results, the uncontrolled, unblinded nature of these studies does not allow proper assessment of the safety and efficacy this product.

Integra Dermal Regeneration Template

See the section below addressing Omnigraft.

Integra Flowable Wound Matrix

In 2017, Campitiello and colleagues published an RCT comparing Integra Flowable Wound Matrix vs. standard care for the treatment of 46 subjects with DFUs with irregular geometries. There were 23 subjects in each group who were evaluated once a week for 6 weeks. The authors reported that the overall complete healing rate was 69.56%, with the rate in the Integra group being 86.95% vs. 52.17% in the control group (OR=1.67, p=0.001). Mean time to healing was 29.73 days in the Integra group vs. 42.78 in the control group (p<0.000). The amputation and rehospitalization rates in the Integra group were 4.34% vs. 30.43% in controls (RR=0.16, p=0.028). The authors concluded that Integra Flowable Wound Matrix was significantly superior to the wet dressing, but that additional research will shed more light on the promising advantages of this material in healing diabetic foot ulcers.

Keramatrix

This product is composed of freeze dried acellular animal-derived keratin and has been approved through the FDA's 510K process. At this time, the most rigorous evidence is a small nonrandomized controlled study involving 40 subjects with superficial or partial thickness burn injuries treated with Keramatrix, compared to 40 historical controls who received standard of care treatment (Loan, 2016). The results indicated a significantly faster mean healing time in the Keramatrix group vs. controls (8.7 days vs. 14.4 days, p<0.05), hospital inpatient days (0 days vs. 2.6 days, p<0.05), and number of outpatient appointments following initial therapy (1.2 vs. 3.3, p<0.05). No differences in complications were reported.

KeraSys

Kerasys is composed of decellularized xenogeneic porcine small intestinal submucosa and has been approved through the FDA's 510K process. The only available study described in the published peer-reviewed literature addressing the use of this product was published by Nagi and others in 2013. Their study was a retrospective,

noncomparative, consecutive case series of 42 eyes with tube-related exposure complications due to glaucoma drainage device surgery. KeraSys was used to cover the defect. The authors reported that 4 (10%) eyes experienced patch-related complications. Two had exposure at 8 months postoperatively, 1 had exposure at 13 months postoperatively, and 1 with exposure at 4 weeks postoperatively. They concluded that, "The effectiveness of the KeraSys patch graft is limited by the higher than expected early exposure rate found in this case series."

Kerecis™ Omega3 (formerly MariGen Omega3)

Karecis Omega3 is an acellular dermal matrix derived from fish skin and cleared through the FDA's 510K process.

The available evidence addressing the clinical safety and efficacy of Kerecis is limited. The only comparative study currently available was a double-blind, parallel-group non-inferiority RCT involving 81 subjects with 162 full-thickness surgical wounds (Baldursson, 2015). Each subject underwent the creation of two 4 mm full thickness wounds made on the proximal anteriolateral aspect of their non-dominant arm, 2 cm apart. Each subject had one wound treated with Kerecis and the other wound with Oasis porcine-derived graft product, and were followed for 28 days. At the study endpoint, 95% (76/80) of wounds in the Kerecis group and 96.3% (79/82) of wounds in the Oasis group were healed. The authors reported that this result was within the 95% two-sided confidence interval for non-inferiority margin of 0.1. They also noted that the OR of a Kerecis-treated wound being healed vs. an Oasis-treated wound was 4.75 (p=0.041), indicating that Kerecis added significantly faster wound healing vs. Oasis. No significant immunological responses were noted in the Kerecis group. While this study is promising, it should be noted that the safety and efficacy of the product used in the comparison group was not well studied, and the selection does not truly allow an understanding of the benefits of Kerecis. Additional studies involving larger study populations and an appropriate comparison group are warranted.

It should be noted that only one other study addressing the clinical outcomes of Kerecis has been published (Yang, 2016). However, this study was very small, involving only 5 subjects, and did not involve any comparison group. The value of this publication in understanding the generalizable safety and efficacy of Kerecis is limited.

Additional investigation into the safety and clinical utility of Kerecis is needed.

MatrACELL

MatrACELL is a decellularized allograft product composed of human cardiovascular tissue treated as human tissue for transplantation under the FDA's HCT/P process.

Currently the only study published regarding the use of this product was published by Hopkins (2014). This nonrandomized controlled study involved 108 consecutive subjects undergoing cardiovascular reconstructive procedures using MatrACELL pulmonary artery patches during pulmonary arterioplasty. A second retrospective cohort of 100 subjects who received arterioplasty patches using classical cryopreserved pulmonary artery allografts (n=59 subjects) or synthetic materials (n=41 subjects) was used for comparison. The reported results included that 106 subjects with 118 decellularized patches had no device-related serious adverse events, no device failures, and no evidence of calcifications on chest roentgenograms. In contrast, the control subjects experienced an overall 14.0% patch failure rate requiring device-related reoperations ($p<0.0001$) at mean duration of 194 ± 104 days (range, 25 to 477 days). The authors concluded that the intermediate-term data obtained in this study suggest favorable performance by decellularized pulmonary artery patches, with no material failures or reoperations provoked by device failure.

Additional study is warranted to fully evaluate the safety and efficacy of this product.

MatriDerm

MatriDerm is a decellularized dermis allograft product treated as human tissue for transplantation under the FDA's HCT/P process. The largest available study involves 30 subjects undergoing nasal tip skin grafts non-randomly assigned to receive either conventional full-thickness skin grafting, retroauricular perichondrodermal composite grafts, or skin transplantation supplemented with MatriDerm (Riml, 2011). Ten subjects were assigned to each group. This retrospective study was conducted in a randomized and blinded manner by assigned reviewers using the Manchester scale. The authors report that 2 (20%) of the MatriDerm subjects developed fistulae, and concluded that MatriDerm was not suitable for nasal tip reconstruction.

Another study by Haslik and colleagues evaluated the use of MatriDerm for the management of full-thickness skin grafts (2010). This small case series study involved 17 subjects with upper extremity skin wounds, all of whom received MatriDerm in conjunction with unmeshed skin grafts. The reported take rate was 96%. A 12 month follow-up Vancouver scale score of 1.7 and DASH (disability of arm-shoulder-hand) score showed excellent hand function in subjects with burn injury and subjects with a defect due to the harvest of a radial forearm flap achieved satisfying hand function.

Further study with larger, better designed trials is required in order to fully evaluate the safety and efficacy of MatriDerm.

MediHoney

The use of honey has been proposed for the treatment of various skin conditions including burns, chronic ulcers, and superficial abrasions. It has been hypothesized that honey, with its antibacterial properties, can significantly improve skin healing when applied topically to skin wounds. Several randomized controlled trials have been published involving MediHoney, a product cleared through the FDA's 510K process, most addressing the treatment of venous leg and foot ulcers. Jull and colleagues published the largest of these trials, which included 368 subjects randomized to receive treatment with either calcium alginate dressing impregnated with manuka honey or standard care with whatever dressings were appropriate for the individual at that time (2008). After following the participants for a total of 12 weeks of follow-up, the authors concluded that there was no significant difference in outcomes between the two groups. It was noted that the honey-treated group experienced significantly greater numbers of adverse events (p=0.013). Contradicting these findings is a study by Gethin and Cowman (2008). In this study, 108 subjects with venous ulcers were randomized to receive treatment with either honey dressing or standard hydrogel therapy. The findings were that the honey-treated group had significantly better results in terms of median reduction in wound size at 12 weeks (44% vs. 33% , p=0.037), but no significant differences between groups in other primary endpoints were reported.

The other most studied condition addressed in the literature is the treatment of burns. The largest study currently available addressing burns involved 150 subjects randomized to receive treatment with either silver sulphadiazine (SSD) or honey (Malik, 2010). Each subject acted as his or her own control, with one burn site randomly treated with SSD and the other with honey. The authors report that the honey-treated sites had significantly faster re-epithelialization and healing of superficial and partial thickness burns than the SSD sites (13.47 days vs. 15.62 days, p<0.0001). Additionally, the honey-treated sites achieved complete healing significantly faster than SSD sites (21 days vs. 24 days, p<0.0001).

Lund and colleagues compared the use of honey-coated dressing for breast malignant wounds. In this study, 67 subjects, 79% of whom had breast cancer, were randomized to receive treatment with either honey-coated dressing (n=34) or silver dressing (n=33). The authors report no significant differences between groups and they concluded that the possible antibacterial effect of either treatment "could not be confirmed in these malignant wounds."

At this time, the evidence addressing the use of honey for skin wounds is lacking. The current studies are mostly unblinded, controlled studies, and a large variety of controls have been used. These factors make comparison study outcomes difficult to interpret. Further investigation with large well-done blinded trials using standardized controls is warranted.

Menaflex (formerly "Collagen meniscus implant" or CMI)

Collagen meniscus implants (e.g., Menaflex) have been proposed as a treatment method for individuals with a damaged knee meniscus. Menaflex is a human-derived acellular collagen product. At this time, there is only one large trial for this type of procedure (Rodkey, 2008). This study involved 311 subjects with irreparable injury of the medial meniscus or a previous partial medial meniscectomy. The study population was divided into two groups, those with prior meniscal surgery (chronic group) and those with no prior surgery (acute group). These populations were further randomized to receive either treatment with a collagen meniscus implant or a partial meniscectomy only. The mean duration of follow-up was 59 months (range, 16 to 92 months). Repeat arthroscopies done in the experimental group at 1 year showed significantly (p=0.001) increased meniscal tissue compared with that seen after the original index surgery. In the chronic group, participants who had received the collagen implant regained a significantly higher degree of pre-surgery activity than did the controls (p=0.02). This group also underwent significantly fewer non-protocol reoperations (p=0.04). The authors reported no significant differences between the two treatment groups in the acute arm of the study.

Zaffahnini and colleagues conducted a long-term trial of the performance of the Menaflex implant in 33 subjects. This nonrandomized controlled trial allowed subjects to choose treatment with either Menaflex (n=17) or partial medial meniscectomy (n=16). Subjects were evaluated at baseline, 5 years and then 10 years after surgery. At 10 years, the authors report that the Menaflex group showed significant improvement compared to meniscectomy with regard to visual analog scale for pain (p=0.004), International Knee Documentation Committee knee form (p=0.0001), Teger index (p=0.026), SF-36 Physical Health Index (p=0.026), and SF-36 Mental Health Index (p=0.004). Radiographic evaluation showed significantly less medial joint space narrowing in the Menaflex group than in controls (p=0.0003). There were no significant differences reported between groups regarding Lysholm score (p=0.062) and Yulish score (p=0.122). Genovese score remained constant between 5 and 10 years after surgery (p=0.5).

A much smaller case series study of 22 subjects followed for 10 years was reported by Monllau and colleagues (2011). The results of this study demonstrated that several measures improved, including the visual analog pain scale and radiographic joint line narrowing. The Lysholm score was significantly improved, from 59.9 at baseline, 89.6 at 1 year ($p<0.001$), and 87.5 at 10 years ($p<0.001$). Failure rate was only reported to be 8% in the 25 subjects initially implanted.

Van Der Straeten published the results of a cohort study of 313 subjects who received treatment with the collagen meniscal implant and were followed for a mean follow-up of 6.8 years (2016). A total of 56.5% of the implants were still intact and in place; 27.4% had been removed. This included 63 implants converted to a knee arthroplasty (19.2%). The overall cumulative allograft survivorship was 15.1% at 24.0 years. Simultaneous osteotomy significantly deteriorated survival (0% at 24.0 years) ($p=0.010$). The authors stated that 61% of subjects underwent at least one additional surgery (range 1-11) for clinical symptoms after implantation. They concluded that the collagen meniscal implant did not delay or prevent tibiofemoral OA progression.

Another large cohort study was reported by Waterman (2016). This study involved 230 active duty military personnel who underwent treatment with the collagen meniscal implant. A total of 51 complications occurred in 46 (21.1%) subjects, including a secondary tear or extrusion (9%). The authors reported that 10 subjects (4.4%) required secondary meniscal debridement at a mean of 2.14 years. Revision was done in 1 subject (0.4%) and 20 subjects (0.9%) subsequently underwent total knee arthroplasty. After implantation, 50 subjects (22%) underwent knee-related military discharge at a mean of 2.49 years postoperatively. They concluded that while there were low reoperation and revision rates, their investigation indicated that 22% of subjects who received implants were unable to return to military duty due to persistent knee limitations at short-term follow-up.

While these studies show that there is some potential benefit to the use of meniscal collagen implants in some populations, further data from rigorously designed and conducted trials is warranted to further understand the clinical implications of this technology.

Menaflex was originally cleared by the FDA in the 510K process. Subsequent to further review by the FDA, this clearance was revoked. The manufacturer, ReGen Biologics, Inc. went bankrupt shortly thereafter. The Menaflex device is currently not marketed in the U.S.

Neuragen

Neuragen collagen tube conduits are composed of bovine-derived acellular collagen and have been cleared through the FDA's 510K process. This product is proposed for use in peripheral nerve repair. At this time, only two studies have been published in peer-reviewed journals describing this use (Farole, 2008; Wangensteen, 2010). The study by Wangensteen and colleagues was a retrospective analysis of 96 subjects with various nerve injuries who underwent 126 nerve repairs with Neruogen conduits. Only 64 (66.7%) subjects were seen at follow-up. Twenty-six of 126 repairs had quantitative testing of nerve recovery, with 35% reporting improvement and 31% going on to additional surgery. Sixty of 126 repairs underwent qualitative testing, with 45% reporting improvement and 5% going on to additional surgery. Overall, sensory recovery was between 35-45%.

The Farole study is a small case series study involving only 8 subjects with facial nerve damage followed for at least 1 year. The authors report 4 subjects had good improvement. Using the criteria described by another author, 4 cases were found to have good improvement, 4 with some improvement, and 1 had no improvement. None of the cases had worsening of symptoms.

Further study is needed to fully evaluate the safety and efficacy of this product.

Omnigraft

Omnigraft, also known as Integra Dermal Regeneration Template, is a product composed of bovine-derived collagen, shark-derived chondroitin and silicone. This product has been approved through the FDA's PMA process. At this time there is limited evidence in the published peer-reviewed literature addressing the use of this product.

In 2016, Driver and colleagues reported the results of an RCT involving 307 subjects with DFUs assigned to treatment with either standard care (n=153) or treatment with Omnigraft (n=154) and followed initially for 16 weeks or until confirmation of complete wound closure, and then for a further 12 weeks. The investigators reported that complete DFU closure during the treatment phase was significantly greater with Omnigraft vs. control treatment (51% vs. 32%; p=0.001). The median time to complete DFU closure was 43 days for Omnigraft subjects vs. 78 days for controls, in wounds that healed. The rate of wound size reduction was significantly better in the Omnigraft subjects (7.2% per week vs. 4.8% per week, p=0.012). They concluded that for the treatment of chronic DFUs, Omnigraft treatment decreased the time to complete wound closure, increased the rate of wound closure, improved components of quality of life and had less adverse events compared with the standard of care treatment.

Further investigation into the safety and efficacy of Omnigraft is needed.

Pelvicol

Pelvicol is a porcine-derived acellular dermal collagen product cleared through the FDA's 510K process. The use of Pelvicol was evaluated in 132 subjects with pelvic organ prolapse. This RCT involved 64 subjects who underwent anterior and posterior colporrhaphy and 68 who received colporrhaphy with Pelvicol. At 3 months follow-up, there were significantly more surgical failures and recurrences in the Pelvicol group, but by the 3 year follow-up period recurrence rates were similar. No significant differences were noted with regard to symptom resolution, sexual activity, or complications rates. The authors conclude that, "Pelvicol did not provide advantages over conventional colporrhaphy in recurrent pelvic organ prolapse concerning anatomical and subjective outcomes."

Kahn (2015) published the results of an RCT involving 201 subjects undergoing surgical treatment for stress urinary incontinence. Subjects received treatment with either tension-free vaginal tape (TVT), autologous fascial sling (AFS), or Pelvicol. The authors reported that 162 (80.6%) subjects were available for follow-up at a median follow-up of 10 years. They reported the 1 year "success rates", defined as being completely dry or improved, as 93% in the TVT group, 90% in the AFS group and 61% in the Pelvicol group. There were no significant differences between groups at 10 years. Comparing the 1 and 10 year success rates, there were significant reductions in the TVT and AFS groups ($p<0.05$ for both), but not for the Pelvicol group ($p=1.0$). Similar results were reported with the rates of "dry" subjects at 1 and 10 years, with rates for TVT reported as being 55% and 31.7%, 48% and 50.8% for AFS, and 22% and 15.7% for Pelvicol. These rates significantly favored AFS ($p<0.001$ vs. Pelvicol and $p=0.001$ vs. TVT). The Pelvicol arm of the study was discontinued by the data monitoring group after it was clear that the Pelvicol group had significantly poorer results vs. TVT and AFS. The results of this study indicate that the use of Pelvicol for the treatment of stress urinary incontinence may present a significant risk of harm compared to other available treatments, and further investigation may be warranted.

Peri-Strips Dry

Peri-Strips Dry is a product derived from decellularized bovine pericardium and cleared through the FDA's 510K process. At this time there is only one peer-reviewed published article addressing the use of this product. Stamou and colleagues compared the use of Peri-Strips Dry (n=96) to standard care (n=91) in staple line reinforcement during sleeve gastrectomy procedures (2011). The authors reported that the use of Peri-Strips Dry significantly

reduced the incidence of staple line bleeding (p=0.012) and intra-abdominal collections (p=0.026). Leak rate was not significantly reduced.

Permacol

Permacol is an acellular dermal collagen product derived from porcine pericardium that has been cleared through the FDA's 510K process. Currently, the peer-reviewed published data addressing the use of Permacol is limited to a single retrospective, nonrandomized controlled study of 37 subjects undergoing congenital diaphragmatic hernia repair. Subjects received treatment with either Permacol (n=29) or synthetic Gore-Tex (n=8), with a median follow-up of 57 months for Gore-Tex and 20 months for Permacol. Overall recurrences were reported in 8 (28%) Gore-Tex subjects with a median time to recurrence of 12 months. There were no recurrences reported in the Permacol group. These results are interesting, but due to the small sample size, retrospective nature and lack of randomization, it is not possible to generalize the results to other populations. Further investigation into the safety and efficacy of Permacol is needed.

Phasix-ST

Phasix-ST is a synthetic mesh product composed of poly-4-hydroxybutyrate cleared through the FDA's 510K process. At this time, the only available published study addressing its use is a retrospective case series of 50 subjects undergoing PEH repair (Abdelmoaty, 2019). Subject data was collected from a prospective database of Phasix-ST-treated subjects who had elective, first-time laparoscopic PEH repair with 1-year follow-up. PEH repair combined with fundoplication was done in 29 subjects and PEH repair, fundoplication, and Collis gastroplasty in 21 subjects. Phasix-ST mesh was used for crural reinforcement in all subjects. The authors report no intraoperative complications with the mesh placement, and a diaphragm relaxing incision was performed in 2 subjects. The mean length of hospital stay was 2.8 days, and there was no major morbidity or mortality reported. At 1 year post procedure, recurrent hernia was found in 4 subjects. No subjects with Collis gastroplasty or a relaxing incision had a recurrent hernia, no reoperations were conducted, and no mesh infection or mesh erosion was reported. These results are promising, but provide only limited short-term data from a small non-comparative trial. Further investigation into the safety and efficacy of Phasix -ST is needed.

Promogran

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Promogran is an acellular dermal collagen product of bovine origin cleared through the FDA's 510K process. The use of Promogran has been evaluated in two RCTs. The first, by Veves and others, involved 276 subjects with DFUs randomized to receive treatment with either Pomogran (n=138) or moistened gauze (control group; n=138) (2002). At 12 weeks of treatment, there was no statistically significant difference between groups with regard to complete wound closure (p=0.12), in healing for either the subgroup of subjects with wounds of less than 6 months duration (p=0.056), or the group with wounds of at least 6 months duration (p=0.83). No differences were seen in the safety measurements between groups. The other study by Vin involved 73 subjects with VLUs randomly allocated to receive either Promogran (n=37) or a non-adherent dressing (Adaptic) (n=36). Only 29 subjects completed the 12-week study period (39.7%). No intent-to-treat analysis was provided. Because of this, the data reported is not particularly useful.

Further study is required to fully assess the safety and efficacy of Promogran.

Seamguard

Seamguard is a synthetic product composed of polyglycolic acid and trimethylene carbonate cleared through the FDA's 510K process. It has been evaluated in only a few peer-reviewed published articles. The first, by Salgado and others, was a randomized controlled trial evaluating the use of Seamguard vs. extraluminal suturing or fibrin glue for open bariatric surgical procedures (2011). Twenty subjects were assigned to each group; however, enrollment in the fibrin glue group was stopped due to serious complications, including leaks requiring surgical intervention. The authors report that no significant differences were found between the Seamguard group and the suturing group. This study was not designed or powered to be a non-inferiority study, so these findings are not particularly useful in understanding the safety and efficacy of Seamguard.

In another study by Albanopoulos and colleagues, Seamguard was compared to staple line suturing in laparoscopic sleeve gastrectomy procedures (2012). This study enrolled 90 subjects, 48 who were assigned to the Seamguard group and 42 to the suturing group. As with the Salgado study, the authors reported no significant differences in measured outcomes. One exception to this was a 6.2% complication rate in the Seamguard group vs. no complications in the suturing group.

In 2013, Wallace published the results of a nonrandomized controlled study of 36 subjects undergoing pancreatectomy with the addition of Seamguard to the stapled stump closure. This group was compared to 18 historical controls undergoing the same procedure without Seamguard. Postoperative leak rate was reported in 8%

in the experimental group vs. 39% in the control group. This study is limited due to its small population, use of historical controls and other methodological issues. The available data addressing the use of Seamguard is limited to small studies with significant methodological flaws. Further investigation with robust trials is warranted.

Guerrier and others (2018) published the results of a retrospective review of 256 subjects undergoing laparoscopic sleeve gastrectomy. Subjects received treatment with staple line reinforcement with oversewing (n=28), reinforcement with Seamguard (n=115), or no staple line reinforcement (n=111). Intraoperative staple line bleeding was significantly reduced in the reinforcement group (22.3 vs. 37.8%, p=0.003). Gastric leaks were reported in 9 subjects (3.52%), with no difference between any reinforcement method (2.7 vs 2.1%, p=0.54). The authors did note that oversewing of the staple line was associated with higher incidence of stenosis, a serious complication with significant morbidity and mortality (p<0.01). The authors concluded that their study demonstrated that staple line reinforcement does not provide significant leak reduction, but does reduce intraoperative staple line bleeding. However, this must be viewed in light of increased risk of stenosis development.

Suprathel

Suprathel is a synthetic copolymer consisting mainly of DL-lactide (>70%), trimethylenecarbonate, and e-caprolactone and was cleared under the FDA's 510k process. The available evidence addressing the use of Suprathel is limited to two small studies. The first was a small RCT involving 22 subjects with burn injuries treated with split-thickness skin grafts (Schwarze, 2007). Each donor site was randomly selected and was treated with Suprathel or Jelonet. There was no significant difference between the two materials tested regarding healing time and re-epithelization, but a significantly lower pain score was reported for the subjects treated with Suprathel (p=0.0002). The same group reported the results of another RCT study involving 30 subjects with burn injuries (Schwarze, 2008). Wounds from each subject were randomly selected and partly treated with Omniderm and partly treated with Suprathel. There was no significant difference between the two products regarding healing time and re-epithelization. There was a significantly lower pain score for subjects treated with Suprathel (p=0.0072). Rashaan (2017) reported the use of Suprathel in a population of 21 children with partial thickness burns. The authors reported a median reepithelialization time of 13 days (range 7-29), and 3 subjects required treatment with split skin grafts. There were 7 (33%) subjects with wound colonization before application of Suprathel, which increased to 12 (57%) during treatment. Only 1 subject developed a wound infection. Unfortunately, the small sample of subjects in these studies is not sufficient to allow generalization of the findings to larger populations.

SurgiMend

SurgiMend is a product made from acellular fetal bovine dermis and is cleared under the FDA's 510k process. The available peer-reviewed published literature addressing its use in humans is limited to a few studies. The largest of these was a nonrandomized, retrospective case series reviewing a single surgeon's 5 year experience of 440 consecutive, immediate breast reconstructions in 281 subjects (Butterfield, 2013). In 222 of these subjects, reconstruction was done using SurgiMend and the other 59 used AlloDerm RTM. The investigators reported no significant differences in complication rates between the two products in the incidence of hematoma, infection, major skin necrosis, or breast implant removal. However, the incidence of seroma was significantly more common in the AlloDerm RTM subjects (15.7%) than in the SurgiMend group (8.3%) ($p<0.05$). However, this finding must be considered in light of the fact that the AlloDerm RTM group was followed, on average, for over twice the length of time (15.6 ± 8.79 months for SurgiMend vs. 32.8 ± 15.87 for AlloDerm RTM; $p<0.0001$). The SurgiMend group had a significantly higher rate of any necrosis (11.0% [39/351] for SurgiMend vs. 3.4% [3/89]; $p<0.0265$). In a multivariate analysis, it was found that both a BMI > 30 kg/m^2 and previous radiation therapy significantly increased the rate for complications and expander loss.

A retrospective, nonrandomized comparative trial involving 120 subjects undergoing complex abdominal wall reconstruction was reported by Clemens in 2013. Subjects received either SurgiMend (n=51) or Strattice (n=69) and were followed for a mean of 21 ± 9.9 months. Postoperative surgical complication rates between groups were not statistically different. However, intraoperative complications were significantly higher in the Strattice group vs. the SurgiMend group (7 vs. 0, p=0.02), and the overall complication rate for the SurgiMend group was reported as 25.5% vs. 36.6% for the Strattice group (p=0.04). The authors concluded that the two products appear to result in similar outcomes, but Strattice may result in higher rates of device failure.

Eichler (2015) reported on a retrospective, nonrandomized comparative trial involving 127 breasts undergoing reconstruction with either SurgiMend (n=63) or EpiFlex (n=64), a product not available in the U.S. All procedures were conducted by a single surgeon. The authors reported that gross complication rates were 11.1% for SurgiMend and 40.6% for EpiFlex (p=0.003). Red breast syndrome was reported in 3 SurgiMend and 9 EpiFlex subjects (p=0.003). Seroma occurred in 1 SurgiMend subject and 6 EpiFlex subjects (p=0.07). Revision surgery was needed in 3 SurgiMend and 8 EpiFlex subjects (p=0.21). This study reports favorable benefits for SurgiMend over EpiFlex. However, the small subject pool, lack of blinding and randomization, and retrospective nature of the study limit the utility of these findings.

The same group published another retrospective, nonrandomized comparative trial involving 54 subjects undergoing breast reconstruction procedures with either SurgiMend (n=18) or Tutomesh (n=27) (Eichler, 2017). No difference was noted in the rate of complications, consistent with other previous reports.

Endress (2012) reported the results of a retrospective, nonrandomized case series study involving of 28 subjects who underwent 49 breast reconstructions with SurgiMend compared to 91 subjects who underwent 123 control breast reconstructions with no additional grafting materials. The mean immediate fill volume in the SurgiMend group was 181.2 ± 148.3 mL and 117.7 ± 6.3 mL in the control group ($p<0.001$). The results show that the duration of drainage was significantly shorter in the SurgiMend group vs. controls (8.51 ± 0.4 days vs. 11.07 ± 5.1 days; $p<0.015$). No significant differences in the overall complication rate were noted (20.8% in the SurgiMend group, 13.0% in the control group). The authors provide a subgroup analysis that indicates that the SurgiMend group with complications had significantly longer drain removal time (9.48 vs. 7.97 days), larger initial fill volumes (238.1 vs. 145.3 mL), and a higher BMI (25.8 vs. 22.6 kg/m^2) when compared with the complication-free subgroup. Unfortunately these findings are hampered by the small subject population of the SurgiMend group.

Mazari (2018) reported the results of a retrospective controlled study involving 82 subjects (97 breasts) comparing Strattice (n=54 breasts) and SurgiMend (n=43 breasts) for implant-based immediate breast reconstruction. No differences were noted with regard to implant loss rate (p=0.077). The ADM loss rate was significantly higher in the Strattice group vs. the SurgiMend group (n=7 vs. n=0, p=0.014). Reoperation rates were significantly higher in the Strattice group vs. the SurgiMend group (n=17 vs. n=2, p=0.002). Incidence of red breast was significantly higher in the SurgiMend group (n=9 vs. n=3, p=0.022). No differences between groups was noted with regard to seroma, wound problems, or infection rates.

A retrospective case series study involving 111 subjects (147 breasts) undergoing immediate breast reconstruction with SurgiMend was reported by Scheflan in 2018. Overall rates of minor and major complications after a median follow-up of 24.3 months, were 25.2 percent and 12.9 percent, respectively. Seroma was the most common major complication (8.2%), with necrosis (6.1 %) the second most common. The rate of capsular contracture was 2.7% and explantation occurred in 2.7%. In a univariate analysis, smokers had a greater risk of major complications (p=0.013), and postoperative radiation therapy and obesity were associated with an increased risk of capsular contracture (p=0.006) and explantation (p=0.006), respectively. Multivariate analysis identified several factors that were associated with complications or explantation, including obesity ($p<0.05$), preoperative chemotherapy ($p<0.001$), and mastectomy weight ($p<0.05$). However, the authors note that these associations were in agreement with the results of other ADM studies, and that they do not appear to be unique to SurgiMend.

Overall, the available evidence for SurgiMend is insufficient to adequately demonstrate the comparative efficacy of this product to the existing standard of care. Additional prospective, randomized controlled studies would be helpful in addressing this issue.

Please see the Enduragen section for additional studies involving SurgiMend.

Surgisis

Surgisis is a product composed of decellularized intestinal mucosa of porcine origin and is cleared under the FDA's 510k process. At this time, there are a large number of case series studies published on the use of the Surgisis anal fistula plug (AFP) (Champagne, 2006; Cintron, 2013; Ellis, 2010; Ky, 2008; O'Connor, 2006; Schwandner, 2009; Thekkinkattil, 2009). The vast majority of these involve very small sample sizes and short follow-up times. The uncontrolled nature of these studies minimizes the scientific value of this data.

Several RCTs are currently available addressing the use of Surgisis for the treatment of anal fistulae. The first study, reported by Ortiz et al., involved 43 subjects randomized to receive either endorectal advancement flap surgery or insertion of an anal fistula plug (2009). The drop-out rate was greater than 20% for each group. The authors reported that the relative risk for recurrence was 6.4 for those who received the plug intervention during the 1 year follow-up. Additionally, of the 16 who had previous fistula surgery, 9 had recurrence and 8 of these were from the plug group. Overall, the authors concluded that the anal fistula plug was associated with a low rate of fistula healing, especially in individuals with a history of fistula surgery. The second study included 60 subjects with perianal fistulas who were randomly assigned to receive treatment with Surgisis (n=31) or a mucosal advancement flap (n=29) (van Koperen, 2011). Both subjects and investigators were blinded to group assignment. At a follow-up of 11 months, the recurrence rates were 71% (n=22) in the Surgisis group vs. 52% (n=15) in the mucosal advancement flap group, which was not significantly different. Additionally, no significant differences were reported with regard to postoperative pain, pre- and postoperative incontinence scores, soiling, and quality of life. Senéjoux (2016) reported the results of an open-label, randomized controlled trial comparing seton removal alone (n=52) vs. Surgisis (n=54) in 106 subjects with Crohn's disease and at least one ano-perineal fistula tract drained for more than 1 month. The authors reported that fistula closure at week 12 was achieved in 31.5% of subjects in the Surgisis group vs. 23.1 % in the control group (p=0.19). No interaction in treatment effect was found when data was analyzed to control for case complexity (p=0.45). Adverse events at week 12 were reported in 17 subjects in the Surgisis group vs. 8 controls (p=0.07). The authors concluded that the use of Surgisis was not more

effective than seton removal alone. In 2017, Bondi and others published the results of an RCT involving 94 subjects with cryptogenic trans-sphincteric anal fistulas assigned to treatment with either Surgisis (n=48) or mucosal advancement flap (n=46). The authors reported that the recurrence rate at 12 months was 66% in the Surgisis group and 38% in the flap group (p=0.006). While anal pain was reduced after operation in both groups, anal incontinence did not change in the follow-up period for either. No differences between the groups were reported with regard to pain, incontinence, or quality of life. The authors concluded that there was a considerably higher recurrence rate after the anal fistula plug procedure than following advancement flap repair.

Several studies have reported on the results from nonrandomized controlled, retrospective trials. Ellis and colleagues described the results of a study that involved 95 control subjects who had trans-sphincteric or rectovaginal fistulas repaired via advancement flap repair (2007). The experimental group included only 18 subjects who received treatment with Surgisis. The results indicated a significant benefit to the Surgisis procedure. Another study included 80 subjects who received treatment with either anal fistula plug or endorectal advancement flap (Christoforidis, 2009). The results of this trial demonstrated that treatment success was close to over twice as likely with the flap procedure compared to treatment with a fistula plug after a mean follow-up period of 56 months. Chung and colleagues (2009) reported on the results of a retrospective study that involved 245 subjects who underwent anal fistula repair surgery with either Surgisis (n=27), fibrin glue (n=23), Seton drain (n=86), or an endorectal advancement flap procedure (n=96). The results indicate that the rate of success was similar between the Surgisis group and the endorectal advancement flap group. Hyman and others conducted a study that involved 245 subjects who received one of seven procedures, including the Surgisis plug (n=43), endorectal advancement flap (n=4), Seton drain (n=34), fibrin glue (n=5), fistulotomy (n=156), and other unspecified procedures (n=3) (2009). In contrast to the findings of the Chung study, the authors reported that the Surgisis plug demonstrated the lowest success rate, with only 32% healed at 3 months vs. 87% for the fistulotomy group. In 2014, Blom reported on a case series study involving 126 subjects with anal fistulae treated in four different hospitals. After a median of 13 months, 30 (24%) of the fistulae had closed with no discomfort or secretion reported. The outcomes in the four hospitals varied from 13% to 33% with similar numbers of subjects in each hospital. A success rate of 12% was observed for subjects with anterior fistula compared with 32% for those with posterior tracks [hazard ratio (HR) for successful healing, 2.98] and 41% for those with a lateral internal opening (HR, 3.76). The authors concluded that their study demonstrated low success rates after the first plug-insertion procedure and that anterior fistulae were much less likely to heal compared with fistulae in other locations.

Jayne (2019) reported on the results of an RCT involving 304 subjects with anal fistula treated with either Surgisis or 'surgeon's choice" (e.g. fistulotomy, cutting seton, advancement flap or ligation of intersphincteric fistula tract This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

[LIFT] procedure). The authors reported clinical evidence of fistula healing in 66 subjects (54%) in the Surgisis group vs. 66 subjects (55%) in the control group at 12 months. Furthermore, MRI data showed fistula healing in 54 subjects (49%) in the Surgisis group vs. 63 subjects in the control group. Overall 12-month clinical healing rates were 55% in the Surgisis group vs. 64%, 75%, 53%, and 42% in the cutting seton, fistulotomy, advancement flap and LIFT procedure groups, respectively. The authors commented that overall there was no significant difference between the use of Surgisis and other procedures.

A meta-analysis was reported by Lin (2019) that included 11 studies comparing the use of Surgisis to rectal advancement flap (RAF) for anal fistula repair in 810 subjects. They reported that the pooled analysis indicated that there was no significant difference between the use of Surgisis and RAF in terms of healing rate, recurrence rate and incidence of fistula complications. However, the pooled results of the 4 RCTS and 1 series study with long-term follow-up revealed that the RAF group had a significantly higher healing rate (OR, 0.32; p=0.01) and lower recurrence rate (OR, 4.45; p=0.009) than the AFP group. These results appear to support the use of RAF over Surgisis for anal fistula repair.

Due to the conflicting evidence discussed above, further data is needed in the form of large, well-done, double-blind RCTs in order to properly understand the efficacy of Surgisis.

Surgisis Biodesign

Surgisis is a product composed of decellularized intestinal mucosa of porcine origin and is cleared under the FDA's 510k process. Unlike the anal fistula plug product discussed above, Surgisis Gold is provided in larger sheets. One study by Korwar retrospectively reported the treatment of PEH in 154 consecutive subjects who underwent standardized laparoscopic suture repair of the hiatus with Surgisis reinforcement. Follow-up barium swallow was performed in 122 subjects (79.22%). Symptomatic recurrence was noted in 25 subjects (28.73%), and recurrence on barium swallow was noted in 25 subjects (20.4%). Both symptomatic and barium swallow recurrence were reported in 10 subjects (12.98%). The reoperation rate was 3.25%. The authors concluded that use of Surgisis Biodesign for PEH repair is safe. They further commented that there was a high recurrence rate in long-term follow-up, but that the majority of recurrences are small, asymptomatic, and the reoperation rate is very low.

Surgisis Biodesign was also described in the repair of pelvic floor reconstruction following levator abdominoperitoneal excision of the rectum (Thomas, 2019). This retrospective case series study involved 100 subjects, for whom 1-, 2-, and 5-year mortality rates were 3, 8 and 12%, respectively. The authors reported that 33 This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

perineal wounds had not healed by 1 month, but no mesh was infected and no mesh needed to be removed. Only 1 subject developed a symptomatic perineal hernia requiring repair. On review of imaging, an additional 7 asymptomatic perineal hernias were detected. At 4 years the cumulative radiologically detected perineal hernia rate was 8%.

Ravo (2019) described the results of a trial of 104 subjects with inguinal hernia repair with a continuous suture of transversalis to transversalis fascia repair reinforced with Surgisis. Long term follow-up was scheduled at 1 week, 1 month, 1 year, 3 years, 7 years and 10 years, and was achieved in 100%, 100%, 99%, 93%, 89% and 85% of the subjects, respectively. The authors reported a recurrence rate of 1.9% (2 subjects, one at 1 week in a subject with bilateral IH and one at 7 years). The mean recovery time was 1.2 days (range 1-5 days). Mortality was 0(0%).

Additional evidence is needed from larger, well-designed trials to fully understand the safety and efficacy of Surgisis Biodesign.

Surgisis Gold

Surgisis is a product composed of decellularized intestinal mucosa of porcine origin and is cleared under the FDA's 510k process. Unlike the anal fistula plug product discussed above, Surgisis Gold is provided in larger sheets and proposed for the closure of fascial layers following abdominal surgery procedures. At this time, only one published study addresses this product. Sarr and others (2014) conducted a RCT involving 380 subjects with body mass index (BMI) ≥ 35 kg/m^2 scheduled to undergo open Roux-en-Y gastric bypass surgery. Participants were randomized to receive standard suture closure alone or Surgisis Gold as a reinforcing adjunct. The authors reported that complications were more common in the Surgisis Gold group with significantly more wound events and seroma formation compared with the suture closure alone group. At final follow-up of 2 years post-procedure, 32 of 185 (17%) subjects in the Surgisis Gold group and 38 of 195 (20%) in the control group developed an incisional hernia (p=0.6). Based on these findings, it would seem that the use of Surgisis Gold is not warranted and further investigation is needed regarding the safety and efficacy of this product.

Talymed

Talymed is a synthetic product composed of poly-N-acetyl glucosamine (pGIcNAc) isolated from microalgae and is cleared under the FDA's 510k process. At this time, only a single RCT is available addressing the use of Talymed (Kelechi, 2011). In this reviewer-blinded trial, 82 subjects with venous stasis leg ulcers were randomized

to receive either standard care (n=20) or to 1 of 3 groups that received standard treatment combined with different treatment frequencies with Talymed: (1) applied only once, (2) applied once every other week, or (3) applied once every third week. Seven subjects were lost to follow-up, 5 from the 1 application group and 2 from the every 3 week group. Additionally, another 4 subjects were withdrawn from the study, 3 from the 1 application group and 1 from the every 3 weeks group. This left 62 subjects in the experimental group and 20 in the control group. At 20 weeks, the authors report that 45.0% (n=9 of 20) of subjects receiving standard care alone had complete healing, while 45.0% (n=9 of 20), 86.4% (n=19 of 22), and 65.0% (n=13 of 20) of subjects receiving Talymed only once, every other week, and every 3 weeks, respectively, had complete healing. This single study is insufficient to allow proper evaluation of the safety and efficacy of Talymed.

Tutomesh

Tutomesh is a product composed of decellularized bovine pericardium and is cleared under the FDA's 510k process. The literature addressing this product is sparse at this time. A retrospective review with 41 subjects who underwent 52 breast reconstructions using ADMs was reported by Paprottka (2017). Subjects received treatment with either EpiFlex (not available in the US, n=15), Strattice (n=21), or Tutomesh (n=16). Follow-up was 36 months (range 12-54). Overall complication rate was 17%, and 7% for the EpiFlex group, 14% for the Strattice group, and 31% for the Tutomesh group. Capsular contracture occurred in 6%, more frequently in this study compared to the current literature. The authors recommended the use of human derived grafting materials (EpiFlex) over those from porcine of bovine sources.

Eichler (2017) published a retrospective, nonrandomized comparative trial involving 54 subjects undergoing breast reconstruction procedures using either SurgiMend (n=18) or Tutomesh (n=27) (Eichler, 2017). No difference in complications rates was noted, consistent with other previous reports.

Additional investigation into the safety and efficacy of this product is needed.

Vascu-Guard

Vascu-Guard is a decellularized product derived from bovine pericardium cleared under the FDA's 510k process. Please see the section for Gore® Acuseal Cardiovascular Patch above.

Veritas

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Veritas is a decellularized product derived from bovine pericardium cleared under the FDA's 510k process. The available evidence addressing Veritas is currently limited to a single RCT of 94 subjects assigned to treatment with either anterior colporrhaphy alone vs. colporrhaphy reinforced with Veritas bovine pericardium graft (Guerette, 2009). This study had significant loss to follow-up, with only 72 of 94 (76.6%) subjects at the 1 year time point and 59 of 92 (64.1%) at the completion of the study at 2 years. The authors report no significant differences between groups.

Xelma

Xelma consists of amelogenin proteins purified from porcine teeth, propylene glycol alginate (PGA), and water. It has not yet received marketing approval or clearance by the FDA. Amelogenin is a cell adhesion protein, and when suspended in a gelatinous matrix has been proposed to promote cellular growth. The use of Xelma was reported in a single-blind randomized trial involving 123 subjects with VLUs (Vowden, 2006). Subjects were assigned to receive treatment with either Xelma plus compression therapy (n=62) vs. a mixture of PGA and water plus compression therapy (n=61) and were followed for 12 weeks. The authors of this study state that Xelma outperformed the control group in multiple factors, including percentage of wound size reduction. However, no statistical analysis is presented to support these claims. No data on complication rates was provided. Further investigation into the clinical safety and efficacy is warranted.

Background/Overview

Regulatory Processes for Grafting Materials

Soft tissue grafting materials find their way to U.S. market through several regulatory pathways. Oversight for all these pathways is provided by the U.S Food and Drug Administration (FDA).

The first and most rigorous regulatory path is the Premarket Approval (PMA) Process, which is detailed in the Code of Federal Regulations Title 21 Part 860. Devices required to undergo this process are those deemed to present the most risk of harm to the public. The PMA process involves several steps of pre-clinical and clinical trials (Phase 0 through III). Each step is reviewed by the FDA to evaluate safety and efficacy data. If the FDA finds the data presented acceptable, a larger and more robust study is authorized until Phase III trials have been completed. Devices which pass Phase III are deemed "Approved" by the FDA and may be marketed in the U.S.

This path was used in only a small minority of products addressed in this document. More information regarding the PMA process can be found at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm.

The "510K" process, also referred to as the Premarket Notification (PMN) process, is named after Section 510(k) of the Food, Drug and Cosmetic Act. This section of the Act requires manufacturers of devices that qualify to notify the FDA of their intent to market a medical device at least 90 days in advance. This law applies to any device that: (1) is not required to undergo review under another pathway, (2) was not already in commercial distribution prior to May 28, 1976, and (3) is to be introduced into commercial distribution for the first time or reintroduced in a significantly changed or modified form that alters its safety or effectiveness. The regulations stipulate that devices applying for 510K clearance must demonstrate that they are substantially equivalent to a device with prior PMA approval or marketed prior to May 28, 1976. No significant new data addressing safety or efficacy is required during this process. Devices with this type of review may or may not have undergone rigorous clinical testing to establish the presence or absence of these attributes. Devices passing through this pathway are referred to as "cleared." More information regarding the 510K process can be found at: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/default.htm.

A Humanitarian Device Exemption (HDE) is a regulatory path similar to a PMA, but is exempt from the effectiveness requirements of sections 514 and 515 of the Code of Federal Regulations Title 21 Part 860, which details the PMA process. A device approved under an HDE is referred to as Humanitarian Use Device (HUD). An HUD is defined as a "medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year." The HDE process is intended to facilitate the development of devices that could benefit individuals with rare conditions for whom medical devices are unlikely to be developed through the PMA process. Devices covered under this regulation are exempt from many of the PMA requirements, but have certain restrictions placed on their use outside the investigational setting. More information regarding the HDE process can be found at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/humanitariandeviceexemption/default.htm.

There is a specific pathway available for biological tissue derived from human sources deemed as "minimally manipulated." The FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) is

addressed in the Code of Federal Regulations Title 21, volume 8, Part 1271 "Human Cells, Tissues, And Cellular And Tissue-Based Products." These regulations detail the use of human autologous and allographic tissues for transplantation. They specify that "minimally manipulated" tissues undergo proper safeguards to prevent infection or other safety hazards. It should be made clear that products that reach the market through the HCT/P process do NOT require any testing to prove clinical safety or efficacy. Thus their performance when used in the treatment of human subjects may or may not have been tested in clinical trials. Human-derived tissues that are deemed to have been more than minimally manipulated are required to undergo one of the other regulatory pathways described above. HCT/Ps are regulated under 21 CFR 1271.3(d)(1) and Section 361 of the PHS Act, which can be found at: http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/RegulationofTissues/ucm150485.htm.

In the vast majority of cases, soft tissue grafting products are considered devices by the FDA. However, in some rare cases, based upon the composition, preparation, and method of delivery, some products may be considered drugs and reviewed under the FDA's drug regulatory process. Only one product addressed in this document has been so treated, and is designated an Orphan Drug. This designation for drugs is similar to the HDE designation for devices. The Code of Federal Regulations Title 21, Part 316 details the "Orphan Drug" process and defines an Orphan Drug as a drug intended for use in a rare disease or condition as outlined in section 526 of the Act. As with HDEs, the Orphan Drug designation is intended to facilitate the development of drugs that could benefit individuals with rare conditions for whom drugs are unlikely to be developed through other regulatory processes. More information regarding the Orphan Drug designation can be found at: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm.

Skin Wound Care

The skin is the largest organ of the body. It is composed of two layers, the epidermis and the dermis, and provides functions critical to survival. The skin acts as a protective barrier to fluid losses and dehydration and it protects against infection and injury by providing a barrier to repel bacteria and other organisms. The skin provides sensory contact with our environment that tells us whether we are feeling light touch, pressure, pain, heat, or cold. Damage to the skin that is extensive or prolonged may interfere with these functions or with those of other body systems and may become life-threatening in some circumstances.

The treatment of burns and other wounds that have failed to heal despite conservative measures, referred to as chronic wounds, creates a significant burden on the population in terms of pain, disability, and decreased quality of

life. Chronic wounds may be due to the effects of diabetes, venous insufficiency to the extremities, pressure due to prolonged periods in the same body position, and other types of skin injuries. They can be difficult to treat and may require treatment with various coverings, such as skin grafts or other materials to prevent infection, maintain an environment conducive to healing, or provide a medium for re-growth of new skin. Such coverings come in a wide array of types including synthetic materials, tissues from the individuals themselves (autologous), human donors (allogeneic), or from animals such as cows and pigs (xenographic), or any combination of these materials (composites).

Surgical Reinforcement Procedures

In a wide variety of surgical procedures, there may be a need for additional reinforcement of soft tissues to strengthen the structures being repaired, such as in abdominal wall repair or orthopedic reconstruction procedures. Traditionally this task is undertaken with the use of allogeneic cadaver-derived grafts or synthetic materials such as polypropylene and Gore-Tex®. However, in some cases such materials may not be appropriate, and other materials have been sought.

In other circumstances, the use of grafting materials has been suggested as substitute for surgery.

Product types:

Synthetic Products

Synthetic treatments include various forms of skin-like coverings, barriers, and devices to augment cartilage and other connective tissues. This category includes wound dressings, silicone/nylon membranes and material to augment or replace cartilage, tendons and ligaments.

Completely synthetic wound dressings (e.g., Biobrane) are composed of man-made materials to form a complex multilayer covering for wounds. This type of product may consist of a wide array of materials including silicone, nylon, and others, as well as collagen or other biologic materials.

Allogeneic Products

There are currently several different types of allogeneic (human-derived) wound care products available. One type involves the use of donated human cadaver skin which is then treated with various methods to remove the cellular material and deactivate or kill pathogens (e.g., AlloDerm RTM, GraftJacket, and Neoform Dermis). This process leaves only the collagen protein scaffold, which has been proposed as an acceptable medium for which new skin cells from the individual can populate and grow into when placed over a wound site.

Another type of allogeneic product includes composite products that may contain human skin cells, keratinocytes and/or fibroblasts (depending upon the product), which are imbedded into a decellularized collagen protein scaffold derived from a xenographic source (e.g., Apligraf, OrCel). Some of these products may also consist of layers of synthetic materials like silicone, nylon, or polyglactin (e.g., Dermagraft).

Xenographic and Xenographic-Related or Derived Products

Many wound care and reconstructive products are made from materials derived from various animal sources including cow, horse and pig tissues. Most of these products are created by harvesting living tissues (e.g., skin, intestines, tendons, etc.) from a donor animal, which are then processed to remove the cellular content and leave only the collagen protein scaffold. As with such allogeneic products, this scaffold is intended to act as a welcoming environment into which new autologous cells (e.g., skin, tendon, and cartilage) may grow. Most xenographic products are composed of the decellularized collagen scaffold alone (e.g., Collamend, Cuffpatch, Mediskin, Oasis, OrthoADAPT, Pelvicol, Pelvisoft, PriMatrix, Surgisis, Unite).

Xenographic materials have been proposed for many applications including reconstruction procedures of the breast, pelvic floor, abdominal wall, tendons and others. These products are sewn onto the soft tissues where they are needed to provide support and strengthen the underlying structures. This occurs by the xenograft acting as a bed for new growth of autologous tissue.

Another type of product is a substance made by or derived from xenographic sources. One such product is honey, which has been proposed as a topical treatment for a wide variety of skin conditions.

Composite Autologous / Allogeneic / Xenographic Products

The development of advanced in vitro culturing techniques has allowed the development of new products which combine human dermal cellular materials with those derived from animals (e.g., Epicel). These products involve

the harvesting of human epidermal cells (either from the individual being treated or from donor tissue) which are then cultured with animal cells to produce sheets of biosynthetic skin which have been proposed for use in treating human skin conditions.

Xenographic products may be combined with synthetic materials to create a composite product (e.g., Avaulta Plus, Integra Matrix, and Integra Bilayer Matrix).

Definitions

Bullous keratopathy: A condition where small fluid-filled vesicles, or bullae, form within the cornea.

Conjunctiva: A clear, thin membrane that covers part of the front of the eye and lines the inside of the eyelids.

Corneal melt: Keratolysis, or sterile melting of the cornea, is a condition characterized by a progressing thinning of the cornea, leading to perforation.

Epidermolysis bullosa (EB): A disease characterized by the presence of extremely fragile skin and recurrent blister formation, resulting from minor mechanical friction or trauma.

Equine-derived decellularized collagen products (e.g., OrthADAPT and Unite): This is a type of product derived from purified tissues which are derived from horses. It has been proposed that this type of technology may be used for the repair and reinforcement of soft tissues such as tendons and ligaments, as well as the treatment of skin wounds.

Frey's Syndrome: A condition occurring in some individuals after removal of the parotid salivary gland, in which nerve damage results in flushing and sweating on one side of the face when certain foods are consumed.

Limbal stem cell deficiency: A condition characterized by decreasing function of the stem cells within the epithelial layer of the cornea.

Neurotrophic keratitis: A degenerative disease of the eye due to a loss of corneal sensation leading to progressive damage to the top layer of the cornea.

Penetrating keratoplasty: A surgical procedure that is conducted during corneal transplantation.

Pterygium: A growth involving the conjunctiva of the eye that appears as a growth or bump on the side of the eye near the nose.

Stevens-Johnson syndrome: Also known as toxic epidermal necrolysis, is a rare, serious disorder of the skin and mucous membranes that is characterized by painful rash in it mild form and severe blisters and skin peeling in its more advanced form.

Wound infection: A wound with at least some clinical signs and symptoms of infections such as increased exudates, odor, redness, swelling, heat, pain, tenderness to touch, and purulent discharge; quantitative culture is not required.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Application of amniotic membrane-derived grafts or wound coverings for ophthalmologic conditions:

When services are Medically Necessary:

CPT

65778	Placement of amniotic membrane on the ocular surface; without sutures
65779	Placement of amniotic membrane on the ocular surface; single layer, sutured
65780	Ocular surface reconstruction; amniotic membrane transplantation, multiple layers

HCPCS

V2790	Amniotic membrane for surgical reconstruction, per procedure [vision services]

ICD-10 Diagnosis

C69.00-C69.02	Malignant neoplasm of conjunctiva
C69.10-C69.12	Malignant neoplasm of cornea
H11.001-H11.069	Pterygium of eye
H16.001-H16.079	Corneal ulcer
H16.231-H16.239	Neurotrophic keratoconjunctivitis
H18.10-H18.13	Bullous keratopathy
H18.40-H18.59	Corneal degeneration, hereditary corneal dystrophies
H18.831-H18.839	Recurrent erosion of cornea
H59.091-H59.099	Other disorders of the eye following cataract surgery
L51.1	Stevens-Johnson syndrome
T26.10XA-T26.12XS	Burn of cornea and conjunctival sac
T26.60XA-T26.62XS	Corrosion of cornea and conjunctival sac

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above for all other diagnoses not listed, or when the code describes application of a product indicated in the Position Statement section as investigational and not medically necessary.

Application of skin substitutes and soft tissue grafts:

When services may be Medically Necessary when criteria are met:

CPT	
15150	Tissue cultured skin autograft, trunk, arms, legs; first 25 sq cm or less
15151	Tissue cultured skin autograft, trunk, arms, legs; additional 1 sq cm to 75 sq cm
15152	Tissue cultured skin autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof
15155	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 25 sq cm or less
15156	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; additional 1 sq cm to 75 sq cm
15157	Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof

15271	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15272	Application of skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof
15273	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15274	Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof
15275	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
15276	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof
15277	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
15278	Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof
15777	Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (ie, breast, trunk)
17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue [when specified as implantation of biologic implants for soft tissue reinforcement in tissues other than breast and trunk]

HCPCS

C5271	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area

C5272	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof
C5273	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5274	Application of low cost skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof
C5275	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
C5276	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof
C5277	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
C5278	Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof

ICD-10 Diagnosis

All diagnoses

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above when criteria are not met, or when the code describes application of a product indicated in the Position Statement section as investigational and not medically necessary.

When Services are also Investigational and Not Medically Necessary:

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

CPT

31574	Laryngoscopy, flexible; with injection(s) for augmentation (eg, percutaneous, transoral), unilateral [when specified as using a skin/tissue substitute such as Cymetra]
46707	Repair of anorectal fistula with plug (eg, porcine small intestine submucosa [SIS])

ICD-10 Diagnosis

All diagnoses

Products

When services may be Medically Necessary when criteria are met [for AmnioBand, Apligraf, EpiCord, EpiFix (sheet or membrane form), Grafix PRIME, GraftJacket, Oasis, OrCel, PriMatrix and Dermagraft]:

HCPCS

C9399	Unclassified drugs or biologicals [when specified as OrCel for epidermolysis bullosa only]
Q4100	Skin substitute, not otherwise classified [when specified as OrCel for epidermolysis bullosa only]
Q4101	Apligraf, per square centimeter
Q4102	Oasis Wound Matrix, per square centimeter
Q4106	Dermagraft, per square centimeter [for diabetic foot ulcers and epidermolysis bullosa only]
Q4107	GraftJacket, per square centimeter
Q4110	PriMatrix, per square centimeter
Q4124	Oasis Ultra Tri-Layer Wound Matrix, per square centimeter
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per square centimeter [when specified as Grafix PRIME, for diabetic foot ulcers only]
Q4151	AmnioBand or Guardian, per sq cm [for diabetic foot ulcers only]]
Q4186	EpiFix, per square centimeter
Q4187	EpiCord, per square centimeter [for diabetic foot ulcers only]

ICD-10 Diagnosis

E08.00-E13.9	Diabetes mellitus
I83.001-I83.029	Varicose veins of lower extremities with ulcer

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

I83.201-I83.229	Varicose veins of lower extremities with both ulcer and inflammation
I87.011-I87.019	Postthrombotic syndrome with ulcer
I87.031-I87.039	Postthrombotic syndrome with ulcer and inflammation
I87.2	Venous insufficiency (chronic) (peripheral)
I87.311-I87.319	Chronic venous hypertension (idiopathic) with ulcer
I87.331-I87.339	Chronic venous hypertension (idiopathic) with ulcer and inflammation
L12.30-L12.35	Acquired epidermolysis bullosa [Dermagraft, OrCel]
L97.101-L97.929	Non-pressure chronic ulcer of lower limb, not elsewhere classified
L98.411-L98.499	Non-pressure chronic ulcer of skin, not elsewhere classified
Q81.0-Q81.9	Epidermolysis bullosa [Dermagraft, OrCel]

When services may be Medically Necessary when criteria are met [for AlloDerm RTM, AlloDerm RTU, DermACELL, DermaMatrix, FlexHD, Strattice]:

HCPCS	
C9399	Unclassified drugs or biologicals [when specified as DermaMatrix for breast reconstruction only]
Q4100	Skin substitute, not otherwise specified [when specified as DermaMatrix for breast reconstruction only]
Q4116	AlloDerm, per square centimeter [AlloDerm RTM, AlloDerm RTU for breast reconstruction and abdominal wall wounds]
Q4122	Dermacell, Dermacell AWM or Dermacell AWM porous, per square centimeter [for breast reconstruction or diabetic foot ulcers only]
Q4128	FlexHD, Allopatch HD, or Matrix HD, per square centimeter [when specified as FlexHD for breast reconstruction]
Q4130	Strattice, per square centimeter [for breast reconstruction and abdominal wall wounds]

ICD-10 Diagnosis	
	All diagnoses

When services may be Medically Necessary when criteria are met [for AlloSkin, Biobrane, EZ-Derm, Integra Bilayer Matrix Wound Dressing, TheraSkin]:

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

HCPCS	
C9363	Skin substitute, Integra Meshed Bilayer Wound Matrix, per square centimeter
C9399	Unclassified drugs or biologicals [when specified as Biobrane]
Q4100	Skin substitute, not otherwise specified [when specified as Biobrane]
Q4104	Integra Bilayer Matrix Wound Dressing (BMWD), per square centimeter
Q4115	AlloSkin, per square centimeter
Q4121	TheraSkin, per square centimeter
Q4136	EZ-derm, per square centimeter

ICD-10 Diagnosis	
T20.20XA-T20.39XS	Burn of second or third degree of head, face, and neck
T20.60XA-T20.79XS	Corrosion of second or third degree of head, face, and neck
T21.20XA-T21.39XS	Burn of second or third degree of trunk
T21.60XA-T21.79XS	Corrosion of second or third degree of trunk
T22.20XA-T22.399S	Burn of second or third degree of shoulder and upper limb, except wrist and hand]
T22.60XA-T22.799S	Corrosion of second or third degree of shoulder and upper limb, except wrist and hand
T23.201A-T23.399S	Burn of second or third degree of wrist and hand
T23.601A-T23.799S	Corrosion of second or third degree of wrist and hand
T24.201A-T24.399S	Burn of second or third degree of lower limb, except ankle and foot
T24.601A-T24.799S	Corrosion of second or third degree of lower limb, except ankle and foot
T25.211A-T25.399S	Burn of second or third degree of ankle and foot
T25.611A-T25.799S	Corrosion of second or third degree of ankle and foot
T31.0-T31.99	Burns classified according to extent of body surface involved
T32.0-T32.99	Corrosions classified according to extent of body surface involved

When services are Investigational and Not Medically Necessary:
For the product codes listed above when criteria are not met or for all other diagnoses not listed, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

When Services are also Investigational and Not Medically Necessary:

HCPCS	
C1878	Material for vocal cord medialization, synthetic (implantable) [eg, RenuVoice, RenuGel]

C9352	Microporous collagen implantable tube (NeuraGen Nerve Guide), per centimeter length
C9353	Microporous collagen implantable slit tube (NeuraWrap Nerve Protector), per centimeter length
C9354	Acellular pericardial tissue matrix of non-human origin (Veritas), per square centimeter
C9355	Collagen nerve cuff (NeuroMatrix), per 0.5 centimeter length
C9356	Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per square centimeter
C9358	Dermal substitute, native, non-denatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters
C9360	Dermal substitute, native, non-denatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters
C9361	Collagen matrix nerve wrap (NeuroMend Collagen Nerve Wrap), per 0.5 centimeter length
C9364	Porcine implant, Permacol, per square centimeter
C9399	Unclassified drugs or biologicals [when describing a product with no specific code indicated as investigational and not medically necessary]
G0428	Collagen meniscus implant procedure for filling meniscal defects (e.g., CMI, collagen scaffold, Menaflex)
L8607	Injectable bulking agent for vocal cord medialization, 0.1 ml, includes shipping and necessary supplies
Q4100	Skin substitute, not otherwise specified [when describing a product with no specific code indicated as investigational and not medically necessary]
Q4103	Oasis Burn Matrix, per square centimeter
Q4105	Integra Dermal Regeneration Template (DRT) or Integra Omnigraft dermal regeneration matrix, per square centimeter
Q4108	Integra Matrix, per square centimeter
Q4111	Gammagraft, per square centimeter
Q4112	Cymetra, injectable, 1 cc
Q4113	Graftjacket Xpress, injectable, 1 cc
Q4114	Integra Flowable Wound Matrix, injectable, 1 cc
Q4117	Hyalomatrix, per square centimeter
Q4118	Matristem micromatrix, 1 mg
Q4123	AlloSkin RT, per square centimeter

Q4125	ArthroFlex, per square centimeter
Q4126	Memoderm, dermaspan, tranzgraft or integuply, per square centimeter
Q4127	Talymed, per square centimeter
Q4128	FlexHD, AlloPatch HD, or Matrix HD, per square centimeter [when specified as AlloPatch HD or Matrix HD]
Q4132	Grafix CORE and GrafixPL CORE, per square centimeter
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix and StravixPL, per square centimeter [when specified as GrafixPL PRIME, Stravix, StravixPL]
Q4134	hMatrix, per square centimeter
Q4135	Mediskin, per square centimeter
Q4137	AmnioExCel, AmnioExCel plus or BioDExCel, per square centimeter
Q4138	BioDfence Dryflex, per square centimeter
Q4139	AmnioMatrix or BioDMatrix, injectable, 1 cc
Q4140	BioDfence, per square centimeter
Q4141	Alloskin AC, per square centimeter
Q4142	XCM Biologic Tissue Matrix, per square centimeter
Q4143	Repriza, per square centimeter
Q4145	Epifix, injectable, 1 mg
Q4146	TenSIX, per square centimeter
Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per square centimeter
Q4148	NEOX Cord 1k, NEOX Cord RT, or Clarix Cord 1k, per square centimeter
Q4149	Excellagen, 0.1 cc
Q4150	Allowrap DS or Dry, per square centimeter
Q4152	DermaPure, per square centimeter
Q4153	Dermavest and Plurivest, per square centimeter
Q4154	Biovance, per square centimeter
Q4155	NeoxFlo or ClarixFlo, 1 mg
Q4156	NEOX 100 or Clarix 100, per square centimeter
Q4157	Revitalon, per square centimeter
Q4158	Kerecis Omega3, per square centimeter
Q4159	Affinity, per square centimeter
Q4160	NuShield, per square centimeter
Q4161	Bio-connekt wound matrix, per square centimeter

Q4162	WoundEx Flow, BioSkin Flow, 0.5 cc
Q4163	WoundEx, BioSkin, per square centimeter
Q4164	Helicoll, per square centimeter
Q4165	Keramatrix or Kerasorb, per square centimeter
Q4166	Cytal, per square centimeter [formerly Matristem wound/burn matrix]
Q4167	TruSkin, per square centimeter
Q4168	AmnioBand, 1 mg
Q4169	Artacent Wound, per square centimeter
Q4170	CYGNUS, per square centimeter
Q4171	Interfyl, 1 mg
Q4173	PalinGen or PalinGen Xplus, per square centimeter
Q4174	PalinGen or ProMatrX, 0.36 mg per 0.25 cc
Q4175	Miroderm, per square centimeter
Q4176	NeoPatch, per square centimeter
Q4177	FlowerAmnioflo, 0.1 cc
Q4178	FlowerAmniopatch, per square centimeter
Q4179	FlowerDerm, per square centimeter
Q4180	Revita, per square centimeter
Q4181	Amnio Wound, per square centimeter
Q4183	Surgigraft, per square centimeter
Q4184	Cellesta or Cellesta Duo, per square centimeter
Q4185	Cellesta flowable amnion (25 mg per cc); per 0.5 cc
Q4188	Amnioarmor, per square centimeter
Q4189	Artacent AC, 1 mg
Q4190	Artacent AC, per square centimeter
Q4191	Restorigin, per square centimeter
Q4192	Restorigin, 1 cc
Q4193	Coll-e-derm, per square centimeter
Q4194	Novachor, per square centimeter
Q4195	Puraply, per square centimeter
Q4196	PuraPly AM, per square centimeter
Q4197	PuraPly XT, per square centimeter
Q4198	Genesis amniotic membrane, per square centimeter

Q4201	Matrion, per square centimeter
Q4202	Keroxx (2.5g/cc), 1cc
Q4203	Derma-gide, per square centimeter
Q4204	Xwrap, per square centimeter
Q4205	Membrane graft or Membrane wrap, per square centimeter
Q4206	Fluid flow or Fluid GF, 1 cc
Q4208	Novafix, per square cenitmeter
Q4209	Surgraft, per square centimeter
Q4210	Axolotl graft or Axolotl dualgraft, per square centimeter
Q4211	Amnion bio or AxoBioMembrane, per square centimeter
Q4212	AlloGen, per cc
Q4213	Ascent, 0.5 mg
Q4214	Cellesta cord, per square centimeter
Q4215	Axolotl Ambient or Axolotl Cryo, 0.1 mg
Q4216	Artacent cord, per square centimeter
Q4217	Woundfix, BioWound, Woundfix Plus, BioWound Plus, Woundfix Xplus or BioWound Xplus, per square centimeter
Q4218	Surgicord, per square centimeter
Q4219	SurgiGRAFT-Dual, per square centimeter
Q4220	BellaCell HD or Surederm, per square centimeter
Q4221	Amniowrap2, per square centimeter
Q4222	Progenamatrix, per square centimeter

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

Meta-Analyses and Systematic Reviews

1. Ho G, Nguyen TJ, Shahabi A, et al. A systematic review and meta-analysis of complications associated with acellular dermal matrix-assisted breast reconstruction. Ann Plast Surg. 2012; 68(4):346-356.
2. Kim JY, Davila AA, Persing S, et al. A meta-analysis of human acellular dermis and submuscular tissue expander breast reconstruction. Plast Reconstr Surg. 2012; 129(1):28-41.
3. Lee KT, Mun GH. A meta-analysis of studies comparing outcomes of diverse acellular dermal matrices for implant-based breast reconstruction. Ann Plast Surg. 2017; 79(1):115-123.
4. Sorkin M, Qi J, Kim HM, et al. Acellular dermal matrix in immediate expander/implant breast reconstruction: a multicenter assessment of risks and benefits. Plast Reconstr Surg. 2017; 140(6):1091-1100.
5. Zhong T, Janis JE, Ahmad J, Hofer SO. Outcomes after abdominal wall reconstruction using acellular dermal matrix: a systematic review. J Plast Reconstr Aesthet Surg. 2011; 64(12):1562-1571.

Allogeneic amniotic membrane-derived grafts or wound coverings used for ophthalmologic indications.

Peer Reviewed Publications:

1. Abdulhalim BE, Wagih MM, Gad AA, et al. Amniotic membrane graft to conjunctival flap in treatment of non-viral resistant infectious keratitis: a randomised clinical study. Br J Ophthalmol. 2015; 99(1):59-63.
2. Arora R, Mehta D, Jain V. Amniotic membrane transplantation in acute chemical burns. Eye. 2005; 19:273-278.
3. Asoklis RS, Damijonaityte A, Butkiene L, et al. Ocular surface reconstruction using amniotic membrane following excision of conjunctival and limbal tumors. Eur J Ophthalmol. 2011; 21(5):552-558.
4. Chansanti O, Horatanaruang O. The results of amniotic membrane transplantation for symptomatic bullous keratopathy. J Med Assoc Thai. 2005; 9:S57-62.
5. Chen HC, Tan HY, Hsiao CH, et al. Amniotic membrane transplantation for persistent corneal ulcers and perforations in acute fungal keratitis. Cornea. 2006; 25:564-572.
6. Chen HJ, Pires RT, Tseng SC. Amniotic membrane transplantation for severe neurotrophic corneal ulcers. Br J Ophthalmol. 2000; 84(8):826-33.
7. Cheng AM, Zhao D, Chen R, et al. Accelerated Restoration of Ocular Surface Health in Dry Eye Disease by Self-Retained Cryopreserved Amniotic Membrane. Ocul Surf. 2016; 14:56-63.
8. Dalla Pozza G, Ghirlando A, Busato F, Midena E. Reconstruction of conjunctiva with amniotic membrane after excision of large conjunctival melanoma: a long-term study. Eur J Ophthalmol. 2005; 15(4):446-450.
9. de Farias CC, Allemann N, Gomes JÁ. Randomized trial comparing amniotic membrane transplantation with lamellar corneal graft for the treatment of corneal thinning. Cornea. 2016; 35(4):438-444.

10. Dekaris I, Mravicić I, Barisić A, et al. Amniotic membrane transplantation in the treatment of persistent epithelial defect on the corneal graft. Coll Antropol. 2010; 34 Suppl 2:15.
11. Espana EM, Grueterich M, Sandoval H, et al. Amniotic membrane transplantation for bullous keratopathy in eyes with poor visual potential. J Cataract Refract Surg. 2003; 29:279-784.
12. Georgiadis NS, Ziakas NG, Boboridis KG, et al. Cryopreserved amniotic membrane transplantation for the management of symptomatic bullous keratopathy. Clin Exp Ophthalmol. 2008; 36(2):130-135.
13. Gregory DM. Treatment of acute Stevens-Johnson syndrome and toxic epidermal necrolysis using amniotic membrane: a review of 10 consecutive cases. Ophthalmology. 2011; 118:908-914.
14. Gris O, del Campo Z, Wolley-Dod C, et al. Amniotic membrane implantation as a therapeutic contact lens for the treatment of epithelial disorders. Cornea. 2002; 21:22-27.
15. Gündüz K, Uçakhan OO, Kanpolat A, Günalp I. Nonpreserved human amniotic membrane transplantation for conjunctival reconstruction after excision of extensive ocular surface neoplasia. Eye (Lond). 2006; 20(3):351-357.
16. Hanada K, Nishikawa N, Miyokawa N, Yoshida A. Long-term outcome of amniotic membrane transplantation combined with mitomycin C for conjunctival reconstruction after ocular surface squamous neoplasia excision. Int Ophthalmol. 2017; 37(1):71-78.
17. Hanada K, Shimazaki J, Shimmura S, Tsubota K. Multilayered amniotic membrane transplantation for severe ulceration of the cornea and sclera. Am J Ophthalmol. 2001; 131:324-331
18. Hick S, Demers PE, Brunette I, et al. Amniotic membrane transplantation and fibrin glue in the management of corneal ulcers and perforations: a review of 33 cases. Cornea. 2005; 24:369-377
19. Honavar SG, Bansal AK, Rao GN. Amniotic membrane transplantation for ocular surface reconstruction in Stevens-Johnson syndrome. Ophthalmology 2000; 107:975-979.
20. Iveković B, Tedeschi-Reiner E, Petric I, et al. Amniotic membrane transplantation for ocular surface reconstruction in neurotrophic corneal ulcera. Coll Antropol. 2002; 26(1):47-54.
21. John T, Foulks GN, John K. Amniotic membrane in the surgical management of acute toxic epidermal necrolysis. Ophthalmology 2002; 109(2):351-60.
22. Kheirkhah A, Casas V, Raju VK, Tseng SC. Sutureless amniotic membrane transplantation for partial limbal stem cell deficiency. Am J Ophthalmol. 2008; 145:787-794.
23. Kheirkhah A, Johnson DA, Paranjpe DR, et al. Temporary sutureless amniotic membrane patch for acute alkaline burns. Arch Ophthalmol. 2008; 126:1059-1066.
24. Khokhar S, Natung T, Sony P, et al. Amniotic membrane transplantation in refractory neurotrophic corneal ulcers: a randomized, controlled clinical trial. Cornea. 2005; 24(6):654-60.

25. Kruse FE, Rohrschneider K, Völcker HE. Multilayer amniotic membrane transplantation for reconstruction of deep corneal ulcers. Ophthalmology. 1999; 106:1504-1510.
26. Küçükerdönmez C, Akova YA, Altinörs DD. Comparison of conjunctival autograft with amniotic membrane transplantation for pterygium surgery: surgical and cosmetic outcome. Cornea. 2007; 26:407-413.
27. Lee SH, Tseng SC. Amniotic membrane transplantation for persistent epithelial defects with ulceration. Am J Ophthalmol. 1997; 123:303-312.
28. Letko E, Stechschulte SU, Kenyon KR, et al. Amniotic membrane inlay and overlay grafting for corneal epithelial defects and stromal ulcers. Arch Ophthalmol. 2001; 119:659-663.
29. Luanratanakorn P, Ratanapakorn T, Suwan-Apichon O, Chuck RS. Randomised controlled study of conjunctival autograft versus amniotic membrane graft in pterygium excision. Br J Ophthalmol. 2006; 90:1476-1480
30. McDonald MB, Sheha H, Tighe S, Treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study. Clin Ophthalmol. 2018; 12:677-681.
31. Meller D, Pires RT, Mack RJ, et al. Amniotic membrane transplantation for acute chemical or thermal burns. Ophthalmology. 2000; 107:980-989.
32. Paridaens D, Beekhuis H, van Den Bosch W, Remeyer L, Melles G. Amniotic membrane transplantation in the management of conjunctival malignant melanoma and primary acquired melanosis with atypia. Br J Ophthalmol. 2001; 85(6):658-661.
33. Paris F dos S, Gonçalves ED, Campos MS, et al. Amniotic membrane transplantation versus anterior stromal puncture in bullous keratopathy: a comparative study. Br J Ophthalmol. 2013; 97(8):980-984.
34. Pires RT, Tseng SC, Prabhasawat P, et al. Amniotic membrane transplantation for symptomatic bullous keratopathy. Arch Ophthalmol. 1999; 117: 1291-1297.
35. Prabhasawat P, Barton K, Tseng SCG. Comparison of conjunctival autografts, amniotic membrane grafts, and primary closure for pterygium excision. Ophthalmology 1997; 104:974-985.
36. Prabhasawat P, Tesavibul N, Komolsuradej W. Single and multilayer amniotic membrane transplantation for persistent corneal epithelial defect with and without stromal thinning and perforation. Br J Ophthalmol. 2001; 85:1455-1466.
37. Prabhasawat P, Tesavibul N, Prakairungthong N, Booranapong W. Efficacy of amniotic membrane patching for acute chemical and thermal ocular burns. J Med Assoc Thai. 2007; 90:319-326.
38. Rodríguez-Ares MT, Touriño R, López-Valladares MJ, Gude F. Multilayer amniotic membrane transplantation in the treatment of corneal perforations. Cornea. 2004; 23:577-583.

39. Sangwan VS, Matalia HP, Vemuganti GK, Rao GN. Amniotic membrane transplantation for reconstruction of corneal epithelial surface in cases of partial limbal stem cell deficiency. Indian J Ophthalmol. 2004; 52(4):281-285.
40. Seitz B, Das S, Sauer R, et al. Amniotic membrane transplantation for persistent corneal epithelial defects in eyes after penetrating keratoplasty. Eye (London). 2009; 23:840.
41. Shammas MC, Lai EC, Sarkar JS, et al. Management of acute Stevens-Johnson syndrome and toxic epidermal necrolysis utilizing amniotic membrane and topical corticosteroids. Am J Ophthalmol. 2010; 149:203.
42. Sheha H, Liang L, Li J, Tseng SC. Sutureless amniotic membrane transplantation for severe bacterial keratitis. Cornea. 2009; 28:1118-1123.
43. Siu GD, Young AL, Cheng LL. Long-term symptomatic relief of bullous keratopathy with amniotic membrane transplant. Int Ophthalmol. 2015; 35:777-783.
44. Solomon A, Meller D, Prabhasawat P, et al. Amniotic membrane grafts for nontraumatic corneal perforations, descemetoceles, and deep ulcers. Ophthalmology. 2002; 109:694-703.
45. Srinivas S, Mavrikakis E, Jenkins C. Eur J Ophthalmol. 2007; 17:7-10.
46. Stefaniu GI, Chiotoroiu SM2, Secureanu FA, et al. Use of amniotic membrane in bullous keratopathy palliative care. J Med Life. 2014; 7:88-9.
47. Suri K, Kosker M, Raber IM, et al. Sutureless amniotic membrane ProKera for ocular surface disorders: short-term results. Eye Contact Lens. 2013; 39(5):341-7.
48. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. Ophthalmology. 2005; 112(11):1963-1969.
49. Tanaka TS, Demirci H. cryopreserved ultra-thick human amniotic membrane for conjunctival surface reconstruction after excision of conjunctival tumors. Cornea. 2016; 35(4):445-50.
50. Tananuvat N, Martin T. The results of amniotic membrane transplantation for primary pterygium compared with conjunctival autograft. Cornea. 2004; 23:458-463.
51. Tandon R, Gupta N, Kalaivani M, et al. Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns. Br J Ophthalmol. 2011; 95(2):199-204.
52. Tejwani S, Kolari RS, Sangwan VS, Rao GN. Role of amniotic membrane graft for ocular chemical and thermal injuries. Cornea. 2007; 26:21-26.
53. Tok OY, Tok L, Atay IM, et al. Toxic keratopathy associated with abuse of topical anesthetics and amniotic membrane transplantation for treatment. Int J Ophthalmol. 2015; 18:938-944.
54. Tomlins PJ, Parulekar MV, Rauz S. "Triple-TEN" in the treatment of acute ocular complications from toxic epidermal necrolysis. Cornea. 2013; 32:365-369.

55. Tseng SCG, Prabhasawat P, Lee SH. Amniotic membrane transplantation for conjunctival surface reconstruction. American Journal of Ophthalmology 1997; 124(6):765-74.
56. Uçakhan OO, Köklü G, Firat E. Nonpreserved human amniotic membrane transplantation in acute and chronic chemical eye injuries. Cornea. 2002; 21:169-172.
57. Uhlig CE, Frings C, Rohloff N, et al. Long-term efficacy of glycerine-processed amniotic membrane transplantation in patients with corneal ulcer. Acta Ophthalmol. 2015; 9 3:e481.
58. Westekemper H, Figueiredo FC2, Siah WF, et al. Clinical outcomes of amniotic membrane transplantation in the management of acute ocular chemical injury. Br J Ophthalmol. 2017; 101:103-107.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Clearfield E, Muthappan V, Wang X, Kuo IC. Conjunctival autograft for pterygium. Cochrane Database Syst Rev. 2016; 2:CD011349.
2. Kaufman SC, Jacobs DS, Lee WB, et al. Options and adjuvants in surgery for pterygium: a report by the American Academy of Ophthalmology. Ophthalmology. 2013; 120:201-208.

KeraSys

1. Nagi KS, Cumba RJ, Bell NP, et al. Short-term outcomes of KeraSys patch graft for glaucoma drainage devices: a case series. J Ophthalmol. 2013; 2013:784709.

Prokera

1. McDonald MB, Sheha H, Tighe S, et al. Treatment outcomes in the DRy Eye Amniotic Membrane (DREAM) study. Clin Ophthalmol. 2018; 12:677-681.
2. Nguyen P, Rue K, Heur M, Yiu SC. Ocular surface rehabilitation: Application of human amniotic membrane in high-risk penetrating keratoplasties. Saudi J Ophthalmol. 2014; 28(3):198-202.
3. Vlasov A, Sia RK, Ryan DS, et al. Sutureless cryopreserved amniotic membrane graft and wound healing after photorefractive keratectomy. J Cataract Refract Surg. 2016; 42(3):435-443.

Allograft (unspecified)

1. Buchberger B, Follmann M, Freyer D, et al. The evidence for the use of growth factors and active skin substitutes for the treatment of non-infected diabetic foot ulcers (DFU): a health technology assessment (HTA). Exp Clin Endocrinol Diabetes. 2011; 119(8):472-479.

2. Choi YH, Cho YS, Lee JH, et al. Cadaver skin allograft may improve mortality rate for burns involving over 30% of total body surface area: a propensity score analysis of data from four burn centers. Cell Tissue Bank. 2018; 19(4):645-651.
3. Ibrahim AM, Shuster M, Koolen PG, et al. Analysis of the National Surgical Quality Improvement Program database in 19,100 patients undergoing implant-based breast reconstruction: complication rates with acellular dermal matrix. Plast Reconstr Surg. 2013; 132(5):1057-1066.
4. Zhong T, Temple-Oberle C, Hofer S, et al.; MCCAT Study Group. The Multi Centre Canadian Acellular Dermal Matrix Trial (MCCAT): study protocol for a randomized controlled trial in implant-based breast reconstruction. Trials. 2013; 14:356.

AlloDerm RTM

1. Becker S, Saint-Cyr M, Wong C, et al. AlloDerm versus DermaMatrix in immediate expander-based breast reconstruction: a preliminary comparison of complication profiles and material compliance. Plast Reconstr Surg. 2009; 123(1):1-6.
2. Bindingnavele V, Gaon M, Ota KS, et al. Use of acellular cadaveric dermis and tissue expansion in postmastectomy breast reconstruction. J Plast Reconstr Aesthet Surg. 2007; 60(11):1214-1218.
3. Breuing KH, Colwell AS. Inferolateral AlloDerm hammock for implant coverage in breast reconstruction. Ann Plast Surg. 2007; 59(3):250-255.
4. Breuing KH, Warren SM. Immediate bilateral breast reconstruction with implants and inferolateral AlloDerm slings. Ann Plast Surg. 2005; 55(3):232-239.
5. Diaz JJ Jr, Conquest AM, Ferzoco SJ, et al. Multi-institutional experience using human acellular dermal matrix for ventral hernia repair in a compromised surgical field. Arch Surg. 2009; 144(3):209-215.
6. Diaz JJ Jr, Guy J, Berkes MB, et al. Acellular dermal allograft for ventral hernia repair in the compromised surgical field. Am Surg. 2006; 72(12):1181-1187.
7. Espinosa-de-los-Monteros A, de la Torre JI, Marrero I, et al. Utilization of human cadaveric acellular dermis for abdominal hernia reconstruction. Ann Plast Surg. 2007; 58(3):264-267.
8. Gamboa-Bobadilla GM. Implant breast reconstruction using acellular dermal matrix. Ann Plast Surg. 2006; 56(1):22-25.
9. Glasberg SB, D'Amico RA. Use of regenerative human acellular tissue (AlloDerm) to reconstruct the abdominal wall following pedicle TRAM flap breast reconstruction surgery. Plast Reconstr Surg. 2006; 118(1):8-15.
10. Govindaraj S, Cohen M, Genden EM, et al. The use of acellular dermis in the prevention of Frey's syndrome. Laryngoscope. 2001; 111(11 Pt 1):1993-1998.

11. Helling ER, Dev VR, Garza J, et al. Low fistula rate in palatal clefts closed with the Furlow technique using decellularized dermis. Plast Reconstr Surg. 2006; 117(7):2361-2365.
12. Lee EI, Chike-Obi CJ, Gonzalez P, et al. Abdominal wall repair using human acellular dermal matrix: a follow-up study. Am J Surg. 2009; 198(5):650-657.
13. Lin HJ, Spoerke N, Deveney C, Martindale R. Reconstruction of complex abdominal wall hernias using acellular human dermal matrix: a single institution experience. Am J Surg. 2009; 197(5):599-603.
14. Liu DZ, Mathes DW, Neligan PC, et al. Comparison of outcomes using AlloDerm versus FlexHD for implant-based breast reconstruction. Ann Plast Surg. 2014; 72(5):503-507.
15. Maurice SM, Skeete DA. Use of human acellular dermal matrix for abdominal wall reconstructions. Am J Surg. 2009; 197(1):35-42.
16. Michelotti BF, Brooke S, Mesa J, et al. Analysis of clinically significant seroma formation in breast reconstruction using acellular dermal grafts. Ann Plast Surg. 2013; 71(3):274-277.
17. Milstein CF, Akst LM, Hicks MD, et al. Long-term effects of micronized AlloDerm injection for unilateral vocal fold paralysis. Laryngoscope. 2005; 115(9):1691-1696.
18. Misra S, Raj PK, Tarr SM, Treat RC. Results of AlloDerm use in abdominal hernia repair. Hernia. 2008; 12(3):247-250.
19. Nahabedian MY. Secondary nipple reconstruction using local flaps and AlloDerm. Plast Reconstr Surg. 2005; 115(7):2056-2061.
20. Patton JH Jr, Berry S, Kralovich KA. Use of human acellular dermal matrix in complex and contaminated abdominal wall reconstructions. Am J Surg. 2007; 193(3):360-363.
21. Preminger BA, McCarthy CM, Hu QY, et al. The influence of AlloDerm on expander dynamics and complications in the setting of immediate tissue expander/implant reconstruction: a matched-cohort study. Ann Plast Surg. 2008; 60(5):510-513.
22. Salzberg CA. Nonexpansive immediate breast reconstruction using human acellular tissue matrix graft (AlloDerm). Ann Plast Surg. 2006; 57(1):1-5.
23. Sclafani AP, Jacono AA, Dolitsky JN. Grafting of the peritonsillar fossa with an acellular dermal graft to reduce posttonsillectomy pain. Am J Otolaryngol. 2001; 22(6):409-414.
24. Sclafani AP, Romo T 3rd, Jacono AA, et al. Evaluation of acellular dermal graft in sheet (AlloDerm) and injectable (micronized AlloDerm) forms for soft tissue augmentation. Clinical observations and histological analysis. Arch Facial Plast Surg. 2000; 2(2):130-136.
25. Sinha UK, Saadat D, Doherty CM, Rice DH. Use of AlloDerm implant to prevent Frey syndrome after parotidectomy. Arch Facial Plast Surg. 2003; 5(1):109-112.

26. Sinha UK, Shih C, Chang K, Rice DH. Use of AlloDerm for coverage of radial forearm free flap donor site. Laryngoscope. 2002; 112(2):230-234.
27. Spear SL, Parikh PM, Reisin E, Menon NG. Acellular dermis-assisted breast reconstruction. Aesthetic Plast Surg. 2008; 32(3):418-425.
28. Steele MH, Seagle MB. Palatal fistula repair using acellular dermal matrix: the University of Florida experience. Ann Plast Surg. 2006; 56(1):50-53.
29. Sullivan SA, Dailey RA. Graft contraction: a comparison of acellular dermis versus hard palate mucosa in lower eyelid surgery. Ophthal Plast Reconstr Surg. 2003; 19(1):14-24.
30. Vertrees A, Greer L, Pickett C, et al. Modern management of complex open abdominal wounds of war: a 5-year experience. J Am Coll Surg. 2008; 207(6):801-809.
31. Weichman KE, Wilson SC, Weinstein AL, et al. The use of acellular dermal matrix in immediate two-stage tissue expander breast reconstruction. Plast Reconstr Surg. 2012; 129(5):1049-1058.
32. Woo A, Harless C, Jacobson SR. Revisiting an old place: single-surgeon experience on post-mastectomy subcutaneous implant-based breast reconstruction. Breast J. 2017; 23(5):545-553.

AlloDerm Ready To Use

1. Lewis P, Jewell J, Mattison G, et al. Reducing postoperative infections and red breast syndrome in patients with acellular dermal matrix-based breast reconstruction: the relative roles of product sterility and lower body mass index. Ann Plast Surg. 2015; 74 Suppl 1:S30-S32.
2. Parikh RP, Brown G, Sharma K, et al. Immediate implant-based breast reconstruction with acellular dermal matrix: a comparison of sterile and aseptic AlloDerm in 2039 consecutive cases. Plast Reconstr Surg. 2018; 142(6):1401-1409.
3. Park SJ, Kim Y, Jang SY. The application of an acellular dermal allograft (AlloDerm) for patients with insufficient conjunctiva during evisceration and implantation surgery. Eye (Lond). 2018; 32(1):136-141.
4. Weichman KE, Wilson SC, Saadeh PB, et al. Sterile "ready-to-use" AlloDerm decreases postoperative infectious complications in patients undergoing immediate implant-based breast reconstruction with acellular dermal matrix. Plast Reconstr Surg. 2013; 132(4):725-736.

Allomax

1. Rundell VL, Beck RT, Wang CE, et al. Complication prevalence following use of tutoplast-derived human acellular dermal matrix in prosthetic breast reconstruction: a retrospective review of 203 patients. J Plast Reconstr Aesthet Surg. 2014; 67(10):1345-1351.

2. Venturi ML, Mesbahi AN, Boehmler JH 4th, Marrogi AJ. Evaluating sterile human acellular dermal matrix in immediate expander-based breast reconstruction: a multicenter, prospective, cohort study. Plast Reconstr Surg. 2013; 131(1):9e-18e.

AlloPatch
1. Zelen CM, Orgill DP, Serena T, et al. A prospective, randomised, controlled, multicentre clinical trial examining healing rates, safety and cost to closure of an acellular reticular allogenic human dermis versus standard of care in the treatment of chronic diabetic foot ulcers. Int Wound J. 2017; 14(2):307-315.
2. Zelen CM, Orgill DP, Serena TE, et al. An aseptically processed, acellular, reticular, allogenic human dermis improves healing in diabetic foot ulcers: a prospective, randomised, controlled, multicentre follow-up trial. Int Wound J. 2018; 15(5):731-739.

AmnioBand
1. DiDomenico LA, Orgill DP, Galiano RD, et al. Aseptically processed placental membrane improves healing of diabetic foot ulcerations: prospective, randomized clinical trial. Plast Reconstr Surg Glob Open. 2016; 4(10):e1095.
2. DiDomenico LA, Orgill DP, Galiano RD, et al. A retrospective crossover study of the use of aseptically processed placental membrane in the treatment of chronic diabetic foot ulcers. Wounds. 2017; 29(10):311-316.
3. DiDomenico LA, Orgill DP, Galiano RD, et al. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients. Int Wound J. 2018; 15(6):950-957.

AMNIOEXCEL
1. Snyder RJ, Shimozaki K, Tallis A, et al. A prospective, randomized, multicenter, controlled evaluation of the use of dehydrated amniotic membrane allograft compared to standard of care for the closure of chronic diabetic foot ulcer. Wounds. 2016; 28(3):70-77.

Amniofix
1. Garoufalis M, Nagesh D, Sanchez PJ, et al. Use of dehydrated human amnion/chorion membrane allografts in more than 100 patients with six major types of refractory nonhealing wounds. J Am Podiatr Med Assoc. 2018; 108(2):84-89.

2. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. Foot Ankle Int. 2013a; 34(10):1332-1339.

Amniotic Allografts – Not specified

1. Abdulhalim BE, Wagih MM, Gad AA, et al. Amniotic membrane graft to conjunctival flap in treatment of non-viral resistant infectious keratitis: a randomised clinical study. Br J Ophthalmol. 2015; 99(1):59-63.
2. Amer MI, Abd-El-Maeboud KH, Abdelfatah I, et al. Human amnion as a temporary biologic barrier after hysteroscopic lysis of severe intrauterine adhesions: pilot study. J Minim Invasive Gynecol. 2010; 17(5):605-611.
3. Andonovska D, Dzokic G, Spasevska L, et al. The advantages of the application of amnion membrane in the treatment of burns. Prilozi. 2008; 29(1):183-198.
4. de Farias CC, Allemann N, Gomes JÁ. Randomized trial comparing amniotic membrane transplantation with lamellar corneal graft for the treatment of corneal thinning. Cornea. 2016; 35(4):438-444.
5. de Farias CC, Sterlenich T, de Sousa LB, et al. Randomized trial comparing multilayer amniotic membrane transplantation with scleral and corneal grafts for the treatment of scleral thinning after pterygium surgery associated with beta therapy. Cornea. 2014; 33(11):1197-204.
6. Georgiadis NS, Ziakas NG, Boboridis KG, et al. Cryopreserved amniotic membrane transplantation for the management of symptomatic bullous keratopathy. Clin Exp Ophthalmol. 2008; 36(2):130-135.
7. Harvinder S, Hassan S, Sidek DS, et al. Underlay myringoplasty: comparison of human amniotic membrane to temporalis fascia graft. Med J Malaysia. 2005; 60(5):585-589.
8. Küçükerdönmez C, Akova YA, Altinörs DD. Vascularization is more delayed in amniotic membrane graft than conjunctival autograft after pterygium excision Am J Ophthalmol. 2007; 143(2):245-249.
9. Luanratanakorn P, Ratanapakorn T, Suwan-Apichon O, Chuck RS. Randomised controlled study of conjunctival autograft versus amniotic membrane graft in pterygium excision. Br J Ophthalmol. 2006; 90(12):1476-1480.
10. Mahdy RA, Nada WM, Almasalamy SM, et al. A freeze-dried (lyophilized) amniotic membrane transplantation with mitomycin C and trabeculectomy for pediatric glaucoma. Cutan Ocul Toxicol. 2010; 29(3):164-170.
11. Paris Fdos S, Gonçalves ED, Campos MS, et al. Amniotic membrane transplantation versus anterior stromal puncture in bullous keratopathy: a comparative study. Br J Ophthalmol. 2013; 97(8):980-984.
12. Sharma N, Thenarasun SA, Kaur M, Pushker N, et al. Adjuvant role of amniotic membrane transplantation in acute ocular stevens-johnson syndrome: a randomized control trial. Ophthalmology. 2016; 123(3):484-491.

13. Sheha H, Kheirkhah A, Taha H. Amniotic membrane transplantation in trabeculectomy with mitomycin C for refractory glaucoma J Glaucoma. 2008; 17(4):303-307.
14. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. Ophthalmology. 2005; 112(11):1963-1969.
15. Tandon R, Gupta N, Kalaivani M, et al. Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns. Br J Ophthalmol. 2011; 95(2):199-204.

Apligraf

1. Steinberg JS, Edmonds M, Hurley DP Jr, King WN. Confirmatory data from EU study supports Apligraf for the treatment of neuropathic diabetic foot ulcers. J Am Podiatr Med Assoc. 2010; 100(1):73-77.
2. Veves A, Falanga V, Armstrong DG, Sabolinski ML; Apligraf Diabetic Foot Ulcer Study. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. Diabetes Care. 2001; 24(2):290-295.
3. Waymack P, Duff RG, Sabolinski M. The effect of a tissue engineered bilayered living skin analog, over meshed split-thickness autografts on the healing of excised burn wounds. The Apligraf Burn Study Group. Burns. 2000; 26(7):609-619.

Artelon CMC

1. Nilsson A, Wiig M, Alnehill H, et al. The Artelon CMC spacer compared with tendon interposition arthroplasty. Acta Orthop. 2010; 81(2):237-244.

Artelon TMC

1. Jörheim M, Isaxon I, Flondell M, et al. Short-term outcomes of trapeziometacarpal Artelon implant compared with tendon suspension interposition arthroplasty for osteoarthritis: a matched cohort study. J Hand Surg Am. 2009; 34(8):1381-1387.
2. Nilsson A, Liljensten E, Bergström C, Sollerman C. Results from a degradable TMC joint Spacer (Artelon) compared with tendon arthroplasty. J Hand Surg Am. 2005; 30(2):380-389.

Avance Nerve Graft

1. Brooks DN, Weber RV, Chao JD, et al. Processed nerve allografts for peripheral nerve reconstruction: a multicenter study of utilization and outcomes in sensory, mixed, and motor nerve reconstructions. Microsurgery. 2012; 32(1):1-14.

Avaulta
1. Bondili A, Deguara C, Cooper J. Medium-term effects of a monofilament polypropylene mesh for pelvic organ prolapse and sexual function symptoms. J Obstet Gynaecol. 2012; 32(3):285-290.

Belladerm:
1. Solomon MP, Komlo C, Defrain M. Allograft materials in phalloplasty: a comparative analysis. Ann Plast Surg. 2013; 71(3):297-299.

Biobrane
1. Barret JP, Dziewulski P, Ramzy PI, et al. Biobrane versus 1% silver sulfadiazine in second-degree pediatric burns. Plast Reconstr Surg. 2000; 105(1):62-65.
2. Feldman DL, Rogers A, Karpinski RH. A prospective trial comparing Biobrane, Duoderm and xeroform for skin graft donor sites. Surg Gynecol Obstet. 1991; 173(1):1-5.
3. Gerding RL, Emerman CL, Effron D, et al. Outpatient management of partial-thickness burns: Biobrane versus 1% silver sulfadiazine. Ann Emerg Med. 1990; 19(2):121-124.
4. Lal S, Barrow RE, Wolf SE, et al. Biobrane improves wound healing in burned children without increased risk of infection. Shock. 2000; 14(3):314-318.
5. Prasad JK, Feller I, Thomson PD. A prospective controlled trial of Biobrane versus scarlet red on skin graft donor areas. J Burn Care Rehabil. 1987; 8(5):384-386.
6. Rogers AD, Blackport E, Cartotto R. The use of Biobrane® for wound coverage in Stevens-Johnson Syndrome and toxic epidermal necrolysis. Burns. 2017; 43(7):1464-1472.

Biodesign (See Surgisis section below)

Cardiocel:
1. Bell D, Betts K, Justo R, et al. Multi-centre experience with 500 CardioCel® implants used for the repair of congenital heart defects. Ann Thorac Surg. 2019 Jun 14. pii: S0003-4975(19)30843-4. [Epub ahead of print]
~~1.~~2. Pavy C, Michielon G, Robertus JL, et al. Initial 2-year results of CardioCel® patch implantation in children. Interact Cardiovasc Thorac Surg. 2018; 26(3):448-453.

Clarix

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

1. Bemenderfer TB, Anderson RB, Odum SM, Davis WH. Effects of cryopreserved amniotic membrane-umbilical cord allograft on total ankle arthroplasty wound healing. J Foot Ankle Surg. 2019; 58(1):97-102.

Conexa
1. Maillot C, Harly E, Demezon H, Le Huec JC. Surgical repair of large-to-massive rotator cuff tears seems to be a better option than patch augmentation or débridement and biceps tenotomy: a prospective comparative study. J Shoulder Elbow Surg. 2018; 27(9):1545-1552.

CorMatrix
1. Ashfaq A, Brown T, Reemtsen B. Repair of complete atrioventricular septal defects with decellularized extracellular matrix: initial and midterm outcomes. World J Pediatr Congenit Heart Surg. 2017; 8(3):310-314.
2. Boyd WD, Johnson WE 3rd, Sultan PK, et al. Pericardial reconstruction using an extracellular matrix implant correlates with reduced risk of postoperative atrial fibrillation in coronary artery bypass surgery patients. Heart Surg Forum. 2010; 13(5):E311-E316.
3. Kelley TM Jr, Kashem M, Wang H, et al. Anterior leaflet augmentation with CorMatrix porcine extracellular matrix in twenty-five patients: unexpected patch failures and histologic analysis. Ann Thorac Surg. 2017; 103(1):114-120.
4. Quarti A, Nardone S, Colaneri M, et al. Preliminary experience in the use of an extracellular matrix to repair congenital heart diseases. Interact Cardiovasc Thorac Surg. 2011; 13(6):569-572.

Cortiva
1. Keifer OP, Page EK, Hart A, et al. A Complication Analysis of 2 Acellular Dermal Matrices in Prosthetic-based Breast Reconstruction. Plast Reconstr Surg Glob Open. 2016; 4(7):e800.
2. Parikh RP, Tenenbaum MM, Yan Y, Myckatyn TM. Cortiva versus AlloDerm Ready-To-Use in prepectoral and submuscular breast reconstruction: prospective randomized clinical trial study design and early findings. Plast Reconstr Surg Glob Open. 2018; 6(11):e2013.

Cymetra
1. Karpenko AN, Dworkin JP, Meleca RJ, Stachler RJ. Cymetra injection for unilateral vocal fold paralysis. Ann Otol Rhinol Laryngol. 2003; 112(11):927-934.
2. Milstein CF, Akst LM, Hicks MD, et al. Long-term effects of micronized AlloDerm injection for unilateral vocal fold paralysis. Laryngoscope. 2005; 115(9):1691-1696.

3. Morgan JE, Zraick RI, Griffin AW, et al. Injection versus medialization laryngoplasty for the treatment of unilateral vocal fold paralysis. Laryngoscope. 2007; 117(11):2068-2074.

DermACELL

1. Bullocks JM. DermACELL: a novel and biocompatible acellular dermal matrix in tissue expander and implant-based breast reconstruction. Eur J Plast Surg. 2014; 37(10):529-538.
2. Cazzell S, Moyer PM, Samsell B, et al. A prospective, multicenter, single-arm clinical trial for treatment of complex diabetic foot ulcers with deep exposure using acellular dermal matrix. Adv Skin Wound Care. 2019; 32(9):409-415.
~~2.~~3. Cazzell S, Vayser D, Pham H, et al. A randomized clinical trial of a human acellular dermal matrix demonstrated superior healing rates for chronic diabetic foot ulcers over conventional care and an active acellular dermal matrix comparator. Wound Repair Regen. 2017; 25(3):483-497.
~~3.~~4. Chang EI, Liu J. Prospective unbiased experience with three acellular dermal matrices in breast reconstruction. J Surg Oncol. 2017; 116(3):365-370.
~~4.~~5. Ortiz JA. Clinical outcomes in breast reconstruction patients using a sterile acellular dermal matrix allograft. Aesthetic Plast Surg. 2017; 41(3):542-550.
~~5.~~6. Pittman TA, Fan KL, Knapp A, et al. Comparison of different acellular dermal matrices in breast reconstruction: the 50/50 study. Plast Reconstr Surg. 2017; 139(3):521-528.
~~6.~~7. Walters J, Cazzell S, Pham H, et al. Healing rates in a multicenter assessment of a sterile, room temperature, acellular dermal matrix versus conventional care wound management and an active comparator in the treatment of full-thickness diabetic foot ulcers. Eplasty. 2016; 16:e10.
~~7.~~8. Yonehiro L, Burleson G, Sauer V. Use of a new acellular dermal matrix for treatment of nonhealing wounds in the lower extremities of patients with diabetes. Wounds. 2013; 25(12):340-344.
~~8.~~9. Zenn MR, Salzberg CA. A direct comparison of AlloDerm-Ready to Use (RTU) and DermACELL in immediate breast implant reconstruction. Eplasty. 2016; 16:e23.

Dermagraft

1. Gentzkow GD, Iwasaki SD, Hershon KS, et al. Use of Dermagraft, a cultured human dermis, to treat diabetic foot ulcers. Diabetes Care. 1996; 19(4):350-354.
2. Harding K, Sumner M, Cardinal M. A prospective, multicentre, randomised controlled study of human fibroblast-derived dermal substitute (Dermagraft) in patients with venous leg ulcers. Int Wound J. 2013; 10(2):132-137.

3. Marston WA, Hanft J, Norwood P, et al. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. Diabetes Care. 2003; 26(6):1701-1705.
4. Warriner RA 3rd, Cardinal M.; TIDE Investigators. Human fibroblast-derived dermal substitute: results from a treatment investigational device exemption (TIDE) study in diabetic foot ulcers. Adv Skin Wound Care. 2011; 24(7):306-311.

DermaMatrix

1. Agarwal JP, Mendenhall SD, Anderson LA, et al. The breast reconstruction evaluation of acellular dermal matrix as a sling trial (BREASTrial): design and methods of a prospective randomized trial. Plast Reconstr Surg. 2015; 135(1):20e-28e.
2. Athavale SM, Phillips S, Mangus B, et al. Complications of AlloDerm and DermaMatrix for parotidectomy reconstruction. Head Neck. 2012; 34(1):88-93.
3. Becker S, Saint-Cyr M, Wong C, et al. AlloDerm versus DermaMatrix in immediate expander-based breast reconstruction: a preliminary comparison of complication profiles and material compliance. Plast Reconstr Surg. 2009; 123(1):1-6.
4. Brooke S, Mesa J, Uluer M, et al. Complications in tissue expander breast reconstruction: a comparison of AlloDerm, DermaMatrix, and FlexHD acellular inferior pole dermal slings. Ann Plast Surg. 2012; 69(4):347-349.
5. Lee KT, Mun GH. A meta-analysis of studies comparing outcomes of diverse acellular dermal matrices for implant-based breast reconstruction. Ann Plast Surg. 2017; 79(1):115-123.
6. Mendenhall SD, Anderson LA, Ying J, et al. The BREASTrial: stage I. Outcomes from the time of tissue expander and acellular dermal matrix placement to definitive reconstruction. Plast Reconstr Surg. 2015; 135(1):29e-42e.
7. Mendenhall SD, Anderson LA, Ying J, et al. The BREASTrial Stage II: ADM breast reconstruction outcomes from definitive reconstruction to 3 months postoperative. Plast Reconstr Surg Glob Open. 2017; 5(1):e1209.
8. Michelotti BF, Brooke S, Mesa J, et al. Analysis of clinically significant seroma formation in breast reconstruction using acellular dermal grafts. Ann Plast Surg. 2013; 71(3):274-277.

Enduragen

1. Barmettler A, Heo M. A prospective, randomized comparison of lower eyelid retraction repair with autologous auricular cartilage, bovine acellular dermal matrix (SurgiMend), and porcine acellular dermal matrix (Enduragen) spacer grafts. Ophthalmic Plast Reconstr Surg. 2018; 34(3):266-273.

2. McCord C, Nahai FR, Codner MA, et al. Use of porcine acellular dermal matrix (Enduragen) grafts in eyelids: a review of 69 patients and 129 eyelids. Plast Reconstr Surg. 2008; 122(4):1206-1213.

EpiCord
1. Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. Int Wound J. 2018; 16(1):122-130.

EpiFix
1. Adly OA, Moghazy AM, Abbas AH, et al. Assessment of amniotic and polyurethane membrane dressings in the treatment of burns. Burns. 2010; 36(5):703-710.
2. Bianchi C, Cazzell S, Vayser D, et al. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix®) allograft for the treatment of venous leg ulcers. Int Wound J. 2018; 15(1):114-122.
3. Branski LK, Herndon DN, Celis MM, et al. Amnion in the treatment of pediatric partial-thickness facial burns. Burns. 2008; 34(3):393-399.
4. Forbes J, Fetterolf DE. Dehydrated amniotic membrane allografts for the treatment of chronic wounds: a case series. J Wound Care. 2012; 21(6):290, 292, 294-296.
5. Mostaque AK, Rahman KB. Comparisons of the effects of biological membrane (amnion) and silver sulfadiazine in the management of burn wounds in children. J Burn Care Res. 2011; 32(2):200-209.
6. Patel VR, Samavedi S, Bates AS, et al. Dehydrated human amnion/chorion membrane allograft nerve wrap around the prostatic neurovascular bundle accelerates early return to continence and potency following robot-assisted radical prostatectomy: propensity score-matched analysis. Eur Urol. 2015; 67(6):977-980.
7. Serena TE, Carter MJ, Le LT, et al.; EpiFix VLU Study Group. A multi-center randomized controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. Wound Repair Regen. 2014; 22(6):688-693.
8. Sheikh ES, Sheikh ES, Fetterolf DE. Use of dehydrated human amniotic membrane allografts to promote healing in patients with refractory non healing wounds. Int Wound J. 2014; 11(6):711-717.
9. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. Ophthalmology. 2005; 112(11):1963-1969.

10. Tettelbach W, Cazzell S, Reyzelman AM, et al. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. Int Wound J. 2018; 16(1):19-29.
11. Zelen CM. An evaluation of dehydrated human amniotic membrane allografts in patients with DFUs. J Wound Care. 2013b; 22(7):347-348, 350-351.
12. Zelen CM, Gould L, Serena TE, et al. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. Int Wound J. 2014b; 12(6):724-732.
13. Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. Int Wound J. 2013c; 10(5):502-507.
14. Zelen CM, Serena TE, Fetterolf DE. Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: a long-term follow-up study. Wound Medicine. 2014a; 4:1-4.
15. Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. Int Wound J. 2016a; 13(2):272-282.

E-Z Derm

1. Burkey B, Davis W 3rd, Glat PM. Porcine xenograft treatment of superficial partial-thickness burns in paediatric patients. J Wound Care. 2016; 25(2):S10-15.
2. Healy CM, Boorman JG. Comparison of E-Z Derm and Jelonet dressings for partial skin thickness burns. Burns Incl Therm Inj. 1989; 15(1):52-54.
3. Troy J, Karlnoski R, Downes K, et al. The use of EZ Derm® in partial-thickness burns: an institutional review of 157 patients. Eplasty. 2013; 13:e14.
4. Vanstraelen P. Comparison of calcium sodium alginate (KALTOSTAT) and porcine xenograft (E-Z DERM) in the healing of split-thickness skin graft donor sites. Burns. 1992; 18(2):145-148.

FlexHD

1. Bochicchio GV, De Castro GP, Bochicchio KM, et al. Comparison study of acellular dermal matrices in complicated hernia surgery. J Am Coll Surg. 2013; 217(4):606-613.

2. Brooke A, Mesa J, Uluer M, et al. Complications in tissue expander breast reconstruction: a comparison of AlloDerm, DermaMatrix, and FlexHD acellular inferior pole dermal slings. Ann Plast Surg. 2012; 69(4):347-349.
3. Cahan AC, Palaia DA, Rosenberg M, Bonanno PC. The aesthetic mastectomy utilizing a non-nipple-sparing portal approach. Ann Plast Surg. 2011; 66(5):424-428.
4. Liu DZ, Mathes DW, Neligan PC, et al. Comparison of outcomes using AlloDerm versus FlexHD for implant-based breast reconstruction. Ann Plast Surg. 2014; 72(5):503-507.
5. Michelotti BF, Brooke S, Mesa J, et al. Analysis of clinically significant seroma formation in breast reconstruction using acellular dermal grafts. Ann Plast Surg. 2013; 71(3):274-277.
6. Palaia DA, Arthur KS, Cahan AC, Rosenberg MH. Incidence of Seromas and Infections Using Fenestrated versus Nonfenestrated Acellular Dermal Matrix in Breast Reconstructions. Plast Reconstr Surg Glob Open. 2015; 3(11):e569.
7. Rawlani V, Buck DW 2nd, Johnson SA, et al. Tissue expander breast reconstruction using prehydrated human acellular dermis. Ann Plast Surg. 2011; 66(6):593-597.
8. Seth AK, Hirsch EM, Fine NA, Kim JY. Utility of acellular dermis-assisted breast reconstruction in the setting of radiation: a comparative analysis. Plast Reconstr Surg. 2012; 130(4):750-758.
9. Seth AK, Persing S, Connor CM, et al. A comparative analysis of cryopreserved versus prehydrated human acellular dermal matrices in tissue expander breast reconstruction. Ann Plast Surg. 2013; 70(6):632-635.
10. Sobti N, Liao EC. Surgeon-controlled study and meta-analysis comparing FlexHD and AlloDerm in immediate breast reconstruction outcomes. Plast Reconstr Surg. 2016; 138(5):959-967.
11. Vu MM, De Oliveira GS Jr, Mayer KE, et al. A prospective study assessing complication rates and patient-reported outcomes in breast reconstructions using a novel, deep dermal human acellular dermal matrix. Plast Reconstr Surg Glob Open. 2016; 3(12):e585.

Fortiva

1. Maxwell DW, Hart AM, Keifer OP Jr, et al. A Comparison of acellular dermal matrices in abdominal wall reconstruction. Ann Plast Surg. 2019; 82(4):435-440.

GalaFLEX

1. Adams WP Jr, Baxter R, Glicksman C, et al. The use of poly-4-hydroxybutyrate (P4HB) scaffold in the ptotic breast: a multicenter clinical study. Aesthet Surg J. 2018: 38(5):502-518.

Gentrix

1. Wang CQ, Tran T, Montera B, K, et al. Symptomatic, radiological, and quality of life outcome of paraesophageal hernia repair with urinary bladder extracellular surgical matrix: comparison with primary repair. Surg Laparosc Endosc Percutan Tech. 2019; ~~8 Dec 3. [Epub ahead of print]~~29(3):182-186.

Gore BioA
1. Heydari A, Attinà GM, Merolla E, et al. Bioabsorbable synthetic plug in the treatment of anal fistulas. Dis Colon Rectum. 2013; 56(6):774-779.
2. Jordan SW, Schulz SA, Carraher AM, Cabiling DS. Comparison of polypropylene and bioabsorbable mesh for abdominal wall reinforcement following microsurgical breast reconstruction. J Reconstr Microsurg. 2018 ~~Dec 17. [Epub ahead of print]~~; 35:335-340.
3. Ommer A, Herold A, Joos A, et al. Gore BioA Fistula Plug in the treatment of high anal fistulas--initial results from a German multicenter-study. Ger Med Sci. 2012; 10:Doc13.
4. Stewart DB Sr, Gaertner W, Glasgow S, et al. Clinical practice guideline for the management of anal fissures. Dis Colon Rectum. 2017; 60(1):7-14.

Gore® Acuseal Cardiovascular Patch
1. Stone PA, AbuRahma AF, Mousa AY, et al. Prospective randomized trial of ACUSEAL versus Vascu-Guard patching in carotid endarterectomy. Ann Vasc Surg. 2014; 28(6):1530-8.

Grafix CORE
1. Frykberg RG, Gibbons GW, Walters JL, et al. A prospective, multicentre, open-label, single-arm clinical trial for treatment of chronic complex diabetic foot wounds with exposed tendon and/or bone: positive clinical outcomes of viable cryopreserved human placental membrane. Int Wound J. 2017; 14(3):569-577.
2. Raspovic KM, Wukich DK, Naiman DQ, et al. Effectiveness of viable cryopreserved placental membranes for management of diabetic foot ulcers in a real world setting. Wound Repair Regen. 2018; 26(2):213-220.

Grafix PRIME
1. Ananian CE, Dhillon YS, Van Gils CC, et al. A multicenter, randomized, single-blind trial comparing the efficacy of viable cryopreserved placental membrane to human fibroblast-derived dermal substitute for the treatment of chronic diabetic foot ulcers. Wound Repair Regen. 2018; 26(3):274-283.

2. Johnson EL, Marshall JT, Michael GM. A comparative outcomes analysis evaluating clinical effectiveness in two different human placental membrane products for wound management. Wound Repair Regen. 2017; 25(1):145-149.
3. Lavery LA, Fulmer J, Shebetka KA, et al.; Grafix Diabetic Foot Ulcer Study Group. The efficacy and safety of Grafix(®) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. Int Wound J. 2014; 11(5):554-560.
4. Lavery L, Fulmer J, Shebetka KA, et al. Open-label Extension Phase of a Chronic Diabetic Foot Ulcer Multicenter, Controlled, Randomized Clinical Trial Using Cryopreserved Placental Membrane. Wounds. 2018; 30(9):283-289.
5. Raspovic KM, Wukich DK, Naiman DQ, et al. Effectiveness of viable cryopreserved placental membranes for management of diabetic foot ulcers in a real world setting. Wound Repair Regen. 2018; 26(2):213-220.
6. Regulski M, Jacobstein DA, Petranto RD, et al. A retrospective analysis of a human cellular repair matrix for the treatment of chronic wounds. Ostomy Wound Manage. 2013; 59(12):38-43.

GraftJacket

1. Barber FA, Burns JP, Deutsch A, et al. A prospective, randomized evaluation of acellular human dermal matrix augmentation for arthroscopic rotator cuff repair. Arthroscopy. 2012; 28(1):8-15.
2. Brigido SA, Boc SF, Lopez RC. Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. Orthopedics. 2004; 27(1 Suppl):s145-149.
3. Brigido SA. The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. Int Wound J. 2006; 3(3):181-187.
4. Cazzell S, Vayser D, Pham H, et al. A randomized clinical trial of a human acellular dermal matrix demonstrated superior healing rates for chronic diabetic foot ulcers over conventional care and an active acellular dermal matrix comparator. Wound Repair Regen. 2017; 25(3):483-497.
5. Gupta AK, Hug K, Berkoff DJ, et al. Dermal tissue allograft for the repair of massive irreparable rotator cuff tears. Am J Sports Med. 2012; 40(1):141-147.
6. Marks M, Hensler S, Wehrli M, et al. Trapeziectomy with suspension-interposition arthroplasty for thumb carpometacarpal osteoarthritis: a randomized controlled trial comparing the use of Allograft versus flexor carpi radialis tendon. J Hand Surg Am. 2017; 42(12):978-986.
7. Martin BR, Sangalang M, Wu S, Armstrong DG. Outcomes of allogenic acellular matrix therapy in treatment of diabetic foot wounds: an initial experience. Int Wound J. 2005; 2(2):161-165.

8. Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. Int Wound J. 2009; 6(3):196-208.
9. Walters J, Cazzell S, Pham H, et al. Healing rates in a multicenter assessment of a sterile, room temperature, acellular dermal matrix versus conventional care wound management and an active comparator in the treatment of full-thickness diabetic foot ulcers. Eplasty. 2016; 16:e10.

Hyalomatrix

1. Alvarez OM, Makowitz L, Patel M. Venous ulcers treated with a hyaluronic acid extracellular matrix and compression therapy: interim analysis of a randomized controlled trial. Wounds. 2017; 29(7):E51-E54.
2. Caravaggi C, De Giglio R, Pritelli C, et al. HYAFF 11-based autologous dermal and epidermal grafts in the treatment of noninfected diabetic plantar and dorsal foot ulcers: a prospective, multicenter, controlled, randomized clinical trial. Diabetes Care. 2003; 26(10):2853-2859.
3. Caravaggi C, Grigoletto F, Scuderi N. Wound bed preparation with a dermal substitute (Hyalomatrix® PA) facilitates re-epithelialization and healing: results of a multicenter, prospective, observational study on complex Chronic ulcers (The FAST Study). Wounds. 2011; 23(8):228-235.
4. Faga A, Nicoletti G, Brenta F, et al. Hyaluronic acid three-dimensional scaffold for surgical revision of retracting scars: a human experimental study. Int Wound J. 2013; 10(3):329-235.
5. Gravante G, Delogu D, Giordan N, et al. The use of Hyalomatrix PA in the treatment of deep partial-thickness burns. Burn Care Res. 2007; 28(2):269-274.
6. Gravante G, Sorge R, Merone A, et al. Hyalomatrix PA in burn care practice: results from a national retrospective survey, 2005 to 2006. Ann Plast Surg. 2010; 64(1):69-79.
7. Landi A, Garagnani L, Leti Acciaro A, et al. Hyaluronic acid scaffold for skin defects in congenital syndactyly release surgery: a novel technique based on the regenerative model. J Hand Surg Eur Vol. 2014; 39(9):994-1000.
8. Motolese A, Vignati F, Brambilla R. et al. Interaction between a regenerative matrix and a wound bed in nonhealing ulcers: results of 16 cases. Biomed Res Int. 2013; 2013:1-5.
9. Onesti MG, Fino P, Fioramonti P, et al. Reconstruction after skin cancer excision through a dermal induction template: our experience. Int Wound J. 2016; 13(2):198-203.
10. Vaienti L, Marchesi A, Palitta G, et al. Limb trauma: the use of an advanced wound care device in the treatment of full-thickness wounds. Strategies Trauma Limb Reconstr. 2013; 8(2):111-115.

Integra Dermal Regeneration Template (See Omnigraft)

Integra Flowable Wound Matrix
1. Campitiello F, Mancone M, Della Corte A, et al. To evaluate the efficacy of an acellular flowable matrix in comparison with a wet dressing for the treatment of patients with diabetic foot ulcers: a randomized clinical trial. Updates Surg. 2017; 69(4) 523-529.

Keramatrix
1. Loan F, Cassidy S, Marsh C, Simcock J. Keratin-based products for effective wound care management in superficial and partial thickness burns injuries. Burns. 2016; 42(3):541-547.

Kerecis
1. Baldursson BT, Kjartansson H, Konrádsdóttir F, et al. Healing rate and autoimmune safety of full-thickness wounds treated with fish skin acellular dermal matrix versus porcine small-intestine submucosa: a noninferiority study. Int J Low Extrem Wounds. 2015; 14(1):37-43.
2. Yang CK, Polanco TO, Lantis JC 2nd. A prospective, postmarket, compassionate clinical evaluation of a novel acellular fish-skin graft which contains omega-3 fatty acids for the closure of hard-to-heal lower extremity chronic ulcers. Wounds. 2016; 28(4):112-118.

MatrACELL
1. Hopkins RA, Lofland GK, Marshall J, et al. Pulmonary arterioplasty with decellularized allogeneic patches. Ann Thorac Surg. 2014; 97(4):1407-1412.

Matriderm
1. Haslik W, Kamolz LP, Manna F, et al. Management of full-thickness skin defects in the hand and wrist region: first long-term experiences with the dermal matrix Matriderm. J Plast Reconstr Aesthet Surg. 2010; 63(2):360-364.
2. Riml S, Wallner H, Larcher L, et al. Aesthetic improvements of skin grafts in nasal tip reconstruction. Aesthetic Plast Surg. 2011; 35(4):475-479.

Medihoney
1. Gethin G, Cowman S. Manuka honey vs. hydrogel--a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. J Clin Nurs. 2009; 18(3):466-474.

2. Jull A, Walker N, Parag V, et al. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. Br J Surg. 2008; 95(2):175-182.
3. Lund-Nielsen B, Adamsen L, Gottrup F, et al. Qualitative bacteriology in malignant wounds-a prospective, randomized, clinical study to compare the effect of honey and silver dressings. Ostomy Wound Manage. 2011; 57(7):28-36.
4. Malik K, Malik MA, Aslam A. Honey compared with silver sulphadiazine in the treatment of superficial partial-thickness burns. Int Wound J. 2010; 7(5):413-417.

Menaflex

1. Rodkey, WG, DeHaven KE, Montgomery WH 3rd, et al. Comparison of the collagen meniscus implant with partial meniscectomy. A prospective randomized trial. J Bone Joint Surg Am. 2008; 90(7):1413-1426.
2. Monllau JC, Gelber PE, Abat F, et al. Outcome after partial medial meniscus substitution with the collagen meniscal implant at a minimum of 10 years' follow-up. Arthroscopy. 2011; 27(7):933-943.
3. Van Der Straeten, C, Byttebier P, Eeckhoudt A, Victor J. Meniscal allograft transplantation does not prevent or delay progression of knee osteoarthritis. PLoS One, 2016; 11(5):e0156183.
4. Waterman, B., et al. Survivorship of meniscal allograft transplantation in an athletic patient population. Am J Sports Med, 2016; 44(5):1237-1242.
5. Zaffagnini S, Marcheggiani Muccioli GM, et al. Prospective long-term outcomes of the medial collagen meniscus implant versus partial medial meniscectomy: a minimum 10-year follow-up Study. Am J Sports Med. 2011; 39(5):977-985.

Neuragen

1. Farole A, Jamal BT. A bioabsorbable collagen nerve cuff (NeuraGen) for repair of lingual and inferior alveolar nerve injuries: a case series. J Oral Maxillofac Surg. 2008; 66(10):2058-2062.
2. Wangensteen KJ, Kalliainen LK. Collagen tube conduits in peripheral nerve repair: a retrospective analysis. Hand (N Y). 2010; 5(3):273-277.

Oasis

1. Cazzell SM, Lange DL, Dickerson JE Jr, Slade HB. The management of diabetic foot ulcers with porcine small intestine submucosa tri-layer matrix: a randomized controlled trial. Adv Wound Care (New Rochelle). 2015; 4(12):711-718.
2. Mostow EN, Haraway GD, Dalsing M, et al. Effectiveness of an extracellular matrix graft (Oasis Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. J Vasc Surg. 2005; 41(5):837-843.

3. Niezgoda JA, Van Gils CC, Frykberg RG, Hodde JP. Randomized clinical trial comparing Oasis Wound Matrix to Regranex Gel for diabetic ulcers. Adv Skin Wound Care. 2005; 18(5 Pt 1):258-266.
4. Romanelli M, Dini V, Bertone M. Randomized comparison of Oasis wound matrix versus moist wound dressing in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. Adv Skin Wound Care. 2010; 23(1):34-38.
5. Romanelli M, Dini V, Bertone M, et al. Oasis wound matrix versus Hyaloskin in the treatment of difficult-to-heal wounds of mixed arterial/venous aetiology. Int Wound J. 2007; 4(1):3-7.

Omnigraft (also known as Integra Dermal Regeneration Template)

1. Branski LK, Herndon DN, Pereira C, et al. Longitudinal assessment of Integra in primary burn management: a randomized pediatric clinical trial. Crit Care Med. 2007; 35(11):2615-2623.
2. Dantzer E, Braye FM. Reconstructive surgery using an artificial dermis (Integra): results with 39 grafts. Br J Plast Surg. 2001; 54(8):659-664.

Pelvicol

1. Dahlgren E, Kjølhede P.; RPOP-PELVICOL Study Group. Long-term outcome of porcine skin graft in surgical treatment of recurrent pelvic organ prolapse. An open randomized controlled multicenter study. Acta Obstet Gynecol Scand. 2011; 90(12):1393-1401.
2. Khan ZA, Nambiar A, Morley R, et al. Long-term follow-up of a multicentre randomised controlled trial comparing tension-free vaginal tape, xenograft and autologous fascial slings for the treatment of stress urinary incontinence in women. BJU Int. 2015; 115(6):968-977.

Peri-Strips Dry

1. Stamou KM, Menenakos E, Dardamanis D, et al. Prospective comparative study of the efficacy of staple-line reinforcement in laparoscopic sleeve gastrectomy. Surg Endosc. 2011; 25(11):3526-3530.

Permacol

1. Mitchell IC, Garcia NM, Barber R, et al. Permacol: a potential biologic patch alternative in congenital diaphragmatic hernia repair. J Pediatr Surg. 2008; 43(12):2161-2164.

PriMatrix

1. Karr JC. Retrospective comparison of diabetic foot ulcer and venous stasis ulcer healing outcome between a dermal repair scaffold (PriMatrix) and a bilayered living cell therapy (Apligraf). Adv Skin Wound Care. 2011; 24(3):119-125.
2. Kavros SJ. Acellular fetal bovine dermal matrix for treatment of chronic ulcerations of the midfoot associated with Charcot neuroarthropathy. Foot Ankle Spec. 2012; 5(4):230-234.

Phasix-ST

1. Abdelmoaty WF, Dunst CM, Filicori F, et al. Combination of surgical technique and bioresorbable mesh reinforcement of the crural repair leads to low early hernia recurrence rates with laparoscopic paraesophageal hernia repair. J Gastrointest Surg. 2019 Aug 29. [Epub ahead of print]

Promogran

1. Veves A, Sheehan P, Pham HT. A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs. standard treatment in the management of diabetic foot ulcers. Arch Surg. 2002; 137(7):822-827.
2. Vin F, Teot L, Meaume S. The healing properties of Promogran in venous leg ulcers. J Wound Care. 2002; 11(9):335-341.

Repriza

See Solomon (2013) in the Belladerm section above.

Seamguard

1. Albanopoulos K, Alevizos L, Flessas J, et al. Reinforcing the staple line during laparoscopic sleeve gastrectomy: prospective randomized clinical study comparing two different techniques. Preliminary results. Obes Surg. 2012; 22(1):42-46.
2. Guerrier JB, Mehaffey JH, Schirmer BD, Hallowell PT. Reinforcement of the staple line during gastric sleeve: a comparison of buttressing or oversewing, versus no reinforcement- a single-institution study. Am Surg. 2018; 84(5):690-694.
3. Salgado W Jr, Rosa GV, Nonino-Borges CB, Ceneviva R. Prospective and randomized comparison of two techniques of staple line reinforcement during open Roux-en-Y gastric bypass: oversewing and bioabsorbable Seamguard®. J Laparoendosc Adv Surg Tech A. 2011; 21(7):579-582.
4. Wallace CL, Georgakis GV, Eisenberg DP, et al. Further experience with pancreatic stump closure using a reinforced staple line. Conn Med. 2013; 77(4):205-210.

StrataGraft

1. Holmes JH 4th, Schurr MJ, King BT, et al. An open-label, prospective, randomized, controlled, multicenter, phase 1b study of StrataGraft skin tissue versus autografting in patients with deep partial-thickness thermal burns. Burns. 2019; pii: S0305-4179(19)30432-2.
~~1.~~2. Schurr MJ, Foster KN, Centanni JM, et al. Phase I/II clinical evaluation of StrataGraft: a consistent, pathogen-free human skin substitute. J Trauma. 2009; 66(3):866-873.

Strattice

1. Dikmans RE, El Morabit F, Ottenhof MJ, et al. Single-stage breast reconstruction using Strattice™: a retrospective study. J Plast Reconstr Aesthet Surg. 2016; 69(2):227-233.
2. Glasberg SB, Light D. AlloDerm and Strattice in breast reconstruction: a comparison and techniques for optimizing outcomes. Plast Reconstr Surg. 2012; 129(6):1223-1233.
3. Huntington CR, Cox TC, Blair LJ, et al. Biologic mesh in ventral hernia repair: outcomes, recurrence, and charge analysis. Surgery. 2016; 60(6):1517-1527.
4. Itani KM, Rosen M, Vargo D, et al. RICH Study Group. Prospective study of single-stage repair of contaminated hernias using a biologic porcine tissue matrix: the RICH Study. Surgery. 2012; 152(3):498-505.
5. Lohmander F, Lagergren J, Roy PG, et al. Implant based breast reconstruction with acellular dermal matrix: safety data from an open-label, multicenter, randomized, controlled trial in the setting of breast cancer treatment. Ann Surg. 2019; 269(5):836-841.
~~5.~~6. Maxwell, GP, Gabriel, A. Non-cross-linked porcine acellular dermal matrix in revision breast surgery: long-term outcomes and safety with neopectoral pockets. Aesthet Surg J. 2014; 34(4):551-559.
~~6.~~7. Paprottka FJ, Krezdorn N, Sorg H, et al. Evaluation of complication rates after breast surgery using acellular dermal matrix: median follow-up of three years. Plast Surg Int. 2017; 2017:1283735.
~~7.~~8. Patel, K, Albino FP, Nahabedian MY, Bhanot P. Critical analysis of Strattice performance in complex abdominal wall reconstruction: intermediate-risk patients and early complications. Int Surg. 2013; 98(4):379-384.
~~8.~~9. Patel KM, Nahabedian MY, Gatti M, Bhanot P. Indications and outcomes following complex abdominal reconstruction with component separation combined with porcine acellular dermal matrix reinforcement. Ann Plast Surg. 2012; 69(4):394-398.
~~9.~~10. Richmond B, Ubert A, Judhan R, et al. Component separation with porcine acellular dermal reinforcement is superior to traditional bridged mesh repairs in the open repair of significant midline ventral hernia defects. Am Surg. 2014; 80(8):725-731

~~10.~~11. Rosen MJ, Krpata DM, Ermlich B, Blatnik JA. A 5-year clinical experience with single-staged repairs of infected and contaminated abdominal wall defects utilizing biologic mesh. Ann Surg. 2013; 257(6):991-996.

Suprathel

1. Rashaan ZM, Krijnen P, Allema JH, et al. Usability and effectiveness of Suprathel® in partial thickness burns in children. Eur J Trauma Emerg Surg. 2017; 43(4):549-556.
2. Schwarze H, Küntscher M, Uhlig C, et al. Suprathel, a new skin substitute, in the management of donor sites of split-thickness skin grafts: results of a clinical study. Burns. 2007; 33(7):850-854.
3. Schwarze H, Küntscher M, Uhlig C, et al. Suprathel, a new skin substitute, in the management of partial-thickness burn wounds: results of a clinical study. Ann Plast Surg. 2008; 60(2):181-185.

SurgiMend

1. Barmettler A, Heo M. A Prospective, randomized comparison of lower eyelid retraction repair with autologous auricular cartilage, bovine acellular dermal matrix (SurgiMend), and porcine acellular dermal matrix (Enduragen) spacer grafts. Ophthalmic Plast Reconstr Surg. 2018; 34(3):266-273.
2. Butterfield JL. 440 Consecutive immediate, implant-based, single-surgeon breast reconstructions in 281 patients: a comparison of early outcomes and costs between SurgiMend fetal bovine and AlloDerm human cadaveric acellular dermal matrices. Plast Reconstr Surg. 2013; 131(5):940-951.
3. Clemens MW, Selber JC, Liu J, et al. Bovine versus porcine acellular dermal matrix for complex abdominal wall reconstruction. Plast Reconstr Surg. 2013; 131(1):71-79.
4. Eichler C, Vogt N, Brunnert K, et al A Head-to-head Comparison between SurgiMend and Epiflex in 127 Breast Reconstructions. Plast Reconstr Surg Glob Open. 2015; 3(6):e439.
5. Endress R, Choi MS, Lee GK. Use of fetal bovine acellular dermal xenograft with tissue expansion for staged breast reconstruction. Ann Plast Surg. 2012; 68(4):338-341.
6. Mazari FAK, Wattoo GM, Kazzazi NH, et al. The comparison of Strattice and SurgiMend in acellular dermal matrix-assisted, implant-based immediate breast reconstruction. Plast Reconstr Surg. 2018; 141(2):283-293.
7. Scheflan M, Grinberg-Rashi H, Hod K. Bovine acellular dermal matrix in immediate breast reconstruction: a retrospective, observational study with SurgiMend. Plast Reconstr Surg. 2018; 141(1):1e-10e.

Surgisis

1. Blom J, Husberg-Sellberg B, Lindelius A, et al. Results of collagen plug occlusion of anal fistula: a multicentre study of 126 patients. Colorectal Dis. 2014; 16(8):626-630.

2. Bondi J, Avdagic J, Karlbom U, et al. Randomized clinical trial comparing collagen plug and advancement flap for trans-sphincteric anal fistula. Br J Surg. 2017; 104(9):1160-1166.
3. Champagne BJ, O'Connor LM, Ferguson M, et al. Efficacy of anal fistula plug in closure of cryptoglandular fistulas: long-term follow-up. Dis Colon Rectum. 2006; 49(12):1817-1821.
4. Christoforidis D, Pieh MC, Madoff RD, Mellgren AF. Treatment of transsphincteric anal fistulas by endorectal advancement flap or collagen fistula plug: a comparative study. Dis Colon Rectum. 2009; 52(1):18-22.
5. Chung W, Kazemi P, Ko D, et al. Anal fistula plug and fibrin glue versus conventional treatment in repair of complex anal fistulas. Am J Surg. 2009; 197(5):604-608.
6. Cintron JR, Abcarian H, Chaudhry V, et al. Treatment of fistula-in-ano using a porcine small intestinal submucosa anal fistula plug. Tech Coloproctol. 2013; 17(2):187-191.
7. Ellis CN. Bioprosthetic plugs for complex anal fistulas: an early experience. J Surg Educ. 2007; 64(1):36-40.
8. Ellis CN, Rostas JW, Greiner FG. Long-term outcomes with the use of bioprosthetic plugs for the management of complex anal fistulas. Dis Colon Rectum. 2010; 53(5):798-802.
9. Franklin ME Jr, Treviño JM, Portillo G, et al. The use of porcine small intestinal submucosa as a prosthetic material for laparoscopic hernia repair in infected and potentially contaminated fields: long-term follow-up. Surg Endosc. 2008; 22(9):1941-1946.
10. Hyman N, O'Brien S, Osler T. Outcomes after fistulotomy: results of a prospective, multicenter regional study. Dis Colon Rectum. 2009; 52(12):2022-2027.
11. Jayne DG, Scholefield J, Tolan D, et al. Anal fistula plug versus surgeon's preference for surgery for trans-sphincteric anal fistula: the FIAT RCT. Health Technol Assess. 2019; 23(21):1-76.
~~11.~~12. Johnson EK, Gaw JU, Armstrong DN. Efficacy of anal fistula plug vs. fibrin glue in closure of anorectal fistulas. Dis Colon Rectum. 2006; 49(3):371-376.
~~12.~~13. Ky AJ, Sylla P, Steinhagen R, et al. Collagen fistula plug for the treatment of anal fistulas. Dis Colon Rectum. 2008; 51(6):838-843.
14. Lin H, Jin Z, Zhu Y, et al. Anal fistula plug vs rectal advancement flap for the treatment of complex cryptoglandular anal fistulas: a systematic review and meta-analysis of studies with long-term follow-up. Colorectal Dis. 2019; 21(5):502-515.
~~13.~~15. O'Connor L, Champagne BJ, Ferguson MA, et al. Efficacy of anal fistula plug in closure of Crohn's anorectal fistulas. Dis Colon Rectum. 2006; 49(10):1569-1573.
~~14.~~16. Oelschlager BK, Pellegrini, CA, Hunter JG, et al. Biologic prosthesis reduces recurrence after laparoscopic paraesophageal hernia repair: a multicenter, prospective, randomized trial. Ann Surg. 2006; 244(4):481-490.
~~15.~~17. Ortiz H, Marzo J, Ciga MA, et al. Randomized clinical trial of anal fistula plug versus endorectal advancement flap for the treatment of high cryptoglandular fistula in ano. Br J Surg. 2009; 96(6):608-612.

~~16.~~18. Senéjoux A, Siproudhis L, Abramowitz L, et al.; Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif [GETAID]. Fistula plug in fistulising ano-perineal Crohn's disease: a randomised controlled trial. J Crohns Colitis. 2016; 10(2):141-148.
~~17.~~19. Thekkinkattil DK, Botterill I, Ambrose NS, et al. Efficacy of anal fistula plug in complex anorectal fistulae. Colorectal Dis. 2009; 11(6):584-587.
~~18.~~20. van Koperen PJ, Bemelman WA, Gerhards MF, et al. The anal fistula plug treatment compared with the mucosal advancement flap for cryptoglandular high transsphincteric perianal fistula: a double-blinded multicenter randomized trial. Dis Colon Rectum. 2011; 54(4):387-393.

Surgisis Gold
1. Korwar V, Adjepong S, Pattar J, Sigurdsson A. Biological mesh repair of paraesophageal hernia: an analysis of our outcomes. J Laparoendosc Adv Surg Tech A. 2019 Sep 20. [Epub ahead of print].
2. Ravo B, Falasco G. Pure tissue inguinal hernia repair with the use of biological mesh: a 10-year follows up. A prospective study. Hernia. 2019 May 20. [Epub ahead of print].
3. Sarr MG, Hutcher NE, Snyder S, et al. A prospective, randomized, multicenter trial of Surgisis Gold, a biologic prosthetic, as a sublay reinforcement of the fascial closure after open bariatric surgery. Surgery. 2014; 156(4):902-908.
~~1.~~4. Thomas PW, Blackwell JEM, Herrod PJJ, et al. Long-term outcomes of biological mesh repair following extra levator abdominoperineal excision of the rectum: an observational study of 100 patients. Tech Coloproctol. 2019; 23(8):761-767.

Talymed
1. Kelechi TJ, Mueller M, Hankin CS, et al. A randomized, investigator-blinded, controlled pilot study to evaluate the safety and efficacy of a poly-N-acetyl glucosamine-derived membrane material in patients with venous leg ulcers. J Am Acad Dermatol. 2011; 66(6):e209-215.

TheraSkin
1. DiDomenico L, Emch KJ, Landsman AR, Landsman A. A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. Wounds. 2011; 23(7):184-189.
2. Landsman AS, Cook J, Cook E, et al. A retrospective clinical study of 188 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin®) on the treatment of diabetic foot ulcers and venous leg ulcers. Foot Ankle Spec. 2011; 4(1):29-41.

3. Sanders L, Landsman AS, Landsman A, et al. A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. Ostomy Wound Manage. 2014; 60(9):26-38.
4. Towler MA, Rush EW, Richardson MK, Williams CL. randomized, prospective, blinded-enrollment, head-to-head towler venous leg ulcer healing trial comparing living, bioengineered skin graft substitute (Apligraf) with living, cryopreserved, human skin allograft (TheraSkin). Clin Podiatr Med Surg. 2018; 35(3):357-365.

Tutomesh
1. Eichler C, Efremova J, Brunnert K, et al. A head to head comparison between SurgiMend® - fetal bovine acellular dermal matrix and Tutomesh® - a bovine pericardium collagen membrane in breast reconstruction in 45 cases. In Vivo. 2017; 31(4):677-682.
2. Paprottka FJ, Krezdorn N, Sorg H, et al. Evaluation of complication rates after breast surgery using acellular dermal matrix: median follow-up of three years. Plast Surg Int. 2017; 2017:1283735.

Vascu-Guard
1. Stone PA, AbuRahma AF, Mousa AY, et al. Prospective randomized trial of ACUSEAL versus Vascu-Guard patching in carotid endarterectomy. Ann Vasc Surg. 2014; 28(6):1530-8.

Veritas
1. Guerette NL, Peterson TV, Aguirre OA, et al. Anterior repair with or without collagen matrix reinforcement: a randomized controlled trial. Obstet Gynecol. 2009; 114(1):59-65.

Xelma
1. Vowden P, Romanelli M, Peter R, et al. The effect of amelogenins (Xelma) on hard-to-heal venous leg ulcers. Wound Repair Regen. 2006; 14(3):240-246.

XenoGrafts (unspecified) for Burns
1. Broz L, Vogtová D, Königová R. Experience with banked skin in the Prague burn center. Acta Chir Plast. 1999; 41(2):54-58.
2. Ding YL, Pu SS, Wu DZ, et al. Clinical and histological observations on the application of intermingled auto- and porcine-skin heterografts in third degree burns. Burns Incl Therm Inj. 1983; 9(6):381-386.

3. Moserová J, Běhounková-Housková E. Temporary skin substitutes and evaporative water loss. Scand J Plast Reconstr Surg. 1979; 13(1):143-145.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Agency for Healthcare Research and Quality (AHRQ). Technology Assessment: Skin substitutes for treating chronic wounds. December 18, 2012. Available at: https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/skinsubs/HCPR0610_skinsubst-final.pdf~~https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/skinsubs/HCPR0610_skinsubst-final.pdf~~. ~~-~~Accessed on ~~May 28, 2019~~November 11, 2019.
2. American Diabetes Association. Standards of Medical Care in Diabetes—2013. Diabetes Care. 2013; 36(Suppl 1):S11-S66.
3. Centers for Medicare and Medicaid Services. Available at: http://www.cms.hhs.gov/mcd/index_list.asp?list_type=ncd. Accessed on ~~May 8, 2019~~November 11, 2019.
   - National Coverage Determination for Blood-Derived Products for Chronic Non-Healing Wounds. NCD #270.3. Effective July 23, 2004.
   - National Coverage Determination for Porcine Skin and Gradient Pressure Dressings. NCD #270.5. Effective date not posted.
   - National Coverage Determination for Services provided for the Diagnosis and Treatment of Diabetic Sensory Neuropathy with Loss of Protective Sensation (Diabetic Peripheral Neuropathy). NCD #70.2.1. Effective July 1, 2002.
   - National Coverage Determination for Treatment of Decubitus Ulcers. NCD #270.4. Effective date not posted.
   - National Coverage Determination for Collagen Meniscus Implant. NCD #150.12. Effective July 6, 2010.
4. Jones JE, Nelson EA. Skin grafting for venous leg ulcers. Cochrane Database Syst Rev. 2007;(2):CD001737.
5. Santema TB, Poyck PP, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. Cochrane Database Syst Rev. 2016;(2):CD011255.
6. Westby MJ, Dumville JC, Soares MO, et al. Dressings and topical agents for treating pressure ulcers Cochrane Database Syst Rev. 2017;(6):CD011947.

Websites for Additional Information

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

1. National Library of Medicine (NIH). Burns. Available at: https://medlineplus.gov/burns.html~~https://www.nlm.nih.gov/medlineplus/burns.html~~. Accessed on November 11, 2019~~May 28, 2019~~.
2. National Library of Medicine (NIH). Diabetic Foot. Available at: https://medlineplus.gov/diabeticfoot.html~~http://www.nlm.nih.gov/medlineplus/diabeticfoot.html~~. Accessed on ~~May 28, 2019~~November 11, 2019.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	11/07/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Moved AmbioDisk from INV and NMN statement to the MN statement addressing of allogeneic amniotic membrane-derived grafts or wound coverings. Added Artacent Ocular to MN statement addressing of allogeneic amniotic membrane-derived grafts or wound coverings. Added new products to INV and NMN statement. Updated Rationale and References sections.
	10/01/2019	Updated Coding section with 10/01/2019 HCPCS changes; added Q4205-Q4206, Q4208-Q4222, revised descriptors for Q4122, Q4165, Q4184; also added C1878.

	06/18/2019	Correction to MN statement addressing amniotic membrane-derived products for conjunctival and corneal indications made. Kerasys removed and replaced by AmnioGraft.
Revised	06/06/2019	~~Medical Policy & Technology Assessment Committee (~~MPTAC~~)~~ review. Added new MN and INV and NMN statements addressing amniotic membrane-derived products for conjunctival and corneal indications. Added new products to INV and NMN statement. Updated Rationale, Coding and References sections.
Revised	01/24/2019	MPTAC review. Added new MN statements for EpiCord, Grafix PRIME, and the sheet or membrane form of AmnioBand. Revised INV and NMN statements regarding those products. Added EpiBurn to INV and NMN statement. Updated Coding, Rationale, and References sections.
	12/27/2018	Updated Coding section with 01/01/2019 HCPCS changes; removed Q4131, Q4172 deleted 12/31/2018.
Revised	09/13/2018	MPTAC review. Added several products to the INV and NMN section. Updated Rationale, Coding and References sections.
Revised	01/25/2018	MPTAC review. Revised criteria for EpiFix and Integra Bilayer Matrix Wound Dressing. Deleted statement regarding TransCyte. Moved several products from the INV and NMN section to the MN section. Updated Rationale and References sections. Updated Coding section to include removing Q4182 no longer addressed.
	12/27/2017	The document header wording updated from "Current Effective Date" to "Publish Date." Updated Coding section with 01/01/2018 HCPCS changes; added codes Q4176-Q4182, descriptor revisions for Q4132, Q4133, Q4148, Q4156, Q4158, Q4162, Q4163.
Revised	08/03/2017	MPTAC review. Added new products to INV and NMN list. Removed Perlane and Restylane from Inv and NMN list. Updated Rationale, Coding and References sections.
Revised	02/02/2017	MPTAC review. Made minor typographical revisions to Position Statement. Added new products to INV and NMN list. Updated Rationale and References sections.
	01/01/2017	Updated Coding section with 01/01/2017 CPT and HCPCS changes; removed codes C9349, Q4119, Q4120, Q4129 deleted 12/31/2016.

Revised	05/05/2016	MPTAC review. Added AlloDerm Ready to Use as MN for the same indications as AlloDerm Regenerative Tissue Matrix. Added FlexHD as MN for breast reconstruction surgery. Clarified INV and NMN statement regarding fresh frozen allograft products. Added new products to the INV and NMN list. Updated Rationale, Coding, and References sections.
Revised	11/05/2015	MPTAC review. Added Restlyane and Perlane to investigational and not medically necessary list. Updated Rationale and References sections. Updated Coding section with 01/01/2016 HCPCS changes; also removed ICD-9 codes.
	07/01/2015	Updated Coding section with 07/01/2015 HCPCS change to descriptor for C9349.
Revised	05/07/2015	MPTAC review. Added new medically necessary position statement regarding the use of fresh, frozen, unprocessed skin allograft products for the treatment of full-thickness or deep partial-thickness burns when criteria are met. Added new products to investigational and not medically necessary section. Updated Rationale, Coding, and References sections.
Revised	02/05/2015	MPTAC review. Added new medically necessary position statement regarding the use the sheet or membrane form of EpiFix. Revised investigational and not medically necessary statement to differentiate between the sheet or membrane form of EpiFix and the particulate or injectable form of EpiFix. Added new products to investigational and not medically necessary section. Updated Rationale, Background, Coding, and References sections. Revised position statements were finalized in a follow-up vote on 03/04/2015.
	01/01/2015	Updated Coding section with 01/01/2015 HCPCS changes.
Revised	02/13/2014	MPTAC review. Clarified nomenclature of AlloDerm product in medically necessary section. Added new products to investigational and not medically necessary section. Updated Rationale, Background, and References sections.
	01/01/2014	Updated Coding section with 01/01/2014 CPT and HCPCS changes.
Revised	08/08/2013	MPTAC review. Added new products to Investigational and Not Medically Necessary list. Updated Rationale and References sections.
Revised	05/09/2013	MPTAC review. Added new products to Investigational and Not Medically Necessary list. Updated Rationale, Coding, and Reference sections.
	01/01/2013	Updated Coding section with 01/01/2013 HCPCS changes; removed C9366, C9368, C9369 deleted 12/31/2012.

Revised	05/10/2012	MPTAC review. Deleted "autologous" from title. Split off growth factors, silver-based products and autologous tissues for wound treatment and soft tissue to a new policy (MED.00110). Reorganized position statement section. Clarified Medically necessary statement for Apligraf regarding number of applications and deleted corresponding investigational and not medically necessary statement. Added new products to investigational and not medically necessary position statement. Revised Rationale, Background, References, and Index sections. Updated Coding section to include 07/01/2012 HCPCS changes.
	01/19/2012	Updated Coding section with correct diagnosis coding for Apligraf; removed HCPCS codes G0440, G0441 deleted 12/31/2011.
	01/01/2012	Updated Coding section with 01/01/2012 CPT and HCPCS changes; removed codes 15170, 15171, 15175, 15176, 15330, 15331, 15335, 15336, 15340, 15341, 15360, 15361, 15365, 15366, 15400, 15401, 15420, 15421, 15430, 15431, C9365 deleted 12/31/2011; also removed CPT 15150, 15151, 15152, 15155, 15156, 15157.
Revised	05/19/2011	MPTAC review. Added synthetic soft-tissue grafting materials as investigational and not medically necessary to Section I. Added xenographic-related or derived products as investigational and not medically necessary to Section IV. Updated Rationale, References, and Index sections. Updated Coding section with 07/01/2011 HCPCS changes.
Revised	02/17/2011	MPTAC review. Added use of cryopreserved allogeneic human skin to the Allogeneic section as investigational and not medically necessary. Updated Rationale, Coding, References, and Index sections.
	01/01/2011	Updated Coding section with 01/01/2011 HCPCS changes; removed Q4109 deleted 12/31/2010.
Revised	08/19/2010	MPTAC review. Added use of synthetic fistula plugs to synthetic products section as investigational and not medically necessary. Expanded investigational and not medically necessary statement for Dermagraft to cover all indications not listed as medically necessary. Revised language in xenographic investigational and not medically necessary statement. Updated list of xenographic products, including Menaflex™ Collagen Meniscus Implant. Added new section addressing composite autologous / allogeneic / xenographic products. Updated Rationale, Background, Coding, and References sections.

	07/01/2010	Updated Coding section with 07/01/2010 CPT and HCPCS changes.
	01/01/2010	Updated Coding section with 01/01/2010 CPT changes; removed CPT 0170T deleted 12/31/2009.
Revised	08/27/2009	MPTAC review. Added Platelet Rich Plasma as investigational and not medically necessary. Updated coding and Index sections.
Reviewed	05/21/2009	MPTAC review. Added note stating that this document does not address the use of meshes or patches of non-biologic origin when used for standard hernia repair procedures. Updated Index section. Updated coding section with 07/01/2009 HCPCS changes.
Revised	02/26/2009	MPTAC review. Added Investigational and Not Medically Necessary statements for C-QUR and Strattice.
Revised	11/20/2008	MPTAC review. Added AlloDerm as medically necessary for breast reconstruction and complex abdominal wall wound closure. Updated Rationale and Reference sections. Updated coding section with 01/01/2009 HCPCS changes; removed C9357, J7340, J7341, J7342, J7343, J7344, J7346, J7347, J7348, J7349 deleted 12/31/2008.
Revised	08/28/2008	MPTAC review. Added Vitagel to Investigational and Not Medically Necessary statement of Section II Autologous Products. Added Cymetra to Investigational and Not Medically Necessary statement of Section III Allogeneic Products. Updated Background. Coding section updated to include 10/01/2008 ICD-9 changes.
Revised	05/15/2008	MPTAC review. Changed title from "Wound Healing: Skin Substitutes and Blood-Derived Growth Factors" to "Autogous, Allogeneic, Xenographic, Synthetic and Composite Products for Wound Healing and Soft Tissue Grafting." Reorganized Position Statement section. Added position statements regarding the following products: Actisorb, Avaulta Plus, Collamend, CuffPatch, Mediskin, Neoform Dermis, Pelcvicol, Pelvisoft, Silversorb, and Unite. Revised Rationale, Coding, Background, Definitions, References, and Index sections. Deleted information regarding Procuren®. Updated Coding section with 07/01/2008 HCPCS changes.
Revised	02/21/2008	MPTAC review. Added position statements for Integra™ Matrix Wound Dressing, Primatrix, and TissueMend. Expanded investigational and not medically

		necessary statement for Surgisis, Autogel and Safeblood to include all indications. Updated Rationale, Background, Definitions, and References sections.
	01/01/2008	Updated Coding section with 01/01/2008 HCPCS changes; removed HCPCS C9351, J7345 deleted 12/31/2007. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Revised	05/17/2007	MPTAC review. Added the use of AlloDerm for breast reconstruction or augmentation to investigational/not medically necessary statement. Updated Rationale and References sections.
	01/01/2007	Updated Coding section with 01/01/2007 CPT/HCPCS changes.
Revised	09/14/2006	MPTAC review. Added position statement for Surgisis®; updated rationale, background and reference sections. Coding updated; removed CPT 15342, 15343 deleted 12/31/05, HCPCS Q0182, Q0183 deleted 12/31/04.
Revised	03/23/2006	MPTAC review. Added position statement for AlloDerm® and GraftJacket™.
	01/01/2006	Updated Coding section with 01/01/2006 CPT/HCPCS changes
	11/22/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger Wellpoint Harmonization.

Pre-Merger Organizations	**Last Review Date**	**Document Number**	**Title**
Anthem, Inc.	04/28/2005	SURG.00011	Wound Healing: Tissue Engineered Skin Substitutes and Growth Factors
WellPoint Health Networks, Inc.	04/28/2005	3.02.03	Human Skin Equivalent Grafts
	09/23/2004	8.01.08	Autologous Blood Derived Preparations for Wound Healing