Prior Authorization Review Panel  
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

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<th>Plan: Aetna Better Health</th>
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**Type of Submission – Check all that apply:**

- ☐ New Policy
- ☒ Revised Policy*
- ☐ Annual Review – No Revisions
- ☐ Statewide PDL

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

**CPB 0244 Wound Care**

This CPB is revised to state that the following are considered medically necessary: 1) Epifix for the treatment of difficult-to-heal chronic venous partial and full-thickness ulcers of the lower extremity that have failed standard wound therapy of at least 4-weeks duration; 2) DermACELL for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. This CPB has been revised to state that the following are considered experimental and investigational: ACM Surgical Collagen, ACM Surgical Extra Advanced Collagen, ACM Surgical Extra Advanced Collagen Powder, Allogen, AlloGen Liquid, AlloPatch Pliable, AlphaGems, AltiPlast, AltiPly, Ambio Choice, AmnioArmor, AmnioBand Allograft Placental Matrix, AmnioCord, AmnioFill, Amnion Bio, Amnios, AmnioWrap2, AmnyoFluid, Aquacel Ag, Artacent Cord, Arthrex Amnion Matrix, Arthrex Amnion Viscous, Ascent, AxoBioMembrane, Axolotl Ambient, Axolotl Cryo, Axolotl DualGraft, Axolotl Graft, BellaCell HD, BioFix Flow Placental Tissue Matrix Allograft, BioSkin Flow, BioWound Membrane, BioWound Plus Membrane, BioWound XPlus Membrane, Cellesta Cord, Cellesta Duo, Cellesta Flowable Amanion, Colla-Pad, CollaSorb, CollaWound, Coll-e-Derm, Collexa, Derma-Gide, Fluid Flow, Fluid GF, Genesis Amniotic Membrane, Grafix cryo-preserved placental membrane, GraftJacket RTM, Helicoll, InteguPly, Kerasorb Wound Matrix, Keroxx Flowable Wound Matrix, Matrion, Membrane Graft, Membrane Wrap, Merigen, MicroMatrix, MyOwn Skin, Novachor, Novafix, Ologen, Omega3 Wound, Plurivest, ProgenaMatrix, Puracol Plus, Renuva, Restorigen Amnion Patch, Restorigen Amniotic Fluid Therapy, Restrata, SkinTE, Stravix PL, SureDerm, SurgiCORD, surgiGRAFT, surgiGRAFT-DUAL, SurGraft, TheraForm, VersaWrap Tendon Protector, WoundEx Membrane, WoundFix Membrane, WoundFix Plus Membrane, WoundFix XPlus Membrane, and Xwrap Amniotic Membrane Derived Allograft.
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<tr>
<th>Name of Authorized Individual (Please type or print):</th>
<th>Signature of Authorized Individual:</th>
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<tr>
<td>Dr. Bernard Lewin, M.D.</td>
<td>Bernard Lewin, M.D.</td>
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Revised July 22, 2019
Wound Care

I. Medically Necessary Wound Care Products

Aetna considers the following products for wound care medically necessary according to the criteria indicated below:

A. Apligraf (graftskin)

Aetna considers a culture-derived human skin equivalent (HSE) called Apligraf (graftskin) medically necessary for any of the following indications:

1. For use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than 6-weeks duration that have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure; or
2. In conjunction with standard therapy to promote effective wound healing of chronic, non-infected, partial and full-thickness venous stasis ulcers that have failed conservative measures of greater than 4 weeks duration using regular dressing changes and standard therapeutic compression.

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*
Aetna considers Apligraft experimental and investigational for all other indications (e.g., traumatic wounds) because its effectiveness for indications other than the ones listed above has not been established.

B. **Dermagraft**

Aetna considers Dermagraft human fibroblast-derived dermal substitute medically necessary for use

(i) in the treatment of full-thickness diabetic foot ulcers greater than 6-week duration that extend through the dermis, but without tendon, muscle, joint capsule or bone exposure, or (ii) in the treatment of wounds related to dystrophic epidermolysis bullosa. Note: Consistent with the Food and Drug Administration (FDA)-approved labeling of Dermagraft, the product should be used in conjunction with standard wound care regimens. In addition, the product is not considered medically necessary in persons with an inadequate blood supply to the involved foot.

Aetna considers Dermagraft experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established.

Dermagraft is contraindicated and has no proven value in infected ulcers and ulcers with sinus tracts.

C. **Systemic Hyperbaric Oxygen Therapy (HBOT)**

Aetna considers systemic hyperbaric oxygen therapy (HBOT) medically necessary as an adjunctive method for treating non-healing, infected, deep lower extremity wounds in members with diabetes when criteria in CPB 0172 - Hyperbaric Oxygen Therapy (HBOT) (../100_199/0172.html) are met.

D. **TransCyte**

Aetna considers TransCyte (allogeneic human dermal fibroblasts), a biosynthetic dressing, medically necessary for the temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in persons who require such a
covering before autograft placement; and for the treatment of mid-dermal to indeterminate depth burn wounds that typically require debridement and that may be expected to heal without autografting.

Aetna considers TransCyte experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established.

E. Orcel

Aetna considers Orcel (bilayered cellular matrix) medically necessary for healing donor site wounds in burn victims, and for use in persons with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites.

Aetna considers Orcel experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established.

F. Biobrane Biosynthetic Dressing

Aetna considers Biobrane biosynthetic dressing medically necessary for temporary covering of a superficial partial-thickness burn wound.

Aetna considers Biobrane biosynthetic dressing experimental and investigational for all other indications because its effectiveness for indications other than the one listed above has not been established.

G. Integra Dermal Regeneration Template and Integra Bilayer Wound Matrix

Aetna considers Integra Dermal Regeneration Template, Integra Bilayer Matrix Wound Dressing, and Integra Meshed Bilayer Wound Matrix (collagen-glycosaminoglycan copolymers) medically necessary for the treatment of individuals with severe burns where there is a limited amount of their own skin to use for autografts or they are too ill to have more wound sites created.

Aetna considers Integra Dermal Regeneration Template and Integra Omnigraft Dermal Regeneration Template medically necessary for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.
Aetna considers Integra Dermal Regeneration Template and Integra Bilayer Wound Matrix experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established.

H. Alloderm

Aetna considers Alloderm and Alloderm-RTU a ce llu la r d e rm a l tissu e m a trix medically necessary for breast reconstructive surgery; see _CPB 0185 - Breast Reconstruction Surgery (../100_199/0185.html)._ Aetna considers Alloderm and Alloderm-RTU acellular dermal tissue matrix medically necessary for use in surgical repair of complex abdominal wall wounds (e.g., due to infection, fascial defect, etc.).

Aetna considers the use of Alloderm experimental and investigational for all other indications (e.g., hernia repair, reduction of incidence of Frey's syndrome following parotidectomy, and for use in reconstruction of the upper extremity) because its effectiveness for indications other than the one listed above has not been established.

I. Artiss

Aetna considers Artiss fibrin sealant medically necessary for the treatment of individuals with severe burns.

Aetna considers Artiss fibrin sealant experimental and investigational for all other indications because its effectiveness for indications other than the one listed above has not been established.

J. Oasis Wound Matrix

Aetna considers Oasis Wound Matrix medically necessary for treatment of partial and full -thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

Aetna considers Oasis Wound Matrix medically necessary for treatment of difficult-to-heal chronic venous partial and full-thickness ulcers of the lower extremity that have failed standard wound therapy of at least 4-weeks duration.
Aetna considers Oasis Wound Matrix experimental and investigational for all other indications because its effectiveness for indications other than the ones listed above has not been established.

K. **Graftjacket Regenerative Tissue Matrix**

Aetna considers Graftjacket Regenerative Tissue Matrix medically necessary for treatment of full-thickness diabetic foot ulcers greater than 6-weeks duration that extend through the dermis, but without tendon, muscle, joint capsule or bone exposure.

Aetna considers Graftjacket Regenerative Tissue Matrix experimental and investigational for all other indications (e.g., rotator cuff repair) because its effectiveness for indications other than the one listed above has not been established.

L. **Epicel**

Aetna considers Epicel cultured epidermal autograft medically necessary for members who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%.

Note: Epicel may be used in conjunction with split-thickness autografts, or alone in persons for whom split-thickness autografts may not be an option due to the severity and extent of their burns.

Aetna considers Epicel cultured epidermal autograft experimental and investigational for all other indications because its effectiveness for indications other than the one listed above has not been established.

M. **EpiFix**

Aetna considers EpiFix medically necessary for treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

Aetna considers EpiFix medically necessary for treatment of difficult-to-heal chronic venous or diabetic partial and full-thickness ulcers of the lower extremity that have failed standard wound therapy of at least 4-weeks duration.

Aetna considers EpiFix experimental and investigational for all other indications.
N. **Grafix**

Aetna considers Grafix Core and Grafix Prime medically necessary for treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

Aetna considers Grafix experimental and investigational for all other indications.

O. **DermACELL**

Aetna considers DermACELL medically necessary for treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than 6 weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

Aetna considers DermACELL experimental and investigational for all other indications.

P. **Strattice Reconstructive Tissue Matrix**

Aetna considers Strattice Reconstructive Tissue Matrix medically necessary for use in surgical repair of complex abdominal wall wounds (e.g., due to infection, fascial defect, etc.).

II. **Experimental Wound Care Products**

Aetna considers any of the following treatments for wound care experimental and investigational because there is inadequate evidence in the peer-reviewed medical literature to support their clinical effectiveness:
- ACM Surgical Collagen;
- ACM Surgical Extra Advanced Collagen;
- ACM Surgical Extra Advanced Collagen Powder;
- Adherus Dural Sealant;
- Affinity Human Amniotic Allograft;
- Alloderm for use in tympanoplasty;
- AlloGen;
- AlloGen Liquid;
- AlloMax for indications other than breast reconstruction; for AlloMax for breast reconstruction, see CPB 0185 - Breast Reconstruction Surgery (/100_199/0185.html);
- AlloPatch HD Acellular Dermal Matrix;
- AlloPatch Pliable;
- AlloSkin AC Acellular Dermal Matrix;
- Alloskin RT;
- AlloSource cryopreserved human cadaver skin;
- AlloWrap;
- AlphaGems amniotic tissue allograft;
- AltiPlast;
- AltiPly;
- Ambio Choice amniotic membrane;
- AmnioArmor;
- AmnioBand Particulate;
- AmnioBand Viable;
- AmnioBand SL;
- AmnioCare;
- AmnioCord;
- AmnioExCel;
- AmnioFill Human Placental Tissue Allograft;
- AmnioFix Amnion/Chorion Membrane Allograft;
- AmnioGenix;
- AmnioHeal amniotic membrane;
- AmnioniMatrix Human Amniotic Suspension Allograft;
- AmnioMTM;
- Amnion Bio
- Amnios' acellular liquid amnion;
- AmnioShield;
- AmnioStrip;
- Amnio Wound;
- AmnioWrap2;
- Amniotic fluid injection for wound healing (including corneal wound healing) and for prevention of adhesions after orthopedic surgery;
- Amniox (human embryonic membrane) for tarsel tunnel repair and all other indications;
- AmnyoFluid;
- Apligraf for necrotizing lesions;
- Architect ECM;
- Architect PX;
- Artacent Cord;
- Artacent Wound;
- Artelon (poly[urethane urea] elastomer) for anterior cruciate ligament reconstruction, rotator cuff repair, trapezio-metacarpal joint osteoarthritis and all other indications;
- Arthres GraftRope for acromio-clavicular joint separation reconstruction;
- Arthrex Amnion matrix;
- Arthrex Amnion viscous;
- Arthroflex (FlexGraft);
- Ascent;
- Autologous blood-derived products (e.g., autologous platelet-rich plasma, autologous platelet gel, and autologous platelet-derived growth factors (e.g., Autologel, Procuren, SafeBlood);
- Autologous fat for the treatment of scars;
- Avoterm for improvement of skin scarring;
- AxoBioMembrane;
- Axolotl Ambient;
- Axolotl Cryo;
- Axolotl DualGraft;
- Axolotl Graft;
- BellaCell HD;
- BioDexcel;
- BioDfactor Viable Tissue Matrix;
- BioDfence human amniotic allograft;
- BioDfence Dryflex;
- BioDrx;er;
- BioDmatrix;
- BioDRestore Elemental Tissue Matrix;
- Bio-ConneKt;
- BioFix Amniotic Membrane Allograft;
- BioFix Flow Placental Tissue Matrix Allograft;
- Bionect;
- BioSkin Flow;
- Biostat Biologx fibrin sealant for wound healing and all other indications;
- Biotape reinforcement matrix for soft tissue augmentation and all other indications;
- Biovance Amniotic Membrane Allograft;
- BioWound Membrane;
- BioWound Plus Membrane;
- BioWound XPlus Membrane;
- CellECT (human amnion and amniotic fluid allograft);
- CellerateRX;
- Cellesta Cord;
- Cellesta Duo;
- Cellesta Flowable Amnion;
- Clarix 100;
- Clarix Cord 1K;
- Clarix Flo;
- CollaFix;
- Colla-Pad;
- CollaSorb collagen dressing;
- CollaWound collagen sponge;
- Coll-e-Derm;
- Collexa;
- Conexa reconstructive tissue matrix;
- Cook Medical anal fistula plug;
- CorMatrix ECM Patch for cardiac tissue repair and all other indications;
- Cortiva Allograft Dermis;
- C-QUR biosynthetic mesh;
- CRXa;
- CYGNUS Amnion Patch Allografts;
- Cymetra injectable allograft for wound healing (see also CPB 0253 - Vocal Cord Paralysis/Insufficiency Treatments (0253.html));
- Cytal Burn Matrix;
- Cytal Multilayer Wound Matrix;
- Cytal Wound Matrix;
- Dehydrated human amniotic membrane allograft (e.g., AmnioPro, BioFix and FlowerPatch)
- DermACELL, DermACELL AWM, and DermACELL AWM Porous for indications other than diabetic foot ulcers;
- DermaClose RC continuous external tissue expander for facilitation of wound closure and all other indications;
- Derma-Gide;
- Dermagraft for chronic foot ulcer secondary to necrotizing fasciitis;
- DermaMatrix (formerly InteXen) Porcine Dermal Matrix for wound healing and other indications other than breast reconstruction; for DermaMatrix for breast reconstruction, see CPB 0185 - Breast Reconstruction Surgery (../100_199/0185.html);
- DermaPure;
- DermaSpan Acellular Dermal Matrix;
- Dermavest Human Placental Connective Tissue Matrix;
- DryFlex (human amnion allograft) for shoulder repair and all other indications;
- DuraGen Plus dural regeneration matrix for surgical repair of soft tissue deficiencies and all other indications;
- DuraMatrix;
- DuraSeal;
- Durepair Regeneration Matrix;
- Endoform Dermal Template;
- ENDURAGen;
- Epicord;
- Epidex;
- EpiFix amniotic membrane for indications other than diabetic foot ulcers, venous stasis ulcers of the lower extremities, and ocular surface disorders CPB 0293 - Corneal Graft with Amniotic Membrane Transplantation or (see Limbal Stem Cell Transplantation (0293.html))
- EPIFLO transdermal continuous oxygen therapy for wound healing;
- Equine-derived decellularized collagen products (e.g., OrthADAPT, Unite, and Unite Biomatrix);
- EZ Derm for wound healing and all other indications;
- Evicel fibrin sealant for repair of cerebrospinal fluid leakage and all other indications;
- Excellagen;
- FlexHD acellular dermal matrix for wound healing; for FlexHD for breast reconstruction, see CPB 0185 - Breast Reconstruction Surgery (../100_199/0185.html);
- FloGraft Amniotic Fluid-Derived Allograft;
- FlowerDerm;
- FlowerFlo (FlowerAmnioFlo);
- FlowerPatch (FlowerAMINOPatch);
- Fluid Flow;
- Fluid GF;
- Fortaderm;
- Fortaderm Antimicrobial;
- Fortiva Porcine Dermis;
- Gammagraft skin substitute;
- Genesis Amniotic Membrane;
- GORE BIO-A Fistula Plug;
- Grafix Core, Grafix PL Core, Grafix Prime and Grafix PL Prime for indications other than diabetic foot ulcers;
- Grafix cryo-preserved placental membrane;
- GraftJacket RTM;
- GraftJacket Xpress injectable allograft for wound healing and all other indications;
- Guardian;
- Helicoll;
- Hyalomatrix (hMatrix ADM) Tissue Reconstruction Matrix;
- HydroFix;
- Inforce;
- Integra Wound Matrix and Integra Flowable Wound Matrix for the management of wounds including partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, second-degree burns, skin tears) and draining wounds and all other indications;
- InteguPly;
- Interfyl Human Connective Tissue Matrix;
- Keramatrix;
- Kerasorb Wound Matrix;
- Kerox Flowable Wound Matrix;
- LiquidGen;
- MariGen;
- Matriderm;
- Matrion;
- MatriStem Burn Matrix;
- MatriStem Micro Matrix;
- MatriStem Wound Matrix;
- Matrix HD Allograft;
- Matrix PSM;
- MediHoney;
- Mediskin;
- Medeor;
Membrane Graft;
Membrane Wrap;
MemoDerm;
Menaflex Collagen Meniscus Implant (see CPB 0786 - Menaflex (../700_799/0786.html));
Merigen wound dressing
Meso BioMatrix;
MicroMatrix;
MIRODERM;
MyOwn Skin
Neoform Dermis for wound healing; for NeoForm for breast reconstruction, see CPB 0185 - Breast Reconstruction Surgery (../100_199/0185.html);
NeoPatch chorioamniotic membrane allograft;
Neox Cord 1K;
Neox 100;
Neox Flo;
Neuragen;
Neuroflex;
Novachor;
Novafix;
NuCel liquid wound covering;
NuShield, NuShield Orthopaedics, and NuShield Spine;
Oasis burn matrix for wound healing and all other indications;
Oasis Tri-Layer Matrix;
Ologen Collagen Matrix;
Omega3 Wound;
OrthADAPT Bioimplant (type I collagen scaffold) for tendon repair and all other indications;
OrthoFlo;
OsseoGuard;
Ovation;
PalinGen Flow;
PalinGen Hydromembrane;
PalinGen Membrane;
Palingen SportFlow;
PalinGen XPlus Hydromembrane;
PalinGen XPlus Membrane;
Parietex Composite (PCO) Mesh for the treatment of genito-urinary (e.g., uterine or vaginal vault) prolapse;
- Peri-Guard Repair Patch;
- Peri-Strips Dry, and Peri-Strips Dry with Veritas Collagen Matrix;
- Permacol Biologic Implant for soft tissue surgical repairs, including hernia repair, muscle flap reinforcement, rectal prolapse (including intussusception), rectocele repair, abdominal wall defects, plastic and reconstructive surgery, complex abdominal wall repair and all other indications;
- Placental tissue matrix allograft;
- Plurivest Human Placental Connective Tissue Matrix;
- Porcine-derived decellularized collagen products (e.g., Collamend, Cuffpatch, Pelvicol, and Pelvisoft);
- Porcine-derived decellularized fetal skin products (e.g., Mediskin);
- Porcine-derived polypropylene composite wound dressing (e.g., Avaulta Plus);
- PriMatrix Dermal Repair Scaffold;
- ProgenaMatrix;
- ProMatrX ACF;
- Promogran Matrix;
- PTFE felt;
- Puracol Collagen Wound Dressing;
- Puracol Plus Collagen Wound Dressing;
- PuraPly Antimicrobial Wound Matrix (PuraPly AM);
- PuraPly Wound Matrix (PuraPly);
- Puros Dermis;
- Radiofrequency stimulation devices (e.g., Provant Wound Closure System, MicroVas Vascular Treatment System) for wound healing;
- Renuva;
- Repliform;
- Repriza;
- Restorigin Amnion Patch;
- Restorigin Amniotic Fluid Therapy (AFT);
- Restrata;
- Revita;
- Revitalon;
- Seamguard;
- SkinTE for the treatment of burns;
- Silver-coated wound dressings (e.g., Acticoat, Actisorb, Aquacel Ag, and Silversorb) for wound healing and all other indications;
- Solana allograft;
- Sonafine wound dressing;
- SportMatrix;
- SportMesh;
- SteriShield II dual layer amnion patch;
- Strattice Reconstructive Tissue Matrix for wound healing; for Strattice for breast reconstruction, see CPB 0185 - Breast Reconstruction Surgery (../100_199/0185.html);
- Stravix;
- Stravix PL;
- Supraphel;
- SureDerm;
- SurgiCORD;
- surgiGRAFT;
- SurgiGRAFT-DUAL;
- SurgiMend for plastic and reconstructive surgery, muscle flap reinforcement, hernia repair, reinforcement of soft tissues repaired by sutures or suture anchors, during tendon repair surgery (including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons), and all other wound care indications; for SurgiMend for breast reconstruction, see CPB 0185 - Breast Reconstruction Surgery (../100_199/0185.html);
- Surgisis (including Surgisis AFP Anal Fistula Plug, Surgisis Gold Hernia Repair Grafts, and Surgisis Biodesign) (see CPB 0411 - Bone and Tendon Graft Substitutes and Adjuncts (../400_499/0411.html)
- SurGraft;
- Talymed;
- TenoGlide tendon protector sheet (Tendon Wrap™ tendon protector) for the management and protection of tendon injuries and all other indications;
- TenSIX Acellular Dermal Matrix for tendon repair and all other indications;
- TheraForm Standard/Sheet Absorbable Collagen Membrane;
- TheraSkin;
- TissueMend for the repair or reinforcement of soft tissues repaired by sutures or suture anchors during tendon repair surgery, including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons, and all other indications. (Note: Use of TissueMend is considered integral to the surgery and not separately reimbursed);
- Tornier BioFiber Absorbable Biological Scaffold, and Tornier Collagen Coated BioFiber Scaffold;
- Truskin;
- Unite Biomatrix;
- Vaso Shield;
- Veritas Collagen Matrix for use as an implant in the surgical repair of soft tissue deficiencies and all other indications;
- VersaWrap Tendon Protector for the management and protection of tendon injuries and all other indications;
- Viaflow / Viaflow C flowable placental tissue matrices;
- Vitagel surgical hemostat for wound healing and all other indications;
- WoundEx Flow;
- WoundEx Membrane;
- WoundFix Membrane;
- WoundFix Plus Membrane;
- WoundFix XPlus Membrane;
- X-Repair;
- XCM Biologic Tissue Matrix;
- Xelma;
- XenMatrix;
- Xwrap Amniotic Membrane-Derived Allograft;
- XWrap Dry or Hydro Plus.

**Note:** The use of Tisseel is considered integral to the surgery and is not separately reimbursed.

For nerve wraps or cuffs (e.g., Avance nerve graft, Axogen,2 nerve wrap, Integra Neural Wrap, NeuroMatrix collagen nerve cuff, and NeuroMend collagen nerve wrap), see CPB 0416 - Nerve Grafting: Selected Indications (../400_499/0416.html).

For Aetna's policy on systemic and topical hyperbaric oxygen, see CPB 0172 - Hyperbaric Oxygen Therapy (HBOT) (../100_199/0172.html).

See also CPB 0334 - Negative Pressure Wound Therapy (../300_399/0334.html).

**Background**

Bioengineered skin and soft tissue substitutes are cellular or acellular matrices and can be derived from human tissue (autologous or allogeneic), nonhuman tissue (xenographic), synthetic materials or a composite of these materials. Specific manufacturing process vary by company, but generally involve seeding selected cells
onto a matrix, where they receive proteins and growth factors necessary for them to multiply and develop into the desired tissue. The tissue may be used for a variety of conditions and procedures including breast reconstruction, treatment of severe burns, surgical wounds and healing of lower extremity ulcers, such as diabetic and/or venous ulcers.

**Apligraf (Graftskin)**

In recent years, skin grafting has evolved from the initial autograft and allograft preparations to biosynthetic and tissue-engineered human skin equivalents (HSE). Apligraf (graftskin) (Organogenesis, Canton, MA), also referred to human skin equivalent, is a living, cell-based, bilayered skin construct. Like human skin, Apligraf has 2 primary layers, including an outer, epidermal layer made of living human keratinocytes, the most common cell type of the human epidermis, to replicate the structure of the human epidermis. The human keratinocytes and fibroblasts are derived from neonatal foreskins. The dermal layer of Apligraf consists of living human fibroblasts and bovine type 1 collagen, the most common cell type in the human dermis, to create a dermis-like structure that produces additional matrix proteins. Proponents state that Apligraf stimulates the patient's own cells to regenerate tissue and heal the wound through mechanisms that include the secretion of growth factors, cytokines, and matrix proteins (Snyder, et al., 2012). Apligraf does not contain melanocytes, Landgerhans’ cells, macrophages, lymphocytes, or tissue structures such as blood vessels, hair follicles, and sweat glands.

Apligraf has has received a premarket approval (PMA) by the U.S. Food and Drug Administration (FDA) in 1998 for treatment of venous leg ulcers and in 2001 for treatment of diabetic ulcers. Apligraft has been approved for marketing under a premarket approval for "use with standard therapeutic compression for the treatment of noninfected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy."

Multiple supplemental approvals have been added since the first approval, including an indication for treating diabetic foot ulcers. Several of the supplements involve approval of the use of new human keratinocyte or fibroblast cell strains in the manufacture of Apligraf (Snyder, et al., 2012). Venous ulceration, a relatively common manifestation of venous hypertension, is often refractory to conservative treatment and difficult to treat. Human skin equivalents appeared to promote wound healing in 3 ways: (i) apparent graft "take"; (ii) temporary wound closure (persistence of HSE with subsequent wound re-epithelialization from wound margins); and (iii) stimulation of host healing without temporary persistence by acting as a biologic dressing.
Rice et al (2015) used Medicare claims data to assess the real-world medical services utilization and associated costs of Medicare patients with diabetic foot ulcers (DFUs) treated with Apligraf or Dermagraft (human fibroblast-derived dermal substitute (HFDS)) compared with those receiving conventional care (CC). DFU patients were selected from Medicare de-identified administrative claims using ICD-9-CM codes. The analysis followed an 'intent-to-treat' design, with cohorts assigned based on use of (1) BLCC, (2) HFDS, or (3) CC (i.e., ≥1 claim for a DFU-related treatment procedure or podiatrist visit and no evidence of skin substitute use) for treatment of DFU in 2006-2012. Propensity score models were used to separately match BLCC and HFDS patients to CC patients with similar baseline demographics, wound severity, and physician experience measures. Medical resource use, lower-limb amputation rates, and total healthcare costs (2012 USD; from payer perspective) during the 18 months following treatment initiation were compared among the resulting matched samples. Data for 502 matched BLCC-CC patient pairs and 222 matched HFDS-CC patient pairs were analyzed. Increased costs associated with outpatient service utilization relative to matched CC patients were offset by lower amputation rates (-27.6% BLCC, -22.2% HFDS), fewer days hospitalized (-33.3% BLCC, -42.4% HFDS), and fewer emergency department visits (-32.3% BLCC, -25.7% HFDS) among BLCC/HFDS patients. Consequently, BLCC and HFDS patients had per-patient average healthcare costs during the 18-month follow-up period that were lower than their respective matched CC counterparts (-$5253 BLCC, -$6991 HFDS). This study is limited by the fact that it is based upon administrative claims data. The authors stated that its findings relied on accuracy of diagnosis and procedure codes contained in the claims data, and did not account for outcomes and costs beyond 18 months after treatment initiation.

Apligraf was shown in clinical trials to heal even longstanding (greater than 1 year's duration) venous leg ulcers more effectively and faster than compression therapy alone. The results of controlled, multi-center studies indicate that HSE interacts with the patient's own cells, responds to individual wound characteristics, and promotes healing. Further studies are underway to investigate its use for the treatment of pressure sores, dermatological surgery wounds and burns. At this time, there is insufficient information to extend coverage for the use of Apligraf in the treatment of these conditions.

Dermagraft

Dermagraft is a wound care product manufactured from human fibroblast cells derived from newborn foreskin tissue. The fibroblasts are cultured on a bioabsorbable polyglactin mesh. Proteins and growth factors are secreted during the culture period and generate a three dimensional human dermis.

Dermagraft (Advanced BioHealing, Inc., La Jolla, CA) has been approved by the FDA for repair of diabetic foot ulcers. Dermagraft is composed of cryopreserved human-derived fibroblasts and collagen applied to a bioabsorbable mesh (similar to the material used in strong bioabsorbable sutures). The fibroblasts are obtained from human newborn foreskin tissue. During the Dermagraft manufacturing process, the human fibroblasts are seeded onto a bioabsorbable polyglactin mesh scaffold. The fibroblasts proliferate to fill the interstices of this scaffold and secrete human dermal collagen, matrix proteins, growth factors and cytokines, to create a 3-dimensional human dermal substitute containing metabolically active, living cells. Dermagraft does not contain macrophages, lymphocytes, blood vessels, or hair follicles. It comes frozen as a single sheet (2 by 3 inches) for a single application.

In September 2001, FDA approved Dermagraft for marketing under the premarket approval (PMA) process for “use in the treatment of full-thickness diabetic foot ulcers greater than six weeks’ duration which extend through the dermis, but without tendon, muscle, joint capsule or bone exposure. Dermagraft should be used in conjunction with standard wound care regimens and in patients that have adequate blood supply to the involved foot.”

In support of FDA approval, a 12-week multi-center clinical study was performed involving 314 patients with chronic diabetic ulcers who were randomized to Dermagraft or control. Patients in the Dermagraft group received up to 8 applications of Dermagraft over the course of the 12-week study. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. By week 12, the median percent wound closure for the Dermagraft group was 91% compared to 78% for the control group. The study also showed that ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. Patients treated with Dermagraft were 1.7 times more likely to close than control patients at any given time during the study. No serious adverse events were attributed to Dermagraft. There was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft treated group. Of the patients enrolled, 10.4% of the Dermagraft patients developed an infection while 17.9% of the Control patients developed ulcer infection. Overall, 19% of the Dermagraft group developed infection, cellulitis, or osteomyelitis. In the control group, 32.5% patients developed the same adverse events.

Frykberg et al (2015) reported on a study aimed at evaluating the incidence of amputations/bone resections in a randomized controlled trial comparing human fibroblast-derived dermal substitute plus conventional care with conventional care alone for the treatment of patients with diabetic foot ulcers (DFUs) greater than 6 weeks duration. Ulcer-related amputation/bone resection data were extracted from data on all
adverse events reported for the intent-to-treat population (N = 314), and amputations were categorized by type: below the knee, Syme, Chopart, transmetatarsal, ray, toe, or partial toe. Data were analyzed retrospectively for the incidence of amputation/bone resection by treatment. The incidence of amputation/bone resection in the study was 8.9% (28/314) overall, 5.5% (9/163) for patients receiving human fibroblast-derived dermal substitute, and 12.6% (19/151) for patients receiving conventional care (P = .031). Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection. The investigators concluded that there were significantly fewer amputations/bone resections in patients who received human fibroblast-derived dermal substitute versus conventional care, likely related to the lower incidence of infection adverse events observed in the human fibroblast-derived dermal substitute treatment group.

Dermagraft has also been approved by the FDA for use in the treatment of wounds related to dystrophic epidermolysis bullosa. Dystrophic epidermolysis bullosa is a blistering, hereditary skin condition, in which the filaments that anchor the epidermis to the underlying dermis are either absent or do not function.

Harding, et al. (2013) reported on an open-label, prospective, multicenter, randomized controlled study to evaluate the efficacy and safety of human fibroblast-derived dermal substitute (HFDS) plus four-layer compression therapy compared with compression therapy alone in the treatment of venous leg ulcers. The primary outcome variable was the proportion of patients with completely healed study ulcers by 12 weeks. The number healed was further summarized by ulcer duration and baseline ulcer size. Sixty-four (34%) of 186 patients in the HFDS group experienced healing by week 12 compared with 56 (31%) of 180 patients in the control group (P = 0.235). For ulcers ≤ 12 months duration, 49 (52%) of 94 patients in the HFDS group versus 36 (37%) of 97 patients in the control group healed at 12 weeks (P = 0.029). For ulcers ≤ 10 cm(2), complete healing at week 12 was observed in 55 (47%) of 117 patients in the HFDS group compared with 47 (39%) of 120 patients in the control group (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.

A draft assessment of wound care products prepared for AHRQ judged this randomized controlled study by Harding, et al. (2013) to be at low risk of bias.

In May 2006, Advanced BioHealing purchased the global rights to Dermagraft from Smith & Nephew.

TransCyte

According to the manufacturer, Organogenesis Inc., TransCyte is a human fibroblast-derived temporary wound cover consisting of polymer membrane and donated neonatal human fibroblast cells cultured under aseptic conditions in vitro on a nylon mesh (CMS, 2017). As fibroblasts proliferate within the nylon mesh, they secrete human dermal collagen, matrix proteins and growth factors. Following freezing, no cellular metabolic activity remains; however, the tissue matrix and bound growth factors are left intact. TransCyte provides a temporary protective barrier for the wound. TransCyte is intended for use as a temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft placement. TransCyte is also intended for the treatment of mid-dermal to indeterminate depth burn wounds that typically require debridement and that may be expected to heal without autografting. TransCyte is applied to a wound using sutures or other fixation method based on the size of the wound being treated. It is supplied in a cassette containing two aseptically processed sheets, each approximately 5 inches by 7.5 inches.

TransCyte was granted premarket approval (PMA) by the FDA in 1997 for "for use as a temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft placement." TransCyte was not indicated for chronic wounds. TransCyte consists of human dermal fibroblasts grown on nylon mesh, combined with a synthetic epidermal layer. TransCyte can be used as a temporary covering over full thickness and some partial-thickness burns until autografting is possible. It can also be used as a temporary covering for some burn wounds that heal without autografting. TransCyte is packaged and shipped in a cryo-preserved state to burn treatment centers. The surgeon then thaws the product and stretches it over a burn site. In about 7 to 14 days, the TransCyte starts peeling off, and the surgeon trims it away as it peels.

Orcel

Orcel is a bilayered skin substitute that uses human epidermal keratinocytes and dermal fibroblasts that are cultured into two separate layers on a bovine collagen sponge. As healing occurs at the site of the wound, the OrCel dissolves and the patient's own skin cells then replace the OrCel cells to create a new skin surface. Orcel is indicated for dystrophic epidermolysis bullosa in children; andr for full thickness (3rd degree) and partial thickness (2nd degree) burns.

Orcel is an absorbable bilayered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. OrCel (Forticell Bioscience, Inc., formerly Ortec International, Inc., New York, NY) is composed of normal, human, allogeneic, epidermal keratinocytes and dermal fibroblasts (Snyder, et al., 2012). The cells are cultured in two
separate layers into a type I bovine collagen sponge. Neonatal human fibroblasts and keratinocytes are obtained from the same donor. According to the manufacturer, the matrix is designed to provide a structure for host cell invasion along with a mix of cytokines and growth factors. The matrix is absorbed as the wound heals. Because of the extensive culturing process, the cells do not express the antigens responsible for rejection. The cells produce growth factors. When this dressing is applied to the open wound created where the patient's healthy skin was removed, the patient's own skin cells migrate into the dressing and take hold, along with the cultured cells, as healing commences. The dressing is gradually absorbed during the healing process.

Orcel was approved by the FDA under its humanitarian device exemption (HDE) in February 2001 for healing donor site wounds in burn victims, and for use in patients with recessive dystrophic epidermolysis bullosa (RDEB) undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites (Snyder, et al., 2012). Composite Cultured Skin (Ortec International, Inc., New York, NY) is "indicated for use in patients with mitten hand deformities due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as an adjunct to standard autograft procedures (i.e., skin grafts and flaps) for covering wounds and donor sites created after the surgical release of hand contractures (i.e., "mitten" hand deformities)." OrCel has also received PMA approval for treating fresh, clean, split-thickness, donor site wounds in burn patients and may, therefore, be used by physicians off-label on chronic wounds. A PMA application with FDA has been filed for treating venous leg ulcers. Studies will test OrCel in treating diabetic foot ulcers. The manufacturer indicates that it will promote OrCel for treating chronic and acute wounds. Forticell Bioscience, Inc., is the former Ortec International, Inc.

Santema et al (2016) conducted a Cochrane systematic evidence review to determine the benefits and harms of skin grafting and tissue replacement, including Orcel, for treating foot ulcers in people with diabetes. In April 2015 the authors searched: The Cochrane Wounds Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid EMBASE and EBSCO CINAHL. We also searched clinical trial registries to identify ongoing studies. We did not apply restrictions to language, date of publication or study setting. The investigators searched for randomized clinical trials (RCTs) of skin grafts or tissue replacements for treating foot ulcers in people with diabetes. Two review authors independently extracted data and assessed the quality of the included studies. The authors included seventeen studies with a total of 1655 randomized participants in this review. The authors reported that risk of bias was variable among studies. Blinding of participants, personnel and outcome assessment was not performed in most trials, and this lack of a blinded outcome assessor may have
caused detection bias when ulcer healing was assessed. The authors found that nearly all studies (15/17) reported industry involvement; at least one of the authors was connected to a commercial organization or the study was funded by a commercial organization. In addition, the funnel plot for assessing risk of bias appeared to be asymmetrical; suggesting that small studies with 'negative' results are less likely to be published. Thirteen of the studies included in this review compared a skin graft or tissue replacement with standard care. Four studies compared two grafts or tissue replacements with each other. When the authors pooled the results of all the individual studies, the skin grafts and tissue replacement products that were used in the trials increased the healing rate of foot ulcers in patients with diabetes compared to standard care (risk ratio (RR) 1.55, 95% confidence interval (CI) 1.30 to 1.85, low quality of evidence). However, the strength of effect was variable depending on the specific product that was used (e.g. OrCel RR 1.75, 95% CI 0.61 to 5.05, and EpiFix RR 11.08, 95% CI 1.69 to 72.82). The authors found that, based on the four included studies that directly compared two products, no specific type of skin graft or tissue replacement showed a superior effect on ulcer healing over another type of skin graft or tissue replacement. Sixteen of the included studies reported on adverse events in various ways. No study reported a statistically significant difference in the occurrence of adverse events between the intervention and the control group. Only two of the included studies reported on total incidence of lower limb amputations. The authors found fewer amputations in the experimental group compared with the standard care group when they pooled the results of these two studies, although the absolute risk reduction for amputation was small (RR 0.43, 95% CI 0.23 to 0.81; risk difference (RD) -0.06, 95% CI -0.10 to -0.01, very low quality of evidence). The authors concluded that, based on the studies included in this review, the overall therapeutic effect of skin grafts and tissue replacements used in conjunction with standard care shows an increase in the healing rate of foot ulcers and slightly fewer amputations in people with diabetes compared with standard care alone. However, the available data was insufficient for the authors to draw conclusions on the effectiveness of different types of skin grafts or tissue replacement therapies. In addition, evidence of long term effectiveness is lacking and cost-effectiveness is uncertain.

**Autologous Blood Derived Products:** Autologous Platelet-Rich Plasma, Autologous Platelet Gel, and Autologous Platelet-Derived Growth Factors (e.g., Procuren)

Growth factors that are derived from platelets assist in the process of blood vessel formation (angiogenesis) and can be obtained either by using recombinant DNA technology or through centrifuged autologous blood. Autologous growth factors, including autologous platelet-derived growth factors (PDGF), autologous platelet concentrate (APC) and autologous platelet gel (APG), also known as platelet-rich plasma (PRP) or "buffy coat," are harvested from a patient's own (autologous) blood. APC and APG are topically applied to wounds or systemically administered to purportedly accelerate...
healing and reduce complications of chronic nonhealing wounds that fail to respond to conventional methods of wound treatment or used as an adjunct (addition) to surgery to promote hemostasis and reduce wound complications. Examples of autologous blood derived products include, but may not be limited to: Autologel; Procuren; SafeBlood; and Vitagel.

Procuren is a platelet-derived growth factor suggested for use in the management of chronic non-healing wounds. The Agency for Health Care Policy and Research’s Clinical Practice Guideline Treatment of Pressure Ulcers concluded that the effectiveness of growth factors for this indication has not been sufficiently established to warrant recommendation for use. In 1992, the Centers for Medicare and Medicaid Services (CMS) issued a national non-coverage determination for platelet-derived wound healing formulas intended to treat patients with chronic, non-healing wounds. This decision was based on a lack of sufficient published data to determine safety and efficacy, and a Public Health Service technology assessment. A CMS Decision Memorandum (2003) concluded that there is insufficient evidence of the effectiveness of autologous platelet rich plasma (PRP) or autologous platelet-derived growth factor (PDGF) in improving healing in chronic non-healing cutaneous wounds. In a second reconsideration, CMS concluded there is insufficient evidence of effectiveness of autologous PRP for the treatment of chronic non-healing cutaneous wounds or for acute surgical wounds when the autologous PRP is applied directly to the closed incision or dehiscent wounds (CMS, 2007).

Silver-Coated Wound Dressings (Acticoat, Actisorb)

Silver-coated wound dressings produce sustained release of ionic silver to decrease the incidence of infection. As the dressing material accumulates fluid, silver ions are released from the dressing into the wound environment. Silver-coating technology was developed to prevent wound adhesion, limit nosocomial infection, control bacterial growth, and facilitate burn wound care through a silver-coated dressing material. Silver-coated wound dressings such as Acticoat and Actisorb offer new forms of dressing for burn wounds, but require further investigation. Well-controlled clinical trials are needed comparing clinical outcomes of silver-coated wound dressings with standard wound dressings in patients in various phases of burn wound care. An evidence review prepared for the Cochrane Collaboration (Bergin et al., 2006) concluded: "Despite the widespread use of dressings and topical agents containing silver for the treatment of diabetic foot ulcers, no randomised trials or controlled clinical trials exist that evaluate their clinical effectiveness. Trials are needed to determine clinical and cost-effectiveness and long-term outcomes including adverse events."
The Provant Wound Closure System

The Provant Wound Closure System (Regenesis Biomedical Inc., Scottsdale, AZ) uses a low-level radiofrequency signal that proponents state accelerates healing of chronic wounds by stimulating the production of endogenous growth factors and the proliferation of fibroblasts and epithelial cells, in a process the manufacturer has labeled "Cell Proliferation Induction" or CPI. The Provant Wound Closure System (Regenesis was cleared by the FDA as a wound healing device based on a 510(k) premarket notification. Treatment with the Provant System is usually administered for 30 mins right through dressing twice-daily. However, there is insufficient clinical evidence to support its effectiveness. Available evidence on CPI has focused mainly on the effects of low-level radiofrequency signals on growth factors and cell proliferation in vitro. Peer-reviewed literature is limited to a small short-term randomized controlled pilot study which found that the Provant system accelerated closure of pressure wounds (Ritz et al, 2002). This finding needs to be verified by larger multicenter studies. Furthermore, studies would need to assess if CPI adds to the effectiveness of standard methods of chronic wound management.

MicroVas

MicroVas (MicroVas Technologies, Inc., Tulsa OK) is a radiofrequency stimulation device used to increase circulation to an extremity or body part in order to speed wound healing. According to the manufacturer, MicroVas is indicated for the treatment of stage III and IV pressure ulcers. The manufacturer states that the MicroVas is also indicated for the treatment of chronic and non-healing diabetic and venous ulcers, treatment of ischemic rest pain, muscle disuse atrophy, diabetic neuropathy, and paresthesia relating to neuropathy. However, there is a lack of scientific evidence to support its effectiveness for these indications.

A meta-analysis concluded that there is no reliable evidence of benefit of electromagnetic therapy generally in healing of pressure sores (Olyaee Manesh et al, 2006) or venous leg ulcers (Ravaghi et al, 2006). Additionally, a systemic review of the literature on treatment of pressure sores concluded that the effectiveness of electrotherapy on pressure sores is unknown (Cullum and Petherick, 2007).

Graftjacket Tissue Matrix

Graftjacket tissue matrix is a wound care product derived from cadaveric skin, which undergoes a process that removes the epidermis and dermal cells. The human dermal tissue is preserved, which purportedly reduces the rejection response and allows the body to accept the matrix. Over time, the body’s natural repair process supposedly

converts the matrix into living tissue. Graftjacket tissue matrix is indicated for full-thickness diabetic foot ulcers greater than three week duration that extend through the dermis, but without tendon, muscle, joint capsule or bone exposure.

Graftjacket tissue matrix (Wright Medical Technology, Inc, Arlington, TN) is an acellular regenerative tissue matrix that is designed to provide a scaffold for wound repair. Donated human tissue is treated to remove the epidermis and cellular components, but it retains collagen, elastin, and proteoglycans, and the internal matrix of the dermis remains intact (Snyder, et al., 2012). The tissue is then cryogenically preserved. The company states that removal of the cellular component reduces rejection, retention of dermal proteins allows for revascularization and cellular repopulation, and the preserved tissue matrix reduces inflammation.

In a pilot, prospective, randomized study (n = 40), Brigido et al (2004) ascertained the effectiveness of this tissue product in wound repairing of diabetic foot ulcers compared with conventional treatment. Only a single administration of the tissue matrix was required. After 1 month of treatment, preliminary results showed that this novel tissue matrix promoted faster healing at a statistically significant rate over conventional treatment. Results of this study are promising, but they need to be verified by further investigation with larger sample sizes and longer follow-ups.

Graftjacket Xpress Flowable Soft-Tissue Scaffold is a micronized (finely ground) decellularized soft tissue scaffold indicated for the repair or replacement of damaged or inadequate integumental tissue, specifically deep, dermal wounds that exhibit tunneling, and extension from the wound base that may extend deep into the tendon and bone (CMS, 2006). Graftjacket Xpress is a soft tissue graft (reconstituted as a "gel"), which is comprised solely of human dermal tissue, including its native protein and collagen structure and essential biochemical composition. The re-hydrated skin substitute scaffold is placed into the tunnels or tracts, and is intended to produce the same or superior clinical outcomes with a minimally invasive procedure. There is a lack of peer-reviewed published medical literature on the effectiveness and safety of the Graftjacket Xpress.

Lanier et al (2010) retrospectively identified tissue expander/implant breast reconstructions by 5 surgeons at a single institution from 2005 to 2008 and divided into 2 cohorts: (i) use of acellular dermal matrix (ADM) (n = 75) versus (ii) standard submuscular placement (n = 52). The ADM group had a statistically significant higher rate of infection (28.9 % versus 12.0 %, p = 0.022), re-operation (25.0 % versus 8.0 %, p = 0.011), expander explantation (19.2 % versus 5.3 %, p = 0.020), and overall complications (46.2 % versus 22.7 %, p = 0.007). When stratifying by breast size, a higher complication rate was not observed with the use of ADM in breasts less than 600.
g, whereas ADM use in breasts larger than 600 g was associated with a statistically significant higher rate of infection when controlling for the occurrence of skin necrosis. The ADM cohort had a significantly higher mean initial tissue expander fill volume (256 ml versus 74 ml, p < 0.001) and a significantly higher mean initial tissue expander fill ratio (49 % versus 17 %, p < 0.001). The authors concluded that further work is needed to define the ideal patient population for ADM use in tissue expander/implant breast reconstruction.

Spear et al (2011) examined the use of ADM for correction or prevention of implant-associated breast deformities. Patients who underwent primary aesthetic breast surgery or secondary aesthetic or reconstructive breast surgery using ADM and implants between November of 2003 and October of 2009 were reviewed retrospectively. Patient demographics, indications for ADM, and ADM type and inset pattern were identified. Pre-operative and post-operative photographs, success or failure of the procedure, complications, and need for related or unrelated revision surgery were recorded. A total of 52 patients had ADM placed alongside 77 breast prostheses, with a mean follow-up of 8.6 months (range of 0.4 to 30.4 months). Indications included prevention of implant bottoming-out (n = 6), treatment of malposition (n = 32), rippling (n = 20), capsular contracture (n = 16), and skin flap deficiency (n = 16). Seventy-four breasts (96.1 %) were managed successfully with ADM. Three failures consisted of 1 breast with bottoming-out following treatment of capsular contracture, 1 breast with major infection requiring device explantation, and 1 breast with recurrent rippling. There was a 9.1 % total complication rate, consisting of 3 mild infections, 1 major infection necessitating explantation, 1 hematoma, and 1 seroma. The authors concluded that based on this experience in 77 breasts, ADM has shown promise in treating and preventing capsular contracture, rippling, implant malposition, and soft-tissue thinning.

Williams and Holewinski (2015) reported on a small study of a limb preservation strategy that includes application of Graftjacket Regenerative Tissue Matrix. Medical history, physical examination and full wound assessment were completed for all patients. Systemic antibiotics and appropriate offloading were prescribed as needed. Wounds were debrided to create a bleeding bone and/or wound base for HADWM (Graftjacket regenerative tissue matrix, Wright Medical Technology, Inc., licensed by KCI, an Acelity company, San Antonio, TX). Healing progress was monitored over four weeks with weekly postoperative visits. ‘Healed’ was defined as full epithelialisation without drainage. The investigators reported that lower extremity ulcers, 16 in 13 patients, were treated with HADWM between May 2004 and July 2013. The median patient age was 76 years (range: 38-90). The average number of comorbidities was three per patient, while 6 (46%) patients had ≥4 comorbidities. Diabetes mellitus (92%) and peripheral vascular disease (77%) were the two most common. All 16 (100%) wounds healed without

complications. There were no recurrences in the 11 wounds of the nine patients available for follow-up. Of these patients two had previously advised to receive major leg amputations retained functional limbs.

Reyzelman and Bazarov (2015) reported on a review of the clinical literature to estimate the comparative effectiveness Graftjacket regenerative tissue matrix (HADWM) versus standard care in healing diabetic foot ulcers (DFUs). Outcomes from three prospective, controlled clinical trials, which included 154 patients with DFUs, were pooled. A comparative analysis revealed a statistically significant reduction in mean wound healing time, 1.7 weeks, as well as a nearly four-fold improvement in the chance of healing ulcers treated with HADWM versus moist wound-care. The authors concluded that these pooled results suggest that HADWM may improve healing outcomes for these difficult-to-heal lower extremity wounds.

**Graftjacket Regenerative Tissue Matrix for Rotator Cuff Repair**

In a prospective, multi-center, randomized study, Barber et al (2012) evaluated the safety and effectiveness of arthroscopic acellular human dermal matrix augmentation of large rotator cuff tear repairs. Patients undergoing arthroscopic repair of 2-tendon rotator cuff tears measuring greater than 3 cm were randomized by sealed envelopes opened at the time of surgery to arthroscopic single-row rotator cuff repair with Graftjacket acellular human dermal matrix augmentation (group 1) or without augmentation (group 2). Pre-operative and post-operative functional outcome assessments were obtained by use of the American Shoulder and Elbow Surgeons (ASES), Constant, and University of California, Los Angeles scales. Gadolinium-enhanced magnetic resonance imaging (MRI) evaluation of these repairs was obtained at a mean of 14.5 months (range of 12 to 24 months). Adverse events were recorded. There were 22 patients in group 1 and 20 in group 2 with a mean age of 56 years. The mean follow-up was 24 months (range of 12 to 38 months). The ASES score improved from 48.5 to 98.9 in group 1 and from 46.0 to 94.8 in group 2. The scores in group 1 were statistically better than those in group 2 (p = 0.035). The Constant score improved from 41.0 to 91.9 in group 1 and from 45.8 to 85.3 in group 2. The scores in group 1 were statistically better than those in group 2 (p = 0.008). The University of California, Los Angeles score improved from 13.3 to 28.2 in group 1 and from 15.9 to 28.3 in group 2 (p = 0.43). Gadolinium-enhanced MRI scans showed intact cuffs in 85% of repairs in group 1 and 40% in group 2 (p < 0.01). No adverse events were attributed to the presence of the matrix grafts. The authors concluded that acellular human dermal matrix augmentation of large (greater than 3 cm) rotator cuff tears involving 2 tendons showed better ASES and Constant scores and more frequent intact cuffs as determined by gadolinium-enhanced MRI. Intact repairs were found in 85% of the augmented group and 40% of the non-augmented group (p < 0.01). No adverse events related to the acellular human dermal matrix were observed.
(Level II, lesser-quality randomized controlled trial). This was a small study (n = 22) with short-term follow-up (mean follow-up was 24 months). These findings need to be validated by well-designed studies.


The University of New South Wales (Australia)’s clinical practice guidelines on “The Management of Rotator Cuff Syndrome in the Workplace” (2013) had no recommendations for the use of acellular human dermal matrix grafts/Graftjacket.

PriMatrix Acellular Dermal Tissue Matrix

PriMatrix Acellular Dermal Tissue Matrix is an acellular collagen dermal tissue matrix derived from fetal bovine skin. Primatrix creates a scaffold capable of being integrated, remodeled and eventually replaced by functional host tissue.

PriMatrix acellular dermal tissue matrix, formerly known as DressSkin (TEI Biosciences Inc., Boston, MA) was cleared by the FDA via the 510(k) process. PriMatrix is used for the management of wounds including second degree burns, draining, surgical, and trauma wounds, as well as pressure, diabetic, and venous ulcers.

Primatrix is an animal-derived, extracellular matrix dermal substitute intended to act as a scaffold to allow cell and vascular penetration (Snyder et al, 2012). According to the manufacturer, TEI biological matrix products are derived from fetal bovine dermis collagen. In producing this product, the epidermis, hair, muscle, and fascia are removed. The dermis is then treated to remove cells and infectious agents while preserving biological properties and structures. The product is converted to sheets, freeze dried, and sterilized. When applied to a wound, the product product may assist in the wound healing process.

Primatrix Dermal Repair Scaffold was cleared for marketing under the 510(k) process and “is intended for the management of wounds that include: partial and full thickness wounds; pressure, diabetic, and venous ulcers; second degree burns; surgical wounds-donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence; trauma wounds-abrasions, lacerations, and skin tears; tunneled/undermined wounds; draining wounds.” However, there is insufficient scientific evidence regarding the effectiveness of PriMatrix acellular dermal tissue matrix for wound healing. Available evidence is comprised primarily of small, retrospective studies. A systematic evidence
review of would healing products prepared for the Agency for Healthcare Research and Quality found no studies of Primatrix of sufficient quality to meet criteria for inclusion in the systematic evidence review (Snyder et al, 2012).

Neill et al (2012) reported the findings of 7 patients who underwent 2-stage skin grafting with bovine fetal collagen (BFC) as an initial wound cover. Split-thickness skin grafts (STSGs) were successfully placed on the wounds after completion of interval management; BFC proved to be a resilient acellular dermal matrix that could proceed to assimilation and skin grafting under a variety of wound conditions. The authors concluded that BFC may prove to be a valuable material, as the role of acellular dermal matrices in skin grafting becomes better defined. They stated that "Such initial results encourage further use of BFX in cases of interval STSG reconstruction. Subgroups of such patients could lend themselves to prospective studies that could further define this strategy and the contribution of BFC". This was a small (n = 7) case-series report.

Hayn (2013) reported that PriMatrix was used to treat complex surgical or traumatic wounds where the clinical need was to avoid skin flaps and to build new tissue in the wound that could be re-epithelialized from the wound margins or closed with a subsequent application of a STSG. A total of 43 consecutive cases were reviewed having an average size of 79.3 cm(2), 50 % of which had exposed tendon and/or bone. In a subset of wounds (44.7 %), the implantation of PriMatrix was also augmented with negative pressure wound therapy (NPWT). Complete wound healing was documented in over 80 % of the wounds treated, whether the wound was treated with the PriMatrix alone (95.2 %) or when supplemented with NPWT (82.4 %). The scaffold successfully incorporated into wounds with exposed tendon and/or bone to build vascularized, dermal-like tissue. The new tissue in the wound supported STSGs however, in the majority of the cases (88.3 %); wound closure was achieved through re-epithelialization of the incorporated dermal scaffold by endogenous wound keratinocytes. The authors concluded that PriMatrix was found to offer an effective alternative treatment strategy for definitive closure of challenging traumatic or surgical wounds on patients who were not suitable candidates for tissue flaps. Moreover, the authors noted that “A comparison of this study to other clinical reports was limited by its retrospective nature where patients and wounds did not meet any specific inclusion/exclusion criteria. To definitively identify any clinical benefits the PriMatrix wound healing technology offers over other alternatives, formal prospective, randomized clinical studies with long-term follow-up wound assessments are required”.

In a prospective multi-center study, Kavros et al (2014) evaluated the healing outcomes of chronic diabetic foot ulcers treated with PriMatrix, a fetal bovine acellular dermal matrix. Inclusion criteria required the subjects to have a chronic diabetic foot ulcer (DFU)
that ranged in area from 1 to 20 cm² and failed to heal more than 30 % during a 2-week screening period when treated with moist wound therapy. For qualifying subjects, PriMatrix was secured into a clean, sharply debrided wound, dressings were applied to maintain a moist wound environment, and the diabetic ulcer was pressure off-loaded. Wound area measurements were taken weekly for up to 12 weeks and PriMatrix was re-applied at the discretion of the treating physician. A total of 55 subjects were enrolled at 9 U.S. centers with 46 subjects progressing to study completion. Ulcers had been in existence for an average of 286 days and initial mean ulcer area was 4.34 cm². Of the subjects completing the study, 76 % healed by 12 weeks with a mean time to healing of 53.1 ± 21.9 days. The mean number of applications for these healed wounds was 2.0 ± 1.4, with 59.1 % healing with a single application of PriMatrix and 22.9 % healing with 2 applications. For subjects not healed by 12 weeks, the average wound area reduction was 71.4 %. The authors concluded that the findings of this multi-center prospective study suggested that PriMatrix used in conjunction with a center’s standard of care wound therapy offers a cost-effective strategy to heal diabetic foot ulcers over that of other advanced wound therapy products based on 12-week healing outcomes as well as number of applications needed to achieve successful closure. The main drawback of this study was the lack of a direct comparison within the study to standard of care as well as to other advanced therapies. The authors stated that the findings from this study should be expanded to include these clinical efficacy comparisons as well as cost-effectiveness comparisons in order to maximize health benefits per dollar spent for the treatment of diabetic foot ulcers.

**Oasis Wound Dressing**

Oasis wound dressing (Cook Biotech Inc., West Lafayette, IN), a tissue-engineered collagen matrix derived from the porcine small intestinal submucosa (SIS). Oasis Wound Matrix was cleared for marketing under the 510(k) process and is indicated “for the management of wounds including: partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled, undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, second-degree burns, and skin tears); draining wounds. The device is intended for one-time use.”

Oasis Wound Matrix is a naturally derived, extracellular matrix (ECM) created from the submucosal layer of porcine small intestine. Oasis Wound Matrix is indicated for treatment of difficult-to-heal chronic venous or diabetic partial and full-thickness ulcers of the lower extremity that have failed standard wound therapy of at least four weeks duration.
Oasis Wound Matrix is an extracellular matrix derived from porcine small intestinal submucosa (Snyder, et al., 2012). According to the manufacturer, the intestinal material is absorbed into the wound during the healing process. Oasis is applied to wounds after débridement. The edges of the Oasis sheet extend beyond the wound edges and are secured with tissue sealant, bolsters, dissolvable clips, sutures, or staples. The sheet is rehydrated with sterile saline and covered with a nonadherent, primary wound dressing followed by a secondary dressing to contain exudate. Oasis is reapplied every 7 days or as needed.

In a prospective, randomized, controlled multi-center study (n = 120), Mostow and colleagues (2005) examined the effectiveness of Oasis in the treatment of chronic leg ulcers. Patients were randomly assigned to receive either weekly topical treatment of SIS combined with compression therapy (n = 62) or compression therapy alone (n = 58). Ulcer size was determined at enrollment and weekly throughout the treatment. Healing was assessed weekly for up to 12 weeks. Recurrence after 6 months was recorded. The primary outcome measure was the proportion of ulcers healed in each group at 12 weeks. After 12 weeks of treatment, 55 % of the wounds in the Oasis group were healed, as compared with 34 % in the standard-care group (p = 0.0196). None of the healed Oasis-treated subjects who were seen at the 6-month follow-up experienced ulcer recurrence. These investigators concluded that Oasis, as an adjunct therapy, significantly improved healing of chronic leg ulcers over compression therapy alone. Moreover, the authors noted that a definitive link between the composition of Oasis and its positive effects on chronic wounds has not been established. Also, the limited number of wounds examined at the 6-month follow-up suggested that more research especially longer follow-up is needed to ascertain recurrence after treatment with Oasis.

In another randomized, prospective, controlled multi-center study (n = 73), Niezgoda et al (2005) compared healing rates at 12 weeks for patients with full-thickness diabetic foot ulcers treated with Oasis versus Regranex gel. Patients with at least 1 diabetic foot ulcer were entered into the trial and completed the protocol. They were randomized to receive either Oasis (n = 37) or Regranex gel (n = 36) and a secondary dressing. Wounds were cleansed and debrided, if needed, at a weekly clinic visit. Dressings were changed as needed. The maximum treatment period for each patient was 12 weeks. After 12 weeks of treatment, 18 (49 %) Oasis-treated subjects had complete wound closure compared with 10 (28 %) Regranex-treated patients. These researchers concluded that although the sample size was not large enough to demonstrate that the incidence of healing in the Oasis group was statistically superior (p = 0.055), the study results showed that treatment with Oasis is as effective as Regranex in healing full-thickness diabetic foot ulcers by 12 weeks. One of the drawbacks of this study was that the findings did not reach statistical significance, namely, the overall healing rates between groups were
similar. In addition, there were more cases of infection in the Oasis-treated group than the Regranex-treated group. Furthermore, the 6-month follow-up evaluation did not allow for adequate evaluation of long-term effectiveness.

Romanelli et al (2007) compared the effectiveness of Oasis wound matrix versus Hyaloskin in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. The purpose of the study was to examine whether a single extracellular matrix component, such as hyaluronan (Hyaloskin), can stimulate healing of mixed arterial/venous ulcers or whether a more integrated extracellular replacement that contains multiple active extracellular matrix components is needed. Fifty-four patients were prospectively selected for enrollment into a randomized trial. The enrolled patients met the following criteria: age greater than 18 years with mixed arterial/venous leg ulcer by clinical and instrumental assessment, venous reflux by Doppler flow studies, ankle brachial pressure index greater than 0.6 and less than 0.8, ulcer duration greater than 6 weeks and size 2.5 to 10 cm(2), and 50 % or more granulation tissue on the wound bed. Patients were excluded if they were diabetics, were smokers, had clinical signs of wound infection, an ankle brachial pressure index less than 0.06, had necrotic tissue on the wound bed, had known allergy to the treatment products or were unable to deal with the protocol. Patients who met the inclusion/exclusion criteria were randomized to treatment with OASIS (n = 27) or Hyaloskin (n = 27). The sequence of randomization was generated through every other patient selection by the clinician. Patients were advised not to use any compression system during the study. After 16 weeks of treatment, patients in each group were evaluated on 4 criteria: (i) complete wound healing, (ii) time to dressing change, (iii) pain, and (iv) comfort. Complete wound closure was achieved in 82.6 % of Oasis-treated ulcers compared with 46.2 % of Hyaloskin-treated ulcers (p < 0.001). Statistically significant differences favoring the Oasis treatment group were also reported for time to dressing change (p < 0.05), pain (p < 0.05) and patient comfort (p < 0.01). The authors stated that these results suggest that Oasis is an effective treatment for difficult-to-heal mixed arterial/venous ulcers and that replacement of the major components of the dermal extracellular matrix is more effective than replacing it with hyaluronan alone.

In a randomized comparison of Oasis wound matrix versus moist wound dressing, Romanelli et al (2010) evaluated complete wound healing, time to dressing change, and formation of granulation tissue in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. Fifty adults with lower leg ulcers of mixed arterial/venous (n = 23) and venous (n = 27) etiology were prospectively selected for enrollment. Patients had the following characteristics: venous or mixed arterial/venous leg ulcer by clinical and instrumental assessment and ankle brachial index ranging between 0.6 and 0.8, ulcer duration of greater than 6 months, ulcer size of greater than 2.5 cm(2), and 50 %
granulation tissue on wound bed. Patients were excluded for clinical signs of infection, ankle brachial index less than 0.6, necrotic tissue on wound bed, known allergy to treatment products, or if they were unable to deal with the protocol. Patients who met the inclusion/exclusion criteria were randomized to treatment with Oasis (n = 25) or with standard moist wound dressing (petrolatum-impregnated gauze; n = 25). The investigators reported that extracellular matrix-treated ulcers achieved complete healing on average in 5.4 weeks as compared with 8.3 weeks for the control group treated with moist wound dressing (p = 0.02) and at the primary time point evaluated (8 weeks), complete wound closure was achieved in 80% of extracellular matrix-treated ulcers compared with 65% of ulcers in the control group (p < 0.05). Statistically significant differences favoring the extracellular-matrix treatment group were also reported for time to dressing change (p < 0.05), and for percentage of granulation tissue formed (p < 0.05). The authors concluded that overall, the biological extracellular matrix was more beneficial than moist wound dressings for the treatment of patients with mixed arterial/venous or venous ulcers. Although current methods of standard care can be effective in the treatment of lower extremity ulcers, in this study, Oasis significantly reduced time to healing as compared with moist wound dressing in chronic, difficult-to-heal mixed arterial/venous leg ulcers.

O'Donnell and Lau (2006) examined if more "modern" complex wound dressings further improve the healing of venous ulcers over that with simple wound dressings. These investigators conducted a systematic review of RCTs of wound dressing trials that were published from October 1, 1997, through September 1, 2005. They searched MEDLINE, CINAHL, and the Cochrane Controlled Trials Registry Database to identify RCTs. Criteria for ultimate selection included treatment with compression and an objective outcome describing the proportion of wounds healed. A total of 20 RCTs were identified that satisfied these criteria and were classified into 3 wound dressing classes: (i) semi-occlusive/occlusive group (n = 8), (ii) growth factor group (n = 7), and (iii) human skin equivalent group (n = 5). Assessment of study design quality for the 20 RCTs showed a low percentage (less than 49%) of RCTs that incorporated at least 3 of 7 indicators of trial quality, but it seemed better in the 5 RCTs that showed significance for ulcer healing; 4 of the studies used at least 6 of the 7 characteristics of adequate study design. Five (25%) of the 20 RCTs had a statistically significantly improved proportion of ulcers healed in the experimental dressing group over control values: zinc oxide paste bandage (79% versus 56%) and Tegasorb (59% versus 15%) in the semi-occlusive/occlusive group and peri-lesional injection of granulocyte-macrophage colony-stimulating factor (57% versus 19%) and porcine collagen derived from small-intestine submucosa (Oasis; 55% versus 34%) in the growth factor group. In the sole significant RCT from the human skin equivalent group, Apligraf (63%) was superior to Tegapore (48%). Four of these 5 studies also showed an improved time to complete healing by Kaplan-Meier estimate.
The authors concluded that certain wound dressings can improve both the proportion of ulcers healed and the time to healing over that achieved with adequate compression and a simple wound dressing. The selection of a specific dressing, however, will depend on the dressing characteristics for ease of application, patient comfort, wound drainage absorption, and expense.

**Oasis Burn Matrix**

Oasis Burn Matrix (Cook Biotech Inc., West Lafayette, IN) is a extracellular matrix created from the submucosal layer of porcine small intestine. The submucosa is extracted in a manner that removes all cells but leaves the submucosa matrix intact. This matrix is intended to provide an acellular scaffold that accommodates remodeling of host tissue. The Oasis Burn Matrix has increased thickness allowing application for an extended period of time. There is a lack of evidence in the peer-reviewed published medical literature on the effectiveness of the Oasis Burn Matrix.

**Oasis Tri-Layer Matrix**

Oasis tri-layer matrix (Healthpoint Biotherapeutics, Fort Worth, TX) is an extra-cellular matrix derived from porcine small intestinal submucosa (SIS). It is indicated for the management of wounds, including partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (abrasions, lacerations, 2nd degree burns, and skin tears), drainage wounds, and surgical wounds. After the wound bed is free of exudate and devitalized tissue, the wound matrix is applied over the wound. Once applied, tissues adjacent to the SIS matrix deliver cells and nutrients to the wounded tissues using the SIS material as a conduit. The cells rapidly invade the SIS material and capillary growth follows, allowing nutrients to enter the matrix. SIS is strong at the time of placement, and is gradually re-modeled while the host system reinforces and rebuilds the damaged site with host tissue. As healing occurs, sections of Oasis Ultra Tri-Layer Wound Matrix may gradually peel. All dressings should be changed every 7 days, or as necessary. Oasis Ultra Tri-Layer Wound Matrix is supplied in sterile peel-open packages intended for one-time use. It is supplied in 2 sizes: 7 x 10 cm and 7 x 20 cm. According to the manufacturer, OASIS Ultra Tri-Layer Wound Matrix differs from other products because it is a wound matrix with 3 layers. However, there is a lack of evidence regarding the effectiveness of the Oasis tri-layer matrix.

**Epicel**

Epicel (Genzyme Biosurgery, Cambridge, MA) is a cultured epidermal autograft intended to treat deep dermal or full-thickness burns (Snyder, et al., 2012). Skin cells are grown or cultured from a postage-stamp sized sample of the individual’s own healthy skin. Epicel is indicated to replace the epidermis on severely burned patients.

According to the product labeling, “Epicel® cultured epidermal autografts (CEA) is an aseptically processed wound dressing composed of the patient’s own (autologous) keratinocytes grown ex vivo in the presence of proliferation-arrested, murine (mouse) fibroblasts. Epicel® consists of sheets of proliferative, autologous keratinocytes, ranging from 2 to 8 cell layers thick and is referred to as a cultured epidermal autograft.” Epicel is created by co-cultivation of the patient’s cells with murine cells and contains residual murine cells. Therefore, FDA considers Epicel a xenotransplantation product. Epicel was granted an humanitarian device exemption (HDE) by FDA in October 2007 and is “indicated for use in patients who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30 percent. It may be used in conjunction with split-thickness autografts, or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns.” Epicel is not indicated for use in chronic wounds.

Epicel is indicated for use in a subgroup of the burn population that represents the most severely injured patients. The FDA granted Epicel its humanitarian use device designation in 2007 for the treatment of life-threatening wounds resulting from severe burns. Due to the small population for which Epicel is indicated, it is unlikely there will be sufficient evidence to demonstrate the effectiveness of Epicel for the treatment of burns. The primary benefit of Epicel is that the total number of grafts required to treat a patient can be produced from a single biopsy of unburned skin. Patients suffering burns over a significant body surface area can be completely covered regardless of the amount of unburned skin available for split thickness skin grafts. This minimizes the time to wound closure and minimizes the time in which the patient is most susceptible to serious and potentially life threatening complications. Munster (1992) reported on a series of patients (n = 10) treated with cultured epidermal autografts who had a significantly reduced mortality rate (14 %) when compared with control patients (48 %). In a 5-year single-center series, Carsin et al (2000) treated 30 burn patients with cultured epithelial autografts (total body surface area of a mean of 37 %). Cultured epithelial autografts achieved permanent coverage of a mean of 26 % of total body surface area, an area greater than that covered by conventional autografts and survival was 90 % in these severely burned and otherwise traumatized patients. Final cultured epidermal autograft take was a mean of 69 %.
Epicel is made from a patient's own skin cells and then grown on a layer of mouse cells to enhance growth. It is indicated for use in patients who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%. It may be used in conjunction with split-thickness autografts, or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns. Enough skin can be grown from a biopsy the size of a postage stamp to cover the entire body. The process takes approximately 16 days and the skin graft integrates with surrounding tissue 3 to 4 weeks after surgery.

**BioBrane**

BioBrane (Mylan Laboratories, Inc., Canonsburg, PA) is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially imbedded into the film. The fabric presents to the wound bed a complex 3-dimensional structure of tri-filament thread to which collagen has been chemically bound. Blood/sera clot in the nylon matrix, thus, firmly adhering the dressing to the wound until epithelialization occurs.

Phillips et al (1989) reviewed 851 applications of Biobrane on partial skin thickness burn wounds awaiting epithelialization. After the patients had been evaluated and resuscitated as needed, the burn wounds were cleansed and debrided. Those evaluated as shallow were treated with Biobrane application. Joint surfaces were splinted for immobilization. The wound was inspected at 24 and 48 hours and if any fluid had accumulated it was aspirated and the wound was redressed. When the Biobrane was adherent, the wound was covered with a light dressing and joint immobilization was discontinued. Treatment with Biobrane dressing provided certain advantages over other topical wound care. As the dressing changes were performed less frequently outpatient care was possible, with a resultant decrease in both the length of hospital stay and the ultimate cost of burn care. Wound desiccation is prevented and pain is decreased. Accurate diagnosis of wound depth is crucial if Biobrane is to be used. Very deep wounds will not allow Biobrane adherence, neither will it occur if the wound has a high bacterial count. If joint surfaces are not splinted, the Biobrane will shear and not adhere to the wound. Convex and concave surfaces can be treated with Biobrane, which may need to be meshed.

Bishop (1995) noted that Biobrane offers a number of advantages as a wound dressing for children. It does not require the use of surgical instruments, noisy distractions, painful manipulation of the wound, or regimented daily dressing changes. Biobrane does offer the pediatric patient with burns immediate comfort and protection, and enhances patient compliance and parental satisfaction. This is corroborated by the findings of Cassidy et al (2005). These researchers compared the effectiveness of Biobrane and Duoderm for the treatment of small intermediate thickness burns in children in a prospective,
randomized fashion to determine their relative impact on wound healing, pain scores, and cost. Patients under 18 years of age with intermediate thickness burns on a surface area less than 10% were enrolled and treated with one of the two dressing systems. Data collected included mechanism of injury, time to complete healing, pain scores, and institutional cost of materials until healing was complete. No significant difference in time to healing or pain scores was detected between the 2 groups. The cost of each treatment was statistically more expensive in the Biobrane group. The results of this study showed that Duoderm and Biobrane provide equally effective treatment of partial thickness burns among the pediatric population.

Barret et al (2000) stated that partial-thickness burns in children have been treated for many years by daily, painful tubbing, washing, and cleansing of the burn wound, followed by topical application of anti-microbial creams. Pain and impaired wound healing are the main problems. These investigators hypothesized that the treatment of 2nd-degree burns with Biobrane is superior to topical treatment. A total of 20 pediatric patients were prospectively randomized into 2 groups to compare the effectiveness of Biobrane versus 1% silver sulfadiazine. The rest of the routine clinical protocols were followed in both groups. Demographic data, wound healing time, length of hospital stay, pain assessments and pain medication requirements, and infection were analyzed and compared. Main outcome measures included pain, pain medication requirements, wound healing time, length of hospital stay, and infection. The application of Biobrane to partial-thickness burns proved to be superior to the topical treatment. Patients included in the biosynthetic temporary cover group presented with less pain and required less pain medication. Length of hospital stay and wound healing time were also significantly shorter in the Biobrane group. None of the patients in either group presented with wound infection or needed skin autografting. The authors concluded that the treatment of partial-thickness burns with Biobrane is superior to topical therapy with 1% silver sulfadiazine. Pain, pain medication requirements, wound healing time, and length of hospital stay are significantly reduced. Furthermore, in a review on tissue-engineered temporary wound coverings, Ehrenreich and Ruszczak (2006) stated that “[b]oth Biobrane and TransCyte have a strong body of evidence supporting their use in acute wounds. The most important clinical advantages of both products are prevention of wound desiccation, reduction in pain, reduced dressing changes, and in most reported studies, an acceleration in healing….TransCyte may be justified in full thickness and deep partial thickness injuries, whereas Biobrane is more appropriate for more superficial wounds”.

Vloemans et al (2014) performed a systematic review of wound management and dressing materials to select the best treatment option for children with burns. A search in Medline and Embase revealed 51 articles for a critical appraisal. The articles were
divided into randomized controlled trials, cohort studies and a group of case-reports. Total appraisal did not differ much among the groups; the level of evidence was highest in the randomized controlled trials and lowest in the case-reports. In 16 out of 34 comparative studies, silver sulfadiazine or a silver sulfadiazine/chlorhexidine-gluconate combination was the standard of wound care treatment. The competitor dressing was Biobrane in six studies and amnion membrane in three. Tulle gauze, or tulle gauze impregnated with an antibacterial addition were the standard of care treatment in seven studies. The authors concluded that, in general, membranous dressings like Biobrane and amnion membrane performed better than the standard of care on epithelialization rate, length of hospital stay and pain for treatment of partial thickness burns in children. However, hardly any of the studies investigated long-term results like scar formation.

Austin et al (2015) reported on a five year retrospective cohort study evaluating upper extremity burns treated with temporary wound coverage (Biobrane or cadaveric allograft). The primary outcome was to determine the impact choice of wound coverage had on operative time and cost. The secondary outcome was the need for revision of upper extremity debridement prior to definitive autografting. The investigators included 45 patients in this study: 15 treated with cadaveric allograft and 30 treated with Biobrane skin substitute. The investigators found that Biobrane had a significantly lower procedure time (21.12 vs. 54.78 min per %TBSA excised, p=0.02) and cost (1.30 vs. 2.35 dollars per minute per %TBSA excised, p=0.002). Both techniques resulted in 2 revisions due to complications. The investigators concluded that Biobrane is superior to cadaveric allograft as a temporizing skin substitute in the acute burn wound, both in terms of procedure time and associated cost. The investigators stated that they believe that this is largely due to the relative ease of application of Biobrane.

Krezdorn et al (2017) conducted a retrospective cohort study of adult patients that have been admitted with scalds in one center between 2011 and 2014. The investigators assessed two groups, group 1 with Biobrane as initial treatment and group 2 with topical treatment using polyhexanid hydrogel and fatty gauze. Primary outcome variables were rate of secondary deepening, surgery, infection (defined as positive microbiological swabs and antibiotic treatment) and length of stay. Total body surface area (TBSA) as well as diabetes mellitus (DM), hypertension, smoking and alcohol consumption as potential confounders were included. The study included 52 patients; 36 patients received treatment with Biobrane and 16 with ointment and fatty gauze. No significant differences were found for age and TBSA whereas gender ratio was different (25/11 male/female in group 1 vs 4/12 in group 2, p=0.003). Rate of secondary deepening, surgery, infection as well as days of hospital stay (DOHS) were comparable. Logistic and multilinear regression showed TBSA to be a predictive factor for infection (p=0.041), and TBSA and age for length of stay (age p=0.036; TBSA p=0.042) in group
1. The investigators concluded that the use of Biobrane in adult scald lesions is safe and non-inferior to topical treatment options. In elder patients and larger TBSA Biobrane may increase the risk of infection or a prolonged stay in hospital.

**AlloDerm**

AlloDerm (Life Cell Corp., The Woodlands, TX), an acellular dermal matrix processed from human allograft skin. AlloDerm is processed from human cadaver skin with the cells responsible for immune response and graft rejection removed. The remainder is a matrix or framework of natural biological components, ready to enable the body to mount its own tissue regeneration process. AlloDerm is indicated for use in association with breast reconstruction procedures.

The product has been promoted from the manufacturer for hernia and breast reconstruction. AlloDerm has been used in the treatment of burn injury. According to the product labeling, "AlloDerm is to be used for repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument."

Donated human skin tissue is supplied by tissue banks and processed into the dermis product. During the processing, cells are removed and the product is freeze-dried (Snyder, et al., 2012). However, there is currently limited evidence to support the use of AlloDerm for wound healing.

Lattari et al (1997) described the use of AlloDerm dermal grafts on 3 patients with full-thickness burns of the distal extremities. Grafts were applied to the hand in 2 cases and the dorsum of the foot in the 3rd case. Range of motion, grip strength, fine motor coordination, and functional performance were quantitatively evaluated. As shown by these patients, cosmetic and functional results were considered good to excellent after the use of AlloDerm grafts with thin autografts.

Tsai et al (1999) presented 12 cases of clinical application of a composite grafting technique in which AlloDerm provided source of dermis, and an ultra-thin autograft (0.004 to 0.006 inch in thickness) provided epidermis. In these patients, the composite grafts were applied to full-thickness burn wounds over various articular skin surfaces. The average skin graft take rate was 91.5%. These ultra-thin autografts allow the donor sites to heal faster. The mean time of donor site re-epithelization was 6 days. All patients had a nearly normal range of joint motion (average 95% of normal) after 1 year's follow-up. Wound assessment over time has shown supple skin that has been resistant to trauma and infection. The cosmetic results were judged to be fair to good by surgeons and patients after 1 year's follow-up.
Gore (2005) stated that because skin thins with advancing age, traditional thickness skin grafts cannot always be obtained in very elderly burn patients without creating a new full-thickness wound at the skin graft donor site. In an attempt to circumvent this problem, AlloDerm and thin autograft (depth 0.005 inches) were used in skin grafting 10 elderly burn patients (age of 78 years +/- 2, TBSA burn 17 % +/- 2; mean +/- SEM) over a 1-year period. The outcome of patients receiving AlloDerm was compared retrospectively to a similar group of 18 elderly patients admitted over the prior year, 8 of whom underwent operative wound excision and autografting (depth 0.014 inches) without AlloDerm. Length of hospital stay was significantly reduced in patients treated with AlloDerm compared to the total group of elderly in whom selective use of operative debridement and skin grafting was used. Functional outcome was improved in those patients who underwent skin grafting regardless of operative technique. Donor site healing time was significantly reduced with AlloDerm (12 days +/- 1 versus 18 days +/- 2), while graft take was similar to conventional autografting. Unfortunately, 3-month mortality remained poor regardless of operative skin grafting or technique used. The authors concluded that these findings suggested that use of AlloDerm may allow more elderly burn patients to undergo operative wound closure, thus improving functional outcome and reducing hospitalization. Unfortunately, long-term survival for very elderly burn patients remains poor.

A number of papers have examined the use of AlloDerm as a tissue graft for contaminated abdominal wall defects and hernia repair. Wound infection and infection of the mesh can be grave complications of hernia repair, often necessitating removal of the mesh and application of a tissue graft. In breast reconstruction, AlloDerm has been used in conjunction with a subpectoral (major) placement of breast implants to achieve more complete implant coverage without the use of other muscles. Although these indications are promising, evidence is limited to small retrospective case series with limited follow-up.

Ventral hernia repair in potentially contaminated or potentially infected fields limit the use of synthetic mesh products. In this scenario, biosynthetic mesh products that are absorbed and/or replaced with the body's own tissue are intended to reduce the incidence of post-operative chronic wound complications. Rapid re-vascularization, re-population, and remodeling of the matrix occur on contact with the patient's own tissue. Only limited, and mostly preliminary data, is available on the use of these types of mesh and concerning the potential complications associated with the use of these types of meshes.
In one of the few published comparative studies of AlloDerm in hernia repair, Gupta et al (2006) compared the efficacy and the complications associated with the use of AlloDerm and Surgisis bioactive mesh (Cook Surgical, Bloomington, IN), a product obtained by the processing of porcine small intestine submucosa, for ventral herniorrhaphy. The investigators reported on the outcomes of 74 patients who underwent ventral hernia repair using these products between June 2002 and March 2005. The first 41 procedures were performed using Surgisis bioactive mesh, and the remaining 33 patients had ventral hernia repair with AlloDerm. The investigators reported that the use of the AlloDerm mesh resulted in 8 hernia recurrences. Fifteen of the 33 patients treated with AlloDerm developed a diastasis or bulging at the repair site. Seroma formation was only a problem in 2 patients. The investigators reported that the Surgisis bioactive mesh resulted in significant seroma formation in over 25% of patients. Explanted material revealed separated layers of unincorporated middle layers of the Surgisis mesh. The investigators reported that 3 of the patients had the mesh placed in a contaminated field with no resultant sequela, and there were no hernia recurrences. Patients also had a significant degree of discomfort and pain during the immediate post-operative period. The investigators concluded that post-operative diastasis and hernia recurrence were a major problem with the AlloDerm mesh. On the other hand, seroma formation was a major problem with the Surgisis mesh repair, as was the post-operative pain. The investigators recommended further design improvements in both forms of these new mesh products.

In another comparative study, Espinosa-de-los-Monteros et al (2007) retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm in 37 patients and compared them with 39 randomly selected abdominal wall reconstructions without AlloDerm. The investigators reported a significant decrease in recurrence rates when AlloDerm was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. On the other hand, no differences were observed when adding AlloDerm as an overlay to patients with large-size hernias treated with underlay mesh.

Jin et al (2007) compared 2 techniques of fascial bridging versus fascial re-inforcement repair with regard to their long-term recurrence rates using Alloderm in patients with abdominal wall defects, and concluded that, because of high recurrence rates with fascial bridging, AlloDerm should be used only as a re-inforcement after primary fascial re-approximation. The investigators retrospectively studied the outcomes of 37 patients with abdominal defects repaired with AlloDerm. Eleven patients underwent bridged fascial repair, and 26 patients had reinforced fascial repair. Mean follow-up was 21.4 months (range of 15 to 36 months). In the bridged group, 1 patient died on post-operative day 20. Of the remaining 10 patients, 8 patients (80%) developed recurrences; 7 patients
required re-operation, but 1 patient refused repair. In the re-inforced group, 4 patients were lost to follow-up and 2 patients died. Four of the remaining 20 patients (20 %) developed recurrences that required repair; this was significantly different from the recurrence rate in the bridged group (p = 0.009).

Bluebond-Lagner et al (2008) reported on recurrent laxity requiring secondary intervention in a series of patients who were repaired with interpositional AlloDerm. The investigators reviewed all patients who underwent repair of massive ventral hernias and identified 7 patients who presented with abdominal wall laxity following component separation with interpositional AlloDerm alone. The investigators reported that all patients developed laxity within 12 months and required a secondary procedure. At the time of re-exploration, severe attenuation in the AlloDerm was noted. The segment was excised, the edges closed primarily, and prolene mesh was placed as an onlay.

Vetrees et al (2008) reported on a retrospective review of outcomes of surgical repair of 83 patients with open abdomen that were treated at Walter Reed Army Medical Center. Surgical management included early definitive abdominal closure (EDAC) (serial abdominal closure with prosthetic Gore-Tex Dualmesh and final closure supplemented with polypropylene mesh or AlloDerm in 56 patients, primary fascial closure in 15 patients, planned ventral hernia (PVH) in 9 patients, and vacuum-assisted closure with AlloDerm in 3 patients). Complications included removal of infected prosthetic mesh in 4 EDAC closure patients; the investigators noted that mesh-related complications had decreased over time. The investigators reported that rates of infection, abdominal wall hematoma, deep venous thrombosis, and pulmonary embolism did not differ between groups. In the EDAC group, infections complicated final polypropylene mesh closure in 3 of 28 patients closed with prosthetic mesh; 1 of 14 patients closed with biologic mesh (AlloDerm) noted increased laxity at the repair site. Of 56 patients treated with EDAC, 2 patients had recurrent ventral hernia. Of the 3 patients closed with AlloDerm and vacuum assisted closure, 1 patient had recurrent ventral hernia. The investigators reported that no final AlloDerm closures required removal after placement, but "long-term results have been disappointing ... The excessive cost of biologic material requires better results than those documented in previous studies." Limitations of this study include its lack of randomization, variation in the described closure methods, its retrospective nature, and limitations of some data points. The investigators concluded that "polypropylene mesh final EDAC closure risks infection and subsequent fistula formation, and long-term follow-up are needed. Use of biologic mesh as either final EDAC closure or with vacuum-assisted closure also requires long-term follow-up to justify its increased cost and increased risk of abdominal wall laxity."
Available published evidence regarding the use of Alloderm in breast reconstructive surgery consists primarily of several small case series (e.g., Salzberg, 2006; Breuning and Colwell, 2007; Zienowicz and Karacaoglu, 2007; Garramone and Lam, 2007; Spear et al, 2008). There are no comparative studies to determine whether the use of Alloderm improves aesthetic outcomes. In addition, the duration of follow-up in published studies is limited so the impact on longer-term complications such as severe contractures cannot be determined.

The only published comparative study of Alloderm (Preminger et al, 2008) in breast reconstructive surgery found that Alloderm did not increase the rate of tissue expansion after tissue expander placement. This matched, retrospective cohort study compared expansion rates in patients who underwent tissue expander/implant reconstruction with Alloderm (n = 45) versus persons who underwent standard tissue expander/implant reconstruction (n = 45). Median number of expansions performed was 5 and 6 in the Alloderm and non-Alloderm cohorts (p = 0.117). The study found no difference in the mean rate of post-operative tissue expansion (Alloderm: 97 ml/injection versus non-Alloderm: 95 ml/injection [p = 0.907]).

Randomized clinical studies are ongoing of Alloderm for tissue expander implant reconstruction and for other indications (MSKCC, 2009).

Hiles and colleagues (2009) noted that biologic grafts for hernia repair are a relatively new development in the world of surgery. A thorough search of the Medline database for uses of various biologic grafts in hernia shows that the evidence behind their application is plentiful in some areas (ventral, inguinal) and nearly absent in others (para-stomal). The assumption that these materials are only suited for contaminated or potentially contaminated surgical fields is not borne out in the literature, with more than 4 times the experience being reported in clean fields and the average success rates being higher (93% versus 87%). Outcomes prove to be dependent on material source, processing methods and implant scenarios with failure rates ranging from zero to more than 30%. Small intestinal submucosa (SIS) grafts have an aggregate failure rate of 6.7% at 19 months whereas acellular human dermis (AHD) grafts have a failure rate of 13.6% at 12 months. Chemically cross-linked grafts have much less published data than the non-cross-linked materials. In particular, the search found 33 articles for SIS, 32 for AHD, and 13 for cross-linked porcine dermis. Furthermore, the cumulative level of evidence for each graft material was fairly low (2.6 to 2.9), and only 1 material (SIS) had level 1 evidence reported in any hernia type (inguinal and hiatal).
Kissane and Itani (2012) studied the experience and outcomes of patients who underwent repair of a ventral incisional hernia with biologic mesh. Online database and detailed reference searches were conducted. Studies chosen for review had a sample size of at least 40 patients, level IV evidence at most, and a Methodological Index for Nonrandomized Studies index of at least 10. Indications for use of biologic mesh, type of mesh, patient comorbidities, and surgical techniques were also noted. A total of 8 studies fulfilled the search criteria and included 635 patients using AlloDerm, Surgisis, and Strattice biologic tissue matrices. In one study, indications and surgical techniques were standardized, and follow-up was prospective. In the other 7 studies, indications, surgical techniques, and follow-up were assessed retrospectively. The mean patient age, when reported, was 55.7 years. Body mass index ranged from 30 to 35 kg/m² in 44 % of the reported patients. In 7 of the 8 studies [565 patients (89 %)], the mean follow-up was 25.8 months and the mean hernia recurrence rate was 21 %. Complication rate exceeded 20 % in most studies. The authors concluded that biologic tissue matrices are mostly used in contaminated fields, which has allowed for a 1-stage repair with no or little subsequent mesh removal. Ventral incisional hernia repair with these matrices continues to be plagued by a high recurrence rate and complications. They stated that prospective, randomized trials are needed to properly direct practice in the use of these meshes and evaluate their ultimate value.

Zeng et al (2012) evaluated the precise effectiveness of AlloDerm implants for preventing Frey syndrome after parotidectomy, using a systematic review and meta-analysis. These investigators searched randomized and quasi-randomized controlled trials in which AlloDerm implants were compared to blank controls for preventing Frey syndrome after parotidectomy, from the PubMed, Embase, the Cochrane Library and the ISI Web of Knowledge databases, without any language restriction. Two reviewers independently searched, identified, extracted data and assessed methodological quality. Relative risks with 95 % confidence intervals (CIs) were calculated and pooled. Five articles involving 409 patients met the inclusion criteria. Meta-analyses showed a significant 85 % relative risk reduction in objective incidence (RR = 0.15, 95 % CI: 0.08 to 0.30; p < 0.00001) and 68 % in subjective incidence (RR = 0.32, 95 % CI: 0.19 to 0.57; p < 0.00001) of Frey syndrome with AlloDerm implants; there was a significant 91 % relative risk reduction in salivary fistula (RR = 0.09, 95 % CI: 0.01 to 0.66; p = 0.02); there was no statistical significance for the incidence of facial nerve paralysis (RR = 0.96, 95 % CI: 0.84 to 1.09; p = 0.51); there was no statistical significance for the incidence of seroma/sialocele (RR = 1.36, 95 % CI: 0.66 to 2.80; p = 0.40); there was a trend for a small effect in improving facial contour. Adverse events related to AlloDerm implants were not found. There is evidence that AlloDerm reduces the incidence of Frey syndrome effectively and safely, and also has the potential to improve facial contour and decrease salivary fistula. However, the authors concluded that it is unclear whether AlloDerm implants improve
facial contour and decrease other complications; they stated that further controlled evaluative studies incorporating more precise measures are required. Also, an UpToDate review on "Salivary gland tumors: Treatment of locoregional disease" (Lydiatt and Quivey, 2012) does not mention the use of AlloDerm.

In a systematic review and meta-analysis, Li et al (2013) examined the safety and effectiveness of different types of grafts for the prevention of Frey syndrome after parotidectomy. The following data bases were searched electronically: MEDLINE (using OVID, from 1948 to July 2011), Cochrane Central Register of Controlled Trials (CENTRAL, issue 2, 2011), EMBASE (1984 to July 2011), World Health Organization International Clinical Trials Registry Platform (July 2011), Chinese BioMedical Literature Database (1978 to July 2011), and the China National Knowledge Infrastructure (1994 to July 2011). The relevant journals and reference lists of the included studies were manually searched for randomized controlled trials (RCTs) studying the effect and safety of different types of grafts for preventing Frey syndrome after parotidectomy. The risk of bias assessment using Cochrane Collaboration's tool and data extraction was independently performed by 2 reviewers. The meta-analysis was performed using Review Manager, version 5.1. A total of 14 RCTs and 1,098 participants were included. All had an unclear risk of bias. The meta-analysis results showed that the use of an acellular dermis matrix can reduce by 82 % the risk of Frey syndrome compared with the no-graft group using an objective assessment (relative risk [RR] 0.18, 95 % confidence interval [CI]: 0.12 to 0.26; p < 0.00001; Grading of Recommendations, Assessment, Development, and Evaluation [GRADE] quality of evidence: high). The acellular dermis matrix can also reduce by 90 % the risk of Frey syndrome compared with the no-graft group using a subjective assessment (RR 0.10, 95 % CI: 0.05 to 0.22; p < 0.00001; GRADE quality of evidence: high). The muscle flaps can reduce by 81 % the risk of Frey syndrome compared with the no-graft group (RR 0.19, 95 % CI: 0.13 to 0.27; p < 0.00001; GRADE quality of evidence: high). No statistically significant difference was found between the acellular dermal matrix and muscle flap groups (RR 0.73, 95 % CI: 0.15 to 3.53, p = 0.70; GRADE quality of evidence: low). No serious adverse events were reported. The authors concluded that the present clinical evidence suggests that grafts are effective in preventing Frey syndrome after parotidectomy. Moreover, they stated that further RCTs are needed to confirm this conclusion and prove the safety of the grafts.

Repliform

Repliform is an acellular human dermis for pelvic floor repair.
LifeCell also produces Repliform, which seems to be the same product as AlloDerm (Snyder, et al., 2012). Repliform Tissue Regeneration Matrix is a human acellular dermis. The donor human skin is processed and then freeze-dried to remove cells while maintaining the collagen, elastin, and proteoglycans. Repliform is processed by LifeCell Corp. and distributed by Boston Scientific Corp. The Boston Scientific Web site promotes Repliform for pelvic floor repair and says it “is intended for the repair or replacement of damaged or inadequate integumental tissue such to repair enteroceles, rectoceles and/or cystoceles and for pelvic floor reinforcement.”

Cymetra

Cymetra (Life Cell Corp., Branchburg, NJ) is an injectable micronized particulate form of AlloDerm that contains the collagens, elastin, proteins and proteoglycans that are present in AlloDerm (Snyder, et al., 2012). Like AlloDerm, Cymetra is made from human allograft skin. Because of the small particle size, Cymetra can be delivered by injection as a minimally invasive tissue graft. According to the manufacturer, Cymetra is ideally suited for the correction of soft-tissue defects requiring minimally invasive techniques, such as injection laryngoplasty.

Most of the published literature on Cymetra has focused on its use in injection laryngoplasty for vocal cord paralysis (see CPB 253 - Injections for Vocal Cord Paralysis (0253.html)), and its use in cosmetic soft tissue augmentation (Hirsch and Cohen, 2006; Narins and Bowman, 2005; Sclafani et al, 2002), with the remainder of the literature addressing miscellaneous applications (Allam, 2007; Levy, et al, 2005; Banta et al, 2003).

E-Z Derm

E-Z Derm Biosynthetic Wound Dressing (Brennen Medical, Inc., St. Paul, MN) is a porcine-derived xenograft that has been chemically cross-linked with an aldehyde to provide durability and storage. The dermal elements from the original pig dermis are likely all deactivated in the chemical process, unlike the frozen pig dermis which is still available. It appears that the product is a collagen scaffold. E-Z Derm has been used as an alternative to allografts in the treatment of burn wounds, especially for partial thickness skin losses, temporary coverage prior to autograft and to protect meshed autografts.

E-Z Derm is a biosynthetic wound dressing made from porcine tissue chemically treated to cross-link collagen with an aldehyde to add strength and allow storage at room temperature (Snyder, et al., 2012). Because E-Z Derm is composed of porcine tissue, it is considered a porcine xenograft. The shelf life is 18 months. The company Web site
promotes E-Z Derm for the temporary coverage of wounds prior to autograft, partial thickness skin loss, to protect meshed autografts, for outpatient skin loss, donor sites, skin ulcerations, and abrasions.

EZ-Derm is a porcine dermis xenograft that is used as temporary coverage for skin loss injuries. It reduces pain, fluid loss, and protein. It provides a barrier to external contamination and it provides a moist wound healing and thus protects underlying tissue in the treatment of burns, abrasions, donor sites, decubitus and chronic vascular ulcers. It can be used on any person except those who have a known sensitivity to porcine products, on patients with histories of multiple serum allergies, or on wounds with large amounts of eschar. As the wound heals, EZ-Derm will naturally slough off; as this occurs the dry edges may be trimmed off to avoid mechanical dislodgment (shearing). EZ Derm, all dermis porcine xenograft is supplied in rolls (3" wide by 12", 24" or 48" long). EZ Derm is also supplied in sheets, 7"x18" and patches, 3"x4" and 2"x2". Shelf life of EZ Derm is 18 months from date of manufacture, at room temperature storage.

E-Z Derm Biosynthetic Wound Dressing was cleared for marketing under the 510(k) process in July 1994. There is very little evidence that the use of E-Z Derm is beneficial in wound healing. In a prospective, randomized trial (n = 32), Healy and Boorman (1989) compared E-Z Derm with Jelonet as a burn dressing in patients with partial skin thickness burns. The bacterial colonization rate, need for surgical treatment, time for spontaneous healing, analgesic requirements and frequency of dressing changes were assessed in each group. No statistically significant differences were found between the 2 groups, for any of these factors.

In a controlled, prospective study (Vanстраelen, 1992), calcium sodium alginate and E-Z Derm were compared in the treatment of split-thickness skin graft donor sites on 20 patients. Half of each donor site was dressed with each material. Time to complete healing, quality of regenerated skin and patient comfort were evaluated. Time to healing was 8.1 days with alginate and 11.3 days with E-Z Derm (p < 0.001). Quality of healed skin was consistently good with the alginate, and better than under E-Z Derm in 95% of patients (p < 0.001). Hypertrophic scarring was not observed under alginate dressings but occurred in 25% of E-Z Derm-dressed sites (p < 0.01). Furthermore, evidence was found that allergic reactions to E-Z Derm could occur. Alginate was preferred by 75% of patients and none preferred E-Z Derm (p < 0.01); the remainder had no preference. The author concluded that E-Z Derm is inferior to calcium sodium alginate as a dressing for split-thickness skin donor sites.

Integra (Collagen-Glycosaminoglycan Copolymer)
Integra is a bilayered matrix wound dressing composed of a porous layer of cross-linked bovine tendon collagen and glycosaminoglycan and a semipermeable polysiloxane (silicone) layer. Integra Dermal Regeneration Template, Integra Bilayer Matrix Wound Dressing, and Integra Meshed Bilayer Wound Matrix (Integra LifeSciences Corporation, Plainsboro, NJ) are identical products composed of an acellular, biodegradable collagen-glycosaminoglycan (C-GAG) copolymer matrix coated with a thin silicone elastomer. Bovine type I collagen and chondroitin-6-sulfate, one of the major glycosaminoglycans, are co-precipitated, freeze-dried and cross-linked. The collagen structure is manufactured. The pore size has been determined to maximize in-growth of cells, and the degree of cross-linking as well as GAG composition, is designed to control the rate of matrix degradation. This extra-cellular matrix analog incorporates in approximately 2 to 3 weeks forming a neoepithelium with new vasculature. The Integra acellular cryo-preserved allodermis is clinically used in conjunction with ultra thin (0.003 to 0.006 inch) meshed split-thickness autografts in large burn wounds. According to the manufacturer, the silicone layer allows for controlled water vapor loss and provides a flexible covering for the wound surface. The collagen-glycosaminoglycan matrix is biodegradable and provides a scaffold for cell entry and capillary growth. The silicone membrane is temporary and the collagen-glycosaminoglycan matrix is remodeled as the wound area is repaired. Integra can be stored at room temperature.

In April 2001, FDA approved Integra dermal regeneration template has received premarket approval from the FDA “for the post excisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient.” Bilayer Matrix Wound Dressing was cleared for marketing under the 510(k) process in August 2002 and is indicated “for the management of wounds including partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic and vascular ulcers, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. This device is intended for one-time use.”

In January 2016, the FDA approved the Integra Dermal Regeneration Template (Omnigraft Dermal Regeneration Template) for certain diabetic foot ulcers that last for longer than 6 weeks and do not involve exposure of the joint capsule, tendon or bone, when used in conjunction with standard diabetic ulcer care. The approval was based upon the clinical results of a multi-center, randomized, controlled clinical trial (the Foot Ulcer New Dermal Replacement Study (FOUNDER) Study) (Driver et al, 2015). Omnigraft Dermal Regeneration Matrix (Omnigraft) is an advanced wound care device, comprised of a porous matrix of cross-linked bovine tendon collagen and...
glycosaminoglycan with a polysiloxane (silicone) layer. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth. Integra Dermal Regeneration Template (IDRT) is indicated for the treatment of burns and scar contractures. Through a supplemental PMA to IDRT, Omnigraft is indicated for use in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. This new indication expands the use of the product to hospital outpatient departments and physician offices.

Integra Meshed Bilayer Wound Matrix is an advanced wound care device comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan with a polysiloxane (silicone) layer. It allows draining of wound exudates and provides a flexible adherent covering for the wound surface. The collagen-glycosaminoglycan biodegradable matrix provides a scaffold for cellular invasion and capillary growth. It is indicated for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafts, post-Moh’s surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. It also may be used with negative pressure wound therapy. The manufacturer states that wound closure is typically complete within 30 days. The dosage is based on size of the wound for this single use product. Integra Meshed Bilayer Wound Matrix is packaged in sterile, single-use, double peel packages containing phosphate buffer. It is available in four sizes: 500 square centimeters (8” x 10” sheets), 250 square centimeters (4”x10” sheets), and 125 centimeters (4”x5” sheets), and 25 square centimeters (2”x2” sheets).

Stern et al (1990) stated that Integra artificial skin is an effective means of treatment for full-thickness burns. In this histological study, serial biopsy specimens were obtained from 131 patients during a period of 7 days to 2 years after application; 6 sequential phases of repair were discerned. Additionally, there were occasional unusual histological features, eosinophilic infiltration, and/or macrophage-derived giant cell formation in the wound area; however, such findings did not clinically correlate with a negative response to Integra. These investigators found that the use of Integra resulted in good repair, with rare exceptions. An intact dermis was achieved as well as definitive closure of a complete epidermal layer with a minimum of scarring.

Dantzer and Braye (2001) presented a series of 31 patients who underwent Integra grafting for reconstructive surgery at a total of 39 operational sites. The average area grafted per procedure was 267 cm2. Complications (e.g., silicone detachment, failure of the graft, and hematoma) were observed in 9 cases. The length of follow-up ranged from
0.5 to 4.0 years. Two patients (2 sites) were lost to follow-up; the final results in the remaining patients were considered to be good in 28 cases, average in 6 cases and poor in 3 cases. The disadvantages of using Integra in reconstructive surgery are the necessity of 2 operations, the risks of infection under the silicone layer, of the silicone becoming detached and of recurrence of contraction. On the other hand, Integra has many advantages including its immediate availability, the availability of large quantities, the simplicity and reliability of the technique, and the pliability and the cosmetic appearance of the resulting cover.

Ryan et al (2002) examined retrospectively the mortality and length of stay (LOS) of 270 adults with acute burns greater than or equal to 20 % of body surface area (BSA), and determined the effect of Integra on outcome. No difference in mortality was found between patients who received Integra (30 %; n = 43) and patients who did not (30 %; n = 227). Surviving Integra patients (n = 30) stayed longer, but they were more extensively injured than survivors who did not receive Integra (n = 158), and therefore longer hospitalizations were expected. In a sub-group analysis, mean LOS of Integra patients with 2 or more mortality risk factors (age over 60 years, burn size greater than 40 % BSA, or inhalation injury; n = 15) was 63 days compared with 107 days in patients with 2 or more risk factors (n = 29) who did not receive Integra (p = 0.014). The authors concluded that the use of Integra in severely injured burned adults was associated with a marked decrease in LOS.

In a post-approval study, Heimbach and associates (2003) assessed the safety and effectiveness of Integra involving 216 burn injury patients who were treated at 13 burn care facilities in the United States. The mean total body surface area burned was 36.5 % (range of 1 to 95 %). Integra was applied to fresh, clean, surgically excised burn wounds. Within 2 to 3 weeks, the dermal layer regenerated, and a thin epidermal autograft was placed. The incidence of invasive infection at Integra-treated sites was 3.1 % (95 % confidence intervals [CI]: 2.0 to 4.5%) and that of superficial infection 13.2 % (95 % CI: 11.0 to 15.7 %). Mean take rate of Integra was 76.2 %; the median take rate was 95 %. The mean take rate of epidermal autograft was 87.7 %; the median take rate was 98 %. The authors concluded that these findings further supported the conclusion that Integra is a safe and effective treatment modality in the hands of properly trained clinicians under conditions of routine clinical use at burn centers.

Heitland and colleagues (2004) stated that the clinical use of Integra has been celebrated enthusiastically as an improvement in burn therapy over a period of more than 10 years. Many case-reports have shown the positive effects of the treatment with Integra as a skin substitute. In this study, these investigators examined the alterations of Integra-usage in Germany. Fifteen German burn centers have been interviewed respectively over a time
period of 6 years with interviews in the years 1999, 2001, and 2003. The goal of this study was to focus on the problems associated with the use of artificial skin and to create a manual for Integra-therapy including indication, pre-, intra-, and post-operative treatment. Since the first Integra Users seminar in Germany in 1999, repeated interviews have been conducted with 15 German burn centers. The collected results of the last 6 years were evaluated. These results demonstrated a change in the indication for the therapy with artificial skin towards extensive full thickness burned patients and as extended indication especially for post-traumatic reconstruction. This study provided guidelines for the usage and handling of Integra and showed that Integra is an important reconstructive dermal substitute for the severely burned or post-traumatic patients if it is handled by a skilled surgeon in a correct way.

In a review on the use of Integra for full-thickness burn surgery, Fette (2005) stated that there are a lot more benefits than harms for patients. Some of the potential benefits include no histological or immunological harms, better scar appearance, less hypertrophic scarring, less itching, better movements, thinner epidermal grafts and smaller meshes possible, immediate availability, and prolonged shelf time. Potential harms include inability to replace both dermal and epidermal components, as well as the need for sequential operative procedures.

Driver et al (2015) noted that individuals with diabetes mellitus are at an increased risk of developing a diabetic foot ulcer (DFU). These researchers evaluated the safety and effectiveness of Integra Dermal Regeneration Template (IDRT) for the treatment of non-healing DFUs. The Foot Ulcer New Dermal Replacement Study was a multi-center, randomized, controlled, parallel group clinical trial conducted under an Investigational Device Exemption (IED). A total of 32 sites enrolled and randomized 307 subjects with at least 1 DFU. Consented patients were entered into the 14-day run-in phase where they were treated with the standard of care (0.9 % sodium chloride gel) plus a secondary dressing and an off-loading/protective device. Patients with less than 30 % re-epithelialization of the study ulcer after the run-in phase were randomized into the treatment phase. The subjects were randomized to the control treatment group (0.9 % sodium chloride gel; n = 153) or the active treatment group (IDRT, n = 154). The treatment phase was 16 weeks or until confirmation of complete wound closure (100 % re-epithelialization of the wound surface), whichever occurred first. Following the treatment phase, all subjects were followed for 12 weeks. Complete DFU closure during the treatment phase was significantly greater with IDRT treatment (51 %) than control treatment (32 %; p = 0.001) at 16 weeks. The median time to complete DFU closure was 43 days for IDRT subjects and 78 days for control subjects in wounds that healed. The rate of wound size reduction was 7.2 % per week for IDRT subjects versus 4.8 % per week for control subjects (p = 0.012). The authors concluded that for the treatment of
chronic DFUs, IDRT 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. They stated that IDRT could greatly enhance the treatment of non-healing DFUs.

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Driver, et al. (2015) to be at low risk of bias.

Integra Flowable Wound Matrix (LifeSciences Corp., Plainsboro, NJ) was cleared through the FDA 510(k) process in 2007. It is comprised of granulated cross-linked bovine tendon collagen and glycosaminoglycan. The granulated collagen-glycosaminoglycan is hydrated with saline and applied in difficult to access wound sites and tunneled wounds via injection with a syringe. It is indicated for the management of wounds including partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (e.g., abrasions, lacerations, second degree burns, skin tears) and draining wounds; however, there is insufficient scientific evidence regarding its effectiveness for these or any other indications.

Integra Matrix Wound Dressing is comprised of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. The collagen-glycosaminoglycan biodegradable matrix is intended to provide a scaffold for cellular invasion and capillary growth. The Integra Matrix Wound Dressing was cleared by the FDA for use in the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds. However, there is insufficient scientific evidence regarding its effectiveness for these or any other indications.

TissueMend®

TissueMend (TEI Biosciences Inc., Boston, MA), marketed by Stryker Orthopaedics (Stryker Howmedica Osteonics, Kalamazoo, MI), is a remodelable collagen matrix derived from bovine skin intended for reinforcement of soft tissues repaired by sutures or suture anchors during tendon repair surgery, including reinforcement of the rotator cuff, patellar, Achilles, biceps, quadriiceps, or other tendons. There is a lack of evidence in the peer-reviewed medical literature to support it's clinical effectiveness.
Veritas® Collagen Matrix

Veritas Collagen Matrix (Synovis Surgical Innovations, St. Paul, MN) was cleared by the FDA via the 510(k) process in 2000. It is an implantable surgical patch comprised of non-crosslinked bovine pericardium. Veritas Collagen Matrix undergoes proprietary processing that allows neo-collagen formation and neo-vascularization of the implanted device and permits replacement of the device with host tissue, or remodeling. Veritas Collagen Matrix is intended for use as an implant for the surgical repair of soft tissue deficiencies, this includes but is not limited to the following: (i) buttressing and reinforcing staple lines during lung resection (e.g., wedge resection, blebectomy, lobectomy, bullectomy, bronchial resection, segmentectomy, pneumonectomy/pneumectomy, pneumoreduction) and other incisions and excisions of the lung and bronchus; (ii) reinforcement of the gastric staple line during the bariatric surgical procedures of gastric bypass and gastric banding; and (iii) abdominal and thoracic wall repair, muscle flap reinforcement, rectal and vaginal prolapse repair, urinary incontinence treatment, reconstruction of the pelvic floor, and repair of hernias (e.g., diaphragmatic, femoral, incisional, inguinal, lumbar, paracolostomy, scrotal, umbilical). Veritas Collagen Matrix received an additional 510(k) clearance by the FDA in 2006 and is intended to minimize tissue attachment to the device in case of direct contact with viscera. There is insufficient scientific evidence regarding the effectiveness of Veritas Collagen Matrix for use as an implant for the surgical repair of soft tissue deficiencies or for any other indication.

NeuroMatrix™ Collagen Nerve Cuff and NeuroMend™ Collagen Nerve Wrap

Peripheral nerves possess the capacity of self-regeneration after traumatic injury. Transected peripheral nerves can be bridged by direct surgical coaptation of the 2 nerve stumps or by interposing autografts or biological (veins) or synthetic nerve conduits. Nerve conduits are tubular structures that guide the regenerating axons to the distal nerve stump. Early synthetic nerve conduits were primarily made of silicone because of the relative flexibility and biocompatibility. Nerve conduits are now made of biodegradable materials such as collagen, aliphatic polyesters, or polyurethanes (Pfister et al, 2007). Studies are in progress to assess the long-term biocompatibility of these implants and their effectiveness in nerve reconstruction.

According to the Collagen Matrix, Inc. (Franklin Lakes, NJ) website, NeuroMatrix is a resorbable, semi-permeable collagen-based tubular matrix that provides a protective environment for peripheral nerve repair after injury and creates a conduit for axonal growth across a nerve gap. The device slowly resorbs in vivo. The device is engineered from highly purified type I collagen fibers and are composed of dense fibers for mechanical strength. Collagen Nerve Cuff was cleared by the FDA via the 510(k)
process in September 2001. It is intended for use in repair of peripheral nerve
discontinuities where gap closure can be achieved by flexion of the extremity; however,
there is insufficient scientific evidence regarding its effectiveness for peripheral nerve
repair or for any other indication.

NeuroMend Nerve Wrap is a resorbable, semi-permeable, type 1 collagen nerve wrap
used in peripheral nerve repair.

NeuroMend (Collagen Matrix, Inc., Franklin Lakes, NJ) is a resorbable, collagen-based
rolled membrane matrix intended for use in the management of peripheral nerve injuries
in which there has been no substantial loss of nerve tissue. It has the same
technological characteristics as NeuroMatrix. Collagen Nerve Wrap was cleared by the
FDA via the 510(k) process on July 14, 2006; however, there is insufficient scientific
evidence regarding its effectiveness for peripheral nerve repair or for any other indication.

TenoGlide™ Tendon Protector Sheet

TenoGlide tendon protector sheet (Tendon Wrap tendon protector, Integra LifeSciences
Corp., Plainsboro, NJ) was cleared through the FDA 510(k) process in 2006. It is an
absorbable implant that provides a non-constricting, protective encasement for injured
tendons and is comprised of a porous matrix of cross-linked bovine Type I collagen and
glycosaminoglycan. According to the manufacturer’s website, TenoGlide provides a
protective biocompatible interface, which provides a protective environment and gliding
surface while the tendon is healing (e.g., tendons damaged by compression from trauma
or after primary repair). However, there is insufficient scientific evidence regarding its
effectiveness for tendon repair or for any other indications.

SurgiMend®

SurgiMend Collagen Matrix (TEI Biosciences, Boston, MA) was cleared through the FDA
510(k) process in 2007. It is an acellular dermal tissue matrix derived from fetal or
neonatal bovine dermis and is intended for implantation to reinforce soft tissue where
weakness exists and for the surgical repair of damaged or ruptured soft tissue
membranes. According to the 510(k) letter to the manufacturer, it is specifically indicated
for plastic and reconstructive surgery, muscle flap reinforcement, hernia repair (e.g.,
abdominal, inguinal, femoral, diaphragmatic, scrotal, umbilical, and incisional hernias),
reinforcement of soft tissues repaired by sutures or suture anchors, during tendon repair
surgery, including re-inforcement of the rotator cuff, patellar, Achilles, biceps, quadriceps,
or other tendons. It is not intended to replace normal body structure or provide the full
mechanical strength to support tendon repair of the rotator cuff, patellar, Achilles, biceps,
quadriceps or other tendons. Sutures used to repair the tear and sutures or bone anchors used to attach the tissue to the bone provide biomechanical strength for the tendon repair.

There is insufficient scientific evidence regarding the effectiveness of SurgiMend for use as an implant for the surgical repair of soft tissue deficiencies or for any other indications. There are few published reports of SurgiMend (Cheng & St. Cyr, 2012). Endress, et al. (2012) reported on a retrospective comparison of 49 breast reconstructions in 28 patients with SurgiMend with 123 reconstructions in 91 patients without the use of a graft. The study found no significant differences in overall complication rates in the group managed with SurgiMend (20.8%) versus the group managed without use of a graft (13.0%). The authors reported that the duration of drainage was significantly shorter in the group managed with SurgiMend (8.5 days) versus the comparison group (11 days). Gaster, et al. (2013) reported on a prospective study of 17 breast reconstructions in 12 patients with SurgiMend. The authors reported that SurgiMend demonstrated a very infrequent inflammatory response. The authors stated that further studies are needed to characterize the molecular mechanisms underlying tissue incorporation of this product.

Gammagraft Skin Substitute

Gammagraft (Promethean LifeSciences, Inc., Pittsburgh, PA) is an irradiated human skin allograft acquired from cadaveric donors. According to the manufacturer, its main applications are as a temporary graft for treating burns, partial and full thickness wounds, and chronic wounds including venous stasis ulcers, diabetic foot ulcers, and full-thickness wounds (Promethean LifeSciences, 2008). The manufacturer states that Gammagraft has both the epidermal and the dermal layers of human skin which makes it more durable and effective as a vapor barrier than most wound covers, especially some artificial skins, which lack the keratinocyte layer that is found in the epidermis. The manufacturer states that the irradiation process that Gammagraft undergoes produces 2 key advantages: the irradiation acts as a preservation and sterilization agent significantly reducing any risk of viral transmission of disease and allowing Gammagraft to be stored at room temperature for up to 2 years. The graft is stored in an aluminum foil package and preserved in a penicillin/gentamycin solution. The manufacturer explains that the ability to store Gammagraft at room temperature for up to 2 years makes Gammagraft readily available for use upon opening a foil pack, without the need for thawing, cleansing, and rehydration. The manufacturer also states that Gammagraft can be applied in a clinical setting without incurring operating room time for application. To use Gammagraft, the wound area is debrided, the graft is placed and a nonadherent dressing is applied, followed by a gauze dressing (Snyder, et al., 2012).
According to the manufacturer, for years, cadaver derived allograft skin has been the gold standard in the treatment of wounds and burns. For this reason, all bioengineered grafts have attempted to replicate the performance of allograft skin, and in this sense are "skin substitutes," whereas GammaGraft is human skin allograft. However, some allografts (i.e. GammaGraft) are mislabeled as "skin substitutes." Allografts differ in structure, tissue origin, and in some cases, differ from bioengineered "skin substitutes" in terms of how they are approved by the FDA. Both GammaGraft and Alloskin, are human cadaver skin that has simply been preserved. They are regulated by the FDA as human tissue for transplantation and not devices. Other products regulated under the same regulations do not retain the original structure of the donor skin and in fact, still other products are of bovine or porcine origin and may or may not be combined with synthetic materials.

There is a lack of evidence in the peer-reviewed published medical literature on the safety and effectiveness of Gammagraft Skin Substitute.

Artiss

Artiss (Baxter Healthcare Corp., Deerfield, IL), a slow-setting fibrin sealant consisting of human fibrinogen and low concentration human thrombin, received FDA approval in March, 2008 for use in attaching skin grafts onto burn patients without the use of staples or sutures. Artiss sets in approximately 60 seconds as opposed to rapid-setting fibrin sealants, which set in 5 to 10 seconds. This gives the physician additional time to position the skin graft over a burn before the graft starts to adhere to the skin. The sealant is available in a pre-filled syringe (frozen) formulation and a lyophilized form. Both dosage forms, once prepared and ready to use, can be sprayed, thus enabling application in a thin and even layer.

The FDA approved Artiss based on the results of a phase III study. The multi-center, prospective, randomized, controlled study (Foster et al, 2008) compared the use of Artiss to staples in 138 burn patients requiring skin grafting. Patients had burn wounds measuring less than or equal to 40 % of total body surface area with 2 comparable test sites measuring between 1 and 4 % total body surface area each. Wound closure at day 28 was assessed using test site planimetry and review of day 28 photographs by 3 independent blinded evaluators (primary endpoint analysis). Secondary efficacy measures included hematoma/seroma on day 1, engraftment on day 5, and wound closure on day 14. Investigator and patient-reported outcomes were also assessed. The proportion of test sites with complete wound closure at day 28 was 70.3 % in Artiss treated sites and 65.8 % in stapled sites, as assessed by planimetry. Blinded review of day 28 photographs confirmed that the rate of complete wound closure was similar between the 2 treatments, although the overall assessed rates of closure were lower than
those determined by planimetry: Artiss (43.3 %) and staples (37.0 %). The lower limit of the 97.5 % CI of the difference between Artiss and staples was -0.029, which is above the pre-defined non-inferiority margin of -0.1. Therefore, Artiss is at least as efficacious as staples at the 97.5 % 1-sided level for complete wound closure by day 28. Hematoma/seroma on day 1 occurred at significantly (p < 0.0001) fewer Artiss-treated sites (29.7 % [95 % CI: 22.2 to 38.1 %]) compared with stapled sites (62.3 % [95 % CI: 53.7 to 70.4 %]). Engraftment on day 5 was deemed to be 100 % in 62.3 % (95 % CI: 53.7 to 70.4 %) of the Artiss-treated sites and 55.1 % (95 % CI: 46.4 to 63.5 %) of the stapled sites (p = 0.0890). Complete wound closure by day 14 occurred in 48.8 % (95 % CI: 39.9 to 57.8 %) of the Artiss-treated sites and 42.6 % (95 % CI: 34.0 to 51.6 %) of the stapled sites (p = 0.2299). Artiss scored better than staples for all investigator-assessed outcomes (e.g., quality of graft adherence, preference for method of fixation, satisfaction with graft fixation, and overall quality of healing). Likewise, Artiss scored significantly better than staples for all patient-assessed outcomes (e.g., anxiety about pain and treatment preference). The safety profile of Artiss was excellent as indicated by the lack of any related serious adverse experiences. The authors concluded that Artiss is safe and effective for attachment of skin grafts with outcomes at least as good as or better than staple fixation.

**Permacol Biologic Implant**

Permacol Biologic Implant, also known as Permacol Surgical Implant (Covidien, Mansfield, MA), received FDA 510(k) marketing clearance in March 2005. It is an implant composed of acellular cross-linked porcine dermal collagen and is intended as a dermal scaffold for soft tissue surgical repairs, including hernia repair, muscle flap reinforcement, rectal prolapse (including intussusception), rectocele repair, abdominal wall defects, plastic and reconstructive surgery, and complex abdominal wall repair. According to the manufacturer, Permacol is bio-compatible and eventually becomes vascularized enabling incorporation into host tissue with associated cell and microvascular ingrowth.

Armellino et al (2006) described 6 cases of complicated incisional hernia repairs using Permacol. In 1 woman the incisional hernia was associated with an enterovaginal fistula. Three cases presented severe wound infections, 2 of which related to a previous polypropylene mesh repair, while another had an irreducible recurrent incisional hernia and 1 woman presented complete evisceration. None of the patients had post-operative or porcine-graft-related complications. Over a follow-up period of 3 to 24 months no recurrence or wound infection were reported.
Parker et al (2006) reported the results of Permacol in the repair of complicated abdominal wall defects in a retrospective review of medical records (n = 9). Indications for surgery included re-operative incisional hernia repair after removal of an infected mesh (n = 3), reconstruction of a fascial defect after resection of an abdominal wall tumor (n = 2), incisional hernia repair in a patient with a previous abdominal wall infection after a primary incisional hernia repair (n = 1), incisional hernia repair in a patient with an ostomy and an open midline wound (n = 1), emergent repair of incisional hernia with strangulated bowel and multiple intra-abdominal abscesses (n = 1), and excision of infected mesh and drainage of intra-abdominal abscess with synchronous repair of the abdominal wall defect (n = 1). At a median follow-up of 18.2 months, 1 recurrent hernia existed after intentional removal of the Permacol. This patient developed an abdominal wall abscess 7 months after hernia repair secondary to erosion from a suture. Overall, 1 patient developed exposure of the Permacol after a skin dehiscence. The wound was treated with local wound care, and the Permacol was salvaged. Despite the presence of contamination (wound classification II, III, or IV) in 5 of 9 patients (56 %), no infectious complications occurred.

In a retrospective review, Mitchell et al (2008) compared outcomes of congenital diaphragmatic hernia (CDH) repair with synthetic Gore-Tex (W. L. Gore and Associates, Neward, DE) to bioprosthetic Permacol (Tissue Science Laboratories Inc, Andover, MA). Primary repair was performed in 63 patients and patch repair in 37 patients, divided between Gore-Tex (n = 29) and Permacol (n = 8). Overall recurrences were 1 (2 %), 8 (28 %), and 0 in the primary, Gore-Tex, and Permacol groups, respectively. Median follow-up was 57 months for Gore-Tex and 20 months for Permacol. Median time to recurrence in the Gore-Tex group was 12 months, with no Permacol recurrences. Both the Gore-Tex and Permacol groups had similar co-morbidities, including prematurity, congenital heart disease (76 % and 63 %, respectively), and the need for extracorporeal membrane oxygenation support (38 % and 25 %). The authors concluded that Permacol may have lower recurrence rates compared to Gore-Tex and is a promising alternative biologic graft for CDH repair.

Hsu et al (2008) reported the results of a retrospective review of all patients in a single institution who underwent consecutive abdominal wall reconstruction with Permacol during 2006 (n = 28). Factors evaluated were body mass index, relevant co-morbidities, etiology of hernia, hernia defect size based on CT scan and intra-operative measurement, size of Permacol implant, length of hospital stay, and post-operative complications. Surgical technique was standardized among 6 surgeons and involved a single layer of acellular porcine dermis as a subfascial "underlay" graft under moderate tension upon maximal hernia reduction. Tissue expanders were not required for skin closure. Mean intra-operative hernia size was 150cm$^2$ (range of 10cm$^2$ to 600cm$^2$).
Mean age was 55 years with an average body mass index (BMI) of 34 (largest BMI of 61.4). Defects were attributed to either a previous laparotomy incision or open abdomen. Mean hospital stay was 9.67 days. At a mean follow-up of 16 months, there were 3 recurrent hernias (10.7 %) based on physical examination and post-operative CT scan evaluation. One patient developed a superficial wound dehiscence, which was successfully treated with local wound care, and 1 patient developed a cellulitis, which was successfully treated with antibiotic therapy. Four patients (14.3 %) developed a chronic, non-infected fluid collection lasting greater than 1 month that later resolved. No patient required removal of the implant due to infection. The authors concluded that Permacol can be used in the reconstruction of both small and large ventral hernias and that the biodegradable matrix serves as a safe and useful alternative to both synthetic mesh and AlloDerm.

Saray (2003) reported the feasibility of Permacol for facial contour augmentation (n = 8). It was used as a filler implant in reconstruction of post-traumatic soft-tissue defects, correcting post-parotidectomy hallowing and secondary nasal surgery to cover osseocartilaginous irregularities. However, the author reported a potential risk of inflammation and skin contractures in thin-skinned patients when implants were placed superficially.

Giordano et al (2016) reported on the results from the initial 30 patients enrolled in the MASERATI 100 prospective, observational clinical trial of Permacol paste in the treatment of anorectal fistula. Patients (N = 30) with anal fistula presenting to 10 European academic surgical units were treated with a sphincter-preserving technique using Permacol paste. Fistula healing was assessed at 1, 3, 6 and 12 months after treatment, with the primary end-point of fistula healing at 6 months post-surgery. Fecal continence and patient satisfaction were recorded at each follow-up visit and adverse events were monitored throughout the follow-up. Of the 28 patients with data at 6 months post-surgery, 15 (54%) were healed, and the healing rate was maintained at 12 months. Healing after treatment with Permacol paste was similar for intersphincteric to transsphincteric fistulae and primary or recurrent fistulae. Only one patient exhibited an adverse event (perianal abscess) that was possibly related to the treatment. At the last outpatient visit, over 60% of patients were satisfied or very satisfied with the operation.

Giordano et al (2015) conducted a retrospective study to evaluate clinical outcomes following the use of Permacol porcine collagen surgical implant in complex abdominal wall repair. A subset analysis of seven European sites from a multicenter retrospective study included patients undergoing open or laparoscopic surgery and treated with Permacol surgical implant. Inguinal, parastomal, diaphragmatic, perineal, and hiatal repairs were excluded. Only patients with at least 12 months of follow-up after surgery...
were included. A total of 109 patients (56 males and 53 females) were included. Patients had a median of two comorbidities (range 0-6). Thirty-three per cent of patients were treated for recurrent hernia. All but one case used an open approach. Sixty-six per cent were Center for Disease Control wound class II-IV at the time of surgery. Fascial closure was achieved in 69%. Median follow-up length was 720 days (range 368-2857). Recurrence rates at 1 and 2 years were 9.2 and 18.3 %, respectively, and were higher in cases without fascial closure. One-year recurrence was higher following use of an onlay technique \( (P = 0.025) \). In a multivariate analysis, among 16 comorbidities examined only fascial closure significantly impacted 1-year recurrence \( (P = 0.049) \).

Data from case reports suggest that Permacol is a promising dermal scaffold for soft tissue surgical repairs however, there is insufficient evidence of its effectiveness as an alternative to synthetic meshes and information on the potential complications associated with its use is lacking.

**DermaClose RC Continuous External Tissue Expander**

The DermaClose RC Continuous External Tissue Expanders are sterile, single-patient use skin anchors that are made of 316L surgical stainless steel. These skin anchors are placed about 1.5 cm from the edge of the wound, and they penetrate the skin to 4.5 mm into the subcutaneous tissue, and are held in place with 2 standard skin staples. Once the anchors are in place, the line from the DermaClose tension controller is attached around each skin anchor and the knob of the tensioning device is rotated until a clutch mechanism provides an audible indication that full tension has been achieved. The DermaClose now automatically maintains the proper amount of tension to gently stretch the skin on the subcutaneous planes around the wound until the edges of the wound are brought close enough together for final suturing and closure. There is insufficient evidence regarding the effectiveness of DermaClose Continuous External Tissue Expander.

Santiago et al (2016) presented a series of 14 patients who suffered massive extremity soft tissue injuries and were treated with an external tissue expansion system (DermaClose RC). Outcome measurements included time to definitive closure and method of definitive wound closure. A 5-patient subset of this group was prospectively analyzed to determine measurements including initial wound surface area (WSA), percentage reduction in WSA, and related complications. Overall time to wound coverage ranged from 1 to 6 days, with mean time to wound coverage being 4.4 days. Of the 14 patients included in the series, 12 (85.7%) were able to undergo delayed primary closure, whereas 2 required split thickness skin grafting. In the 5-patient subgroup, WSA initially
ranged from 20.25 to 1031.25 cm². Mean wound size was 262.7 cm². Decrease in WSA ranged from 44% to 93% of the initial WSA, with mean decrease being 74.3% (95% confidence interval, 57.33-91.3).

Reinard et al (2016) reviewed the medical records of patients with large cranial defects (>5 cm) following multiple complicated craniotomies who had undergone reconstructive cranioplasty with preoperative tissue expansion using the DermaClose RC device. In addition to gathering data on patient age, sex, primary pathology, number of craniotomies and/or craniectomies, history of radiation therapy, and duration of external scalp tissue expansion, the authors screened patient charts for cerebrospinal fluid (CSF) leak, meningitis, intracranial abscess formation, dermatis, and patient satisfaction rates. The 6 identified patients (5 female, 1 male) had an age range from 36 to 70 years. All patients had complicating factors such as recalcitrant scalp infections after multiple craniotomies or cranial radiation, which led to secondary scalp tissue scarring and retraction. All patients were deemed to be potential candidates for rotational flaps with or without skin grafts. All patients underwent the same preoperative tissue expansion followed by standard cranial bone reconstruction. None of the patients developed CSF leak, meningitis, intracranial abscess, dermatitis, or permanent cosmetic defects. None of the patients required a reoperation. Mean follow-up was 117 days.

Artelon

Artelon (poly[urethane urea] elastomer) is a degradable biomaterial that serves as a scaffold for tissue ingrowth and provides temporary support for healing tissue. Gisselfält et al (2002) described the synthesis, wet spinning, mechanical testing, and degradation of poly(urethane urea)s (PUURs) intended for clinical use in anterior cruciate ligament (ACL) reconstruction. The effects of soft segment chemical composition and molar mass and the kind of diamine chain extender on the material properties were investigated. It was found that the fibers made of PUUR with polycaprolactone diol (PCL530) as soft segment and MDI/1,3-DAP as hard segment (PCL530-3) have high tensile strength and high modulus and when degraded keep their tensile strength for the time demanded for the application. The authors concluded that from a chemical and mechanical point of view PUUR fibers of PCL530-3, Artelon, are suitable for designing a degradable ACL device.

Nilsson et al (2005) stated that a new spacer for the trapezio-metacarpal joint (TMC) based on a biological and tissue-preserving concept for the treatment of TMC osteoarthritis (OA) has been evaluated. The purpose was to combine a spacing effect with stabilization of the TMC joint. Artelon (Artimplant AB, Sweden) TMC Spacer is synthesized of a degradable polyurethaneurea (Artelon), which has been shown to be biocompatible over time and currently is used in ligament augmentation procedures.
Fibers of the polymer were woven into a T-shaped device in which the vertical portion separates the bone edges of the TMC joint and the horizontal portion stabilizes the joint. A total of 15 patients with disabling pain and isolated TMC OA were included in the study; 10 patients received the spacer device and the remaining 5 (control group) were treated with a trapezium resection arthroplasty with abductor pollicis longus (APL) stabilization. The median ages of the 2 groups were 60 and 59 years, respectively. Pain, strength, stability, and range of motion were measured before and after surgery. Radiographical examination was performed in all patients before and after surgery. At follow-up evaluation 3 years after surgery, an unbiased observer evaluated all patients. Biopsy specimens were obtained from 1 patient 6 months after surgery. All patients were stable clinically without signs of synovitis. In both groups all patients were pain-free. The median values for both key pinch and tripod pinch increased compared with before surgery in the spacer group but not in the APL group. The biopsy examinations showed incorporation of the device in the surface of the adjacent bone and the surrounding connective tissue. No signs of foreign-body reaction were seen. The authors concluded that the findings in this study showed significantly better pinch strength after Artelon TMC Spacer implantation into the TMC joint compared with APL arthroplasty. This was a small retrospective study; its findings need to be validated.

Huss et al (2008) stated that full thickness skin wounds in humans heal with scars, but without regeneration of the dermis. A degradable PUUR, Artelon is already used to reinforce soft tissues in orthopedics, and for the treatment of osteoarthritis of the hand, wrist, and foot. These researchers performed in vitro experiments followed by in vivo studies to examine if the PUUR is biocompatible and usable as a template for dermal regeneration. Human dermal fibroblasts were cultured on discs of PUUR, with different macrostructures (fibrous and porous). They adhered to and migrated into the scaffolds, and produced collagen. The porous scaffold was judged more suitable for clinical applications and 4 mm Artelon, 2 mm-thick discs of porous scaffold (12 % w/w or 9 % w/w polymer solution) were inserted intradermally in 4 healthy human volunteers. The implants were well-tolerated and increasing ingrowth of fibroblasts was seen over time in all subjects. The fibroblasts stained immunohistochemically for procollagen and von Willebrand factor, indicating neocollagenesis and angiogenesis within the scaffolds. The authors concluded that PURR scaffold may be a suitable material to use as a template for dermal regeneration.

Wojan et al (2015) conducted a Cochrane review to assess the effects of different surgical techniques, including Artelon joint resurfacing, for trapeziometacarpal (thumb) osteoarthritis. The authors searched the following sources up to August 2013: CENTRAL (The Cochrane Library 2013, Issue 8), MEDLINE (1950 to August 2013), EMBASE (1974 to August 2013), CINAHL (1982 to August 2013), Clinicaltrials.gov (to August 2013) and
World Health Organization (WHO) Clinical Trials Portal (to August 2013). The authors selected randomized controlled trials (RCTs) or quasi-RCTs where the intervention was surgery for people with thumb osteoarthritis. Outcomes were pain, physical function, quality of life, patient global assessment, adverse events, treatment failure or trapeziometacarpal joint imaging. We excluded trials that compared non-surgical interventions with surgery. The authors used standard methodological procedures expected by the Cochrane Collaboration. Two review authors independently screened and included studies according to the inclusion criteria, assessed the risk of bias and extracted data, including adverse events. The authors included 11 studies with 670 participants. Seven surgical procedures were identified (Artelon joint resurfacing, trapeziectomy with ligament reconstruction and tendon interposition (LRTI), trapeziectomy, trapeziectomy with ligament reconstruction, trapeziectomy with interpositional arthroplasty (IA), arthrodesis and Swanson joint replacement). Most included studies had an unclear risk of most biases which raises doubt about the results. No procedure demonstrated any superiority over another in terms of pain, physical function, quality of life, patient global assessment, adverse events, treatment failure (re-operation) or trapeziometacarpal joint imaging. One study demonstrated a difference in adverse events (mild-moderate swelling) between Artelon joint replacement and trapeziectomy with tendon interposition. However, the quality of evidence was very low due to a high risk of bias and imprecision of results. Low quality evidence suggests trapeziectomy with LRTI may not provide additional benefits or result in more adverse events over trapeziectomy alone. Mean pain (three studies, 162 participants) was 26 mm on a 0 to 100 mm VAS (0 is no pain) for trapeziectomy alone, trapeziectomy with LRTI reduced pain by a mean of 2.8 mm (95% confidence interval (CI) -9.8 to 4.2) or an absolute reduction of 3% (-10% to 4%). Mean physical function (three studies, 211 participants) was 31.1 points on a 0 to 100 point scale (0 is best physical function, or no disability) with trapeziectomy alone, trapeziectomy with LRTI resulted in slightly lower function scores (standardized mean difference 0.1, 95% CI -0.30 to 0.32), an equivalent to a worsening of 0.2 points (95% CI -5.8 to 6.1) on a 0 to 100 point scale (absolute decrease in function 0.03% (-0.83% to 0.88%)). Low quality evidence from four studies (328 participants) indicates that the mean number of adverse events was 10 per 100 participants for trapeziectomy alone, and 19 events per 100 participants for trapeziectomy with LRTI (RR 1.89, 95% CI 0.96 to 3.73) or an absolute risk increase of 9% (95% CI 0% to 28%). Low quality evidence from one study (42 participants) indicates that the mean scapho-metacarpal distance was 2.3 mm for the trapeziectomy alone group, trapeziectomy with LRTI resulted in a mean of 0.1 mm less distance (95% CI -0.81 to 0.61). None of the included trials reported global assessment, quality of life, and revision or re-operation rates. Low-quality evidence from two small studies (51 participants) indicated that trapeziectomy with LRTI may not improve function or slow joint degeneration, or produce additional adverse events over trapeziectomy and
ligament reconstruction. The authors stated that they are uncertain of the benefits or harms of other surgical techniques due to the mostly low quality evidence from single studies and the low reporting rates of key outcomes. There was insufficient evidence to assess if trapeziectomy with LRTI had additional benefit over arthrodesis or trapeziectomy with IA. There was also insufficient evidence to assess if trapeziectomy with IA had any additional benefit over the Artelon joint implant, the Swanson joint replacement or trapeziectomy alone. The authors did not find any studies that compared any other combination of the other techniques mentioned above or any other techniques including a sham procedure. The authors concluded that they did not identify any studies that compared surgery to sham surgery and they excluded studies that compared surgery to non-operative treatments. They were unable to demonstrate that any technique confers a benefit over another technique in terms of pain and physical function. Furthermore, the included studies were not of high enough quality to provide conclusive evidence that the compared techniques provided equivalent outcomes.

Currently, there is insufficient evidence to support the use of Artelon for ACL reconstruction, rotator cuff repair, TMC osteoarthritis, and other indications.

**TheraSkin**

TheraSkin (Soluble Systems, Newport News, VA) is a biologically active, cryopreserved human skin allograft with both epidermis and dermis layers. It is similar to living skin equivalent (LSE) and provides a supply of living cells, fibroblasts and keratinocytes and a fully developed extracellular matrix (Snyder, et al., 2012). However, TheraSkin is a minimally manipulated allograft and contains a larger quantity of collagens compared to living skin equivalent. TheraSkin does not contain any synthetic or animal materials. According to the manufacturer, TheraSkin is designed to promote wound healing by providing cellular and extracellular components with growth factors, cytokines and collagen and to be a natural barrier to infection. TheraSkin has been used for repair of human skin, including dehisced surgical wounds, diabetic foot ulcers, necrotizing fasciitis, pressure ulcers, radiation burns and venous stasis ulcers. It has also been used for repair of skin over any wound including those with exposed bone and joint capsule, muscle or tendon. TheraSkin is regulated by the FDA as a human cellular and tissue based product. The FDA generally permits products regulated solely as human tissue to be commercially distributed without premarket clearance or approval. TheraSkin is marketed by Soluble Systems and tissue is provided by the Skin and Wound Allograft Institute (SWAI, Virginia Beach, VA), a wholly owned subsidiary of LifeNet Health, Inc.

TheraSkin is cryopreserved human skin procured from consented and screened tissue donors that is used to provide a physiological and mechanical barrier that reduces environmental contamination and assists in the promotion of granulation tissue and
epithelialization. The finished allograft is between 0.2 to 0.5 mm in thickness and contains both human epidermis and dermis tissues. The product is provided in a meshed form at a 1:1.5 ratio. TheraSkin contains: 1) both collagen and elastin which provide structural support and resilience, 2) a compliment of growth factors to assist healing, 3) multiple cytokines that assist in epithelialization and modulate the proliferation and differentiation of epithelium, and 4) structures that allow phagocytosis of bacteria without requirement of antibody production. TheraSkin is most commonly used in the treatment of partial and full-thickness wounds including chronic wounds, pressure ulcers, diabetic foot ulcers, venous stasis ulcers and burns. TheraSkin is generally applied like an autograft, insuring that the dressing is in close contact with the wound surface and that shear is minimized. According to the manufacturer, clinical experience supports up to five weekly to bi-weekly applications of cryopreserved human skin allograft to close the wound to the point of treatment with non-biologic wound dressings or to prepare the wound bed for autograft.

Landsman et al (2010) evaluated the safety and efficacy of TheraSkin in a retrospective study of 188 patients with either a diabetic foot ulcer (n = 54) or a venous leg ulcer (n = 134). Multi-variate logistic regression was used to evaluate the relationship between baseline wound size and the proportion of healed wounds after 12 and 20 weeks from initial allograft application. The authors found that by the 12th week, diabetic foot ulcers closed 60.38 % of the time and venous leg ulcers closed 60.77 % of the time. After 20 weeks, the number of closed diabetic foot ulcers increased to 74.1 % and the number of venous leg ulcers increased to 74.6 %. The mean wound size in the diabetic foot ulcer group was 6.2cm (± 11.8) and 11.8cm (± 22.5) in the venous leg ulcer group. The mean number of TheraSkin allografts required ranged from 1 to 8, with an average of 2.03 (± 1.47) at the 12-week point and an average of 3.23 (± 2.77) at the 20-week point. Multi-variate logistic regression was used to calculate the odds of wound healing by week 12 and week 20 in each group. No adverse events related to TheraSkin were reported.

Sanders et al (2014) reported on a prospective, multicenter, randomized, controlled clinical trial to compare Dermagraft, an in vitro-engineered, human fibroblast-derived dermal skin (HFDS) substitute, and Theraskin, a biologically active cryopreserved human skin allograft (HSA), to determine the relative number of diabetic foot ulcers (DFUs) healed (100% epithelialization without any drainage) and the number of grafts required by week 12. Secondary variables included the proportion of healed patients at weeks 16 and 20, time to healing during the study, and wound size progression. The 23 eligible participants (11 randomized to the HSA, 12 to the HFDS group) were recruited from two hospital-based outpatient wound care centers. Baseline patient (body mass index, age, gender, race, type and duration of diabetes, presence of neuropathy and/or peripheral arterial disease, tobacco use) and wound characteristics (size and duration) were
recorded, and follow-up visits occurred every week for up to 20 weeks. Subjects included adults with diabetic foot ulcers one month or more in duration. Excluded were subjects with large ulcers (10 cm² or greater), infection, Charcot foot, and inadequate circulation to the foot. Descriptive and multivariate regression analyses were used to compare wound outcomes. At baseline, no statistically significant differences between patients and wounds were observed. At week 12, seven (63.6%) patients in the HSA and four (33.3%) in the HFDS group were healed (P = 0.0498). At the end of the 20-week evaluation period, 90.91% of HSA versus 66.67% of HFDS were healed (P = 0.4282). Among the subset of wounds that healed during the first 12 weeks of treatment, an average of 4.36 (range 2–7) HSA grafts were applied versus 8.92 (range 6–12) in the HFDS subset (P <0.0001, SE 0.77584). Time to healing in the HSA group was significantly shorter (8.9 weeks) than in the HFDS group (12.5 weeks) (log-rank test, P = 0.0323). Limitations of this study include small sample size, omission of reporting certain important baseline variables and outcomes, and lack of blinding of persons assessing outcomes.

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Sanders, et al. (2014) to be at moderate risk of bias.

Other references provided by the manufacturer of TheraSkin are to studies that are either unpublished or are in journals not indexed by the National Library of Medicine MEDLINE database of peer-reviewed journals (Soluble Systems, 2011; Lin, et al., 2011; Budny and Ley, 2013; Treadwell, 2011; DiDomenico, et al., 2011).

A draft guideline by the National Institute for Health and Clinical Excellence (NICE) on the use of skin substitutes in the inpatient management of diabetic foot problems stated that the evidence for the clinical effectiveness of wound dressings in treating diabetic foot problems was of low quality and that only low-quality evidence on dermagraft and graftskin demonstrated positive effects on complete wound healing (at least 50 % wound closure). However, no positive effect was demonstrated on the critical outcome (reduction in amputation). Furthermore, the guideline stated that in the absence of strong evidence on particular wound dressings, clinicians should use the wound dressings with the lowest acquisition cost, taking into account their clinical assessment of the wound, the experience and preferences of the patient, and the clinical circumstances. In addition, the draft guideline stated that the use of skin substitute treatments for the inpatient management of diabetic foot problems should only be offered as part of a clinical trial (NICE, 2011).

Wilson et al (2016) noted that wounds with exposed bone or tendon continue to be a challenge for wound care physicians, and there is little research pertaining to the treatment of these particular wounds with allograft skin. In a retrospective study, these
researchers examined the safety and effectiveness of a biologically active cryo-preserved human skin allograft for treating wounds with exposed bone and/or tendon in the lower extremities. A total of 15 patients with 15 wounds at a single hospital-based wound care center were included in the study; 11 wounds had exposed bone, 1 wound had exposed tendon, and 3 wounds had exposed bone and tendon. Standard treatment principles with adjunctive cadaveric allograft application were performed on all wounds in the study. In this study 14/15 (93.3 %) of the wounds healed completely. The mean duration of days until coverage of the bone and/or tendon with granulation tissue was 36.14 (5.16 weeks) (range of 5 to 117 days). Mean duration to complete healing of the wound was 133 days (19 weeks) (range of 53 to 311 days). The mean number of grafts applied was 2. There were no adverse events (AEs) directly related to the graft; and 0 major amputations and 1 minor amputation occurred. The authors concluded that this study found biologically active cryo-preserved human skin allografts to be safe and effective in treating difficult wounds with exposed bone and/or tendon. To the authors' knowledge, this was the largest study to-date focused on the utilization of allograft skin as an adjunct therapy for lower extremity wounds with exposed tendon and/or bone.

The authors stated that this study was limited by its retrospective design; potential selection bias was inherent to a retrospective study. There were no controls and, thus, no comparative analysis could be carried out. The study was also limited by small sample size (n = 15). However, this was the largest study utilizing human cadaveric skin allograft as an adjunct therapy for lower extremity ulcers with exposed tendon and/or bone. Though wounds were of different etiology -- diabetic foot ulcer, traumatic, surgical, and decubitus -- this did not appear to change outcomes. Some treatment modalities, such as the use of negative pressure wound therapy versus simple bolster dressing, differed between wounds, but no statistical difference was noted between the treatments.

Towler et al (2018) noted that chronic venous leg ulcers (VLUs) are responsible for significant morbidity and health care costs worldwide. In a pilot study, these investigators evaluated the effectiveness 2 biologically active grafts, TheraSkin and Apligraf, in conjunction with compression therapy. The study, not industry-sponsored, was designed and conducted as a prospective, head-to-head, single-site, randomized clinical trial to assess differences in healing rates, adverse outcomes, and treatment costs. The healing rates were different but not statistically significant, there were no adverse outcomes, and TheraSkin averaged $2,495.33 and Apligraf averaged $4,316.67 per subject. The authors concluded that the findings of this study suggested that TheraSkin may provide equivalent or superior outcomes to Apligraf while reducing costs.

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Towler, et al. (2018) to be at moderate risk of bias.
Hyalomatrix

Hyalomatrix (Anika Therapeutics, Inc., Bedford, MA, formerly Fidia Advanced Biopolymers, Abano Terme, Italy) is a bilayered wound dressing composed of a nonwoven pad made of a benzyl ester of hyaluronic acid (HYAFF 11), a long-acting derivative of hyaluronic acid, and a semipermeable silicone membrane providing a microenvironment (Snyder, et al., 2012). The nonwoven pad contacts the wound and, according to the manufacturer, "provides a three dimensional matrix for cellular invasion and capillary growth." The silicone membrane "controls water vapor loss, provides a flexible covering for the wound surface, and adds increased tear strength to the device." The HYAFF 11 matrix is biodegradable. The company believes that "when the integration of the HYAFF based material in the newly formed dermal matrix has progressed, a well-vascularized granulation tissue forms. This provides for wound closure via spontaneous re-epithelialization or acts as a suitable dermal layer for skin grafting."

Hyalomatrix KC Wound Dressing was cleared for marketing under the 510(k) process in July 2001 for "the management of wounds in the granulation phase such as pressure ulcers, venous and arterial leg ulcers, diabetic ulcers, surgical incisions, second degree burns, skin abrasions, lacerations, partial-thickness grafts and skin tears, wounds and burns treated with meshed grafts. It is intended for use as a temporary coverage for wounds and burns to aid in the natural healing process." it also provides a wound preparation to support the implantation of autologous skin grafts. In the FDA 510(k) database, the 510(k) refers to Laserskin Dressing as the device; however, in the 510(k) summary, the proprietary name is Hyalomatrix KC Wound Dressing and the name Laserskin is not mentioned (Snyder, et al., 2012).

Hyalomatrix PA is a bilayered, sterile, flexible, and conformable non-woven pad entirely composed of HYAFF 11, a benzyl ester of hyaluronic acid. The hyaluronic acid is derived from bacterial fermentation. The HYAFF 11 serves as a scaffold to allow cell colonization and capillary growth. On the back layer of the HYAFF 11 is a semipermeable silicone membrane that does not contact the patient and controls water vapor loss. Hyalomatrix PA is applied directly to a wound. After two to three weeks the silicone layer is removed, but the HYAFF II layer is mostly or completely absorbed into the underlying tissue, and the underlying tissue typically has healed or has become ready for grafting. Hyalomatrix PA is packaged in several different sizes: 5 cm x 5 cm sold separately and in boxes of 5 and 10 (in individual pouches); 10 cm x 10 cm sold separately; and 10 cm x 20 cm sold separately.

Hyalomatrix PA Wound Dressing was cleared for marketing under the 510(k) process in December 2007. The company refers to Hyalomatrix PA by its trade name Hyalomatrix. In the 510(k) documents Hyalomatrix is described as a bilayered dressing composed of a
nonwoven pad made of HYAFF 11 and a semipermeable silicone membrane. Hyalomatrix “is indicated for the management of wounds including: partial and full-thickness wounds; second-degree burns; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undetermined wounds; surgical wounds (donor sites/grafs, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, skin tears); and draining wounds. The device is intended for one-time use.” The predicate device was “Hyalomatrix KC (Laserskin) Wound Dressing.”

Jaloskin (Anika Therapeutics, Inc., Bedford, MA) was cleared for marketing under the 510(k) process in January 2010 for “the management of superficial moderately exuding wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites/grafs, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, skin tears) and first and second degree burns.” Jaloskin is a semipermeable, transparent film dressing, composed of HYAFF 11 only. The hyaluronic acid is derived from bacterial fermentation. Anika Therapeutics, Inc. (Bedford, MA), acquired Fidia Advanced Biopolymers S.r.l. (currently Anika Therapeutics S.r.l.) in December 2009. The Anika Therapeutics Web site advertises Hyalomatrix and Jaloskin.

The manufacturer cites preclinical studies to support the theoretical basis for use of Hyalomatrix, showing that fetal skin contains high levels of sustained hyaluronic acid (Longaker, et al., 1989; Longaker, et al., 1991; Wilgus, 2007; Dillon, et al., 1994; Longas, et al., 1987; Moseley, et al., 2003). Fetal skin can regenerate without scarring. With age, the skin’s ability to produce hyaluronic acid decreases, tissue elasticity decreases, and wound healing is fibrotic.

Caravaggi et al (2003) reported on a total of 79 patients with diabetic dorsal (n = 37) or plantar (n = 42) ulcers were randomized to either the control group with nonadherent paraffin gauze (n = 36) or the treatment group with HYAFF-based autologous dermal and epidermal tissue-engineered grafts (n = 43). Weekly assessment, aggressive debridement, wound infection control, and adequate pressure relief (fiberglass off-loading cast for plantar ulcers) were provided in both groups. Complete wound healing was assessed within 11 weeks. Safety was monitored by adverse events. The investigators reported that complete ulcer healing was achieved in 65.3 % of the treatment group and 49.6 % of the control group, a difference that was not statistically significant (p = 0.191). Plantar foot ulcer healing was not statistically significantly different (55 % and 50 %) in the treatment and control groups, but dorsal foot ulcer healing was significantly different, with 67 % in the treatment group and 31 % in the control group (p = 0.049).
Uccioli et al (2011) evaluated the efficacy of a HYAFF autograft in the treatment of diabetic foot ulcers compared with standard care in 180 patients with dorsal or plantar diabetic foot ulcers (unhealed for ≥1 month). Subjects were randomized to receive Hyalograft-3D autograft first and then Laserskin autograft after 2 weeks (n = 90; treatment group) or nonadherent paraffin gauze (n = 90; control group). The primary efficacy outcome was complete ulcer healing at 12 weeks. Wound debridement, adequate pressure relief, and infection control were provided to both groups. There was no significant difference between treatment and control groups in the primary efficacy outcome: at 12 weeks, complete ulcer healing was similar in both groups (24% of treated vs 21% controls).

Caravaggi et al (2011) reported on the FAST study, which evaluated the performance and safety of Hyalomatrix PA dermal substitute in the treatment of chronic wounds of different etiology. This was a multicenter, prospective, observational study involving 70 Italian centers and 262 elderly patients. Patients were observed from the start of treatment with a dermal substitute (Hyalomatrix PA [HPA]) until healthy dermal tissue suitable for a thin autograft was visible or until the growth of new epithelium from the wound edge was reported. Tracking the wound edge advancement was used to assess the dermal substitute's performance. The main endpoint was the reduction in threshold area (≥ 10%) of the ulcer. Treated ulcers were characterized as follows: 46% vascular, 25% diabetic foot, 12% traumatic wounds, 2% pressure ulcers and 15% other. The investigators reported that reepithelization (≥ 10%) was achieved in 83% of ulcers in a median time of 16 days. Twenty-six percent (26%) of wounds achieved 75% reepithelization within the 60-day follow-up period using only HPA treatment. A follow-up showed that 84% of ulcers achieved complete reepithelialization by secondary intention. The primary limitation of this open-label observational study was a lack of best standard-of-care comparison group.

Motolese et al (2013) presented a series of 16 patients affected by venous ulcers who underwent Hyalomatrix PA grafting for reconstructive surgery. The authors reported that the average area grafted per procedure was 153 cm(2). The length of followup ranged from 0.5 to 1 year. The final results were considered to be good in 12 cases, fair in 3 cases, and poor in one case. Limitations of this study include its retrospective design (case series) and lack of comparison group.

Alvarez and colleagues (2017) provided an analysis of a prospective, parallel, randomized, single-center study involving 16 subjects in an outpatient wound care center setting. The aim of the study was to evaluate the safety and effectiveness of a hyaluronic acid extracellular matrix (HA; Hyalomatrix Wound Matrix, Fidia Farmaceutici S.p.a., Abano Terme, Italy) for the treatment of chronic VLUs. Each subject with a VLU was
randomized (1:1) to receive either HA plus compression with a multilayer compression bandage (MLC) or standard care consisting of a non-adherent primary dressing plus a MLC (control). All wounds were VLUs (confirmed by duplex imaging) and all had adequate arterial circulation (ABI greater than 0.75). All VLUs had a history of not healing for more than 6 months, and all were in the lower leg (between the mid-calf and below malleoli). Traditional MLC with a short stretch and elastic cohesive bandage was used in all patients. The primary end-point was incidence of wound healing at 12 and 16 weeks, and secondary end-points were time to healing and ulcer recurrence. Wound evaluations were performed weekly and wound surface area was measured by photodigital planimetry. The incidence of wound healing at 12 weeks was 66.6 % for the HA group and 14.2 % for the control (p = 0.066). At week 16, 87.5 % were healed in the HA group compared with 42.8 % in the control (p = 0.059). The mean time to healing in the HA-treated group was 41 days compared with 104 days in the control (p = 0.029). The authors concluded that the findings of this interim analysis indicated that continuation of the present study is needed. They stated that a more reliable power calculation from these findings forecasts that the inclusion of 50 to 60 participant would be needed to achieve the statistical goal (p < 0.05) related to the primary end-point. The main drawbacks of this study were its small size (n = 16), open-label design, and a single-center setting.

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Alvarez, et al. (2017) to be at moderate risk of bias.

hMatrix

hMatrix acellular dermis is a dermal scaffold processed from donated human skin. The skin is processed to remove the epidermal layer from the dermis as well as the epidermal and dermal cells from the collagen and elastin that constitutes the dermal matrix. The dermal matrix is then packaged and sterilized using low-dose gamma irradiation; the product is stored and supplied frozen. hMatrix is indicated for use to replace damaged or inadequate integumental tissue. It is designed for homologous use only. Specific uses of hMatrix include use as a wound covering, abdominal wall repair, breast reconstruction, and for use in supplemental support, reinforcement, or covering of tendons or periosteum. There are few published studies addressing the use of hMatrix for wound treatment.

hMatrix is a dermal substitute derived from the dermal layer of human skin by removing the epidermal layer and cellular components from the dermis. It is indicated for use to replace damaged or inadequate integumental tissue, indicated for homologous use only. Specific uses of hMatrix include use as a wound covering, abdominal wall repair, breast reconstruction, soft tissue grafting in craniomaxillofacial applications, and for use in
supplement support, reinforcement, or covering of tendons or periosteum. hMatrix contains elastin, collagen, proteoglycans, and vascular channels which provide an ideal environment for revascularization and cellular repopulation when surgically implanted or grafted. When used as a wound covering, hMatrix is placed over the derided wound site and the graft is fixed via the use of sutures or staples. hMatrix is packaged frozen and is designed for single-use. It is provided in three thicknesses in specific sizes ranging from 1cm x 2cm to 5cm x 10cm to allow for patient specific needs, as determined by surgeons.

In an evidence-based review, Clemens and Kronowitz (2012) evaluated the clinical impact of acellular dermal matrix for breast reconstruction in the setting of radiation therapy. The MEDLINE and EMBASE databases were reviewed for articles published between January of 2005 and February of 2012. The authors also reviewed their institutional experience of consecutive patients who met these criteria between January of 2008 and October of 2011. A total of 13 articles were identified for review: 3 animal studies on acellular dermal matrix and 10 with level III evidence of its use in humans. The 10 clinical studies included 246 irradiated patients. The M. D. Anderson experience included 30 irradiated acellular dermal matrix patients for a total of 276 irradiated patients evaluated in this review. Use of acellular dermal matrix in implant-based breast reconstruction in the setting of radiation therapy did not predispose to higher infection or overall complication rates or prevent bioprosthetic mesh incorporation. However, the rate of mesh incorporation may be slowed. Its use allowed for increased intra-operative saline fill volumes, which improved aesthetic outcomes and allowed patients to awake from surgery with a formed breast. The authors concluded that use of acellular dermal matrix for implant-based breast reconstruction does not appear to increase or decrease the risk of complications, but it might provide psychological and aesthetic benefits. They stated that multi-center or single-center RCTs that provide high-quality, level I evidence are warranted.

Shridharani and Tufaro (2012) conducted a systematic review of acellular dermal matrices in head and neck reconstruction. After searching the PubMed database and following further refinement (based on the authors’ inclusion and exclusion criteria), the authors identified 30 studies that provided information about patients who had undergone head and neck reconstruction with the use of acellular dermal matrix. Studies had to report quantifiable objective results in patients who were older than 1 year and younger than 90 years. The authors excluded single case reports, studies with fewer than 10 patients, and studies not published in English. The optimal material used as an implant for reconstruction possesses the following properties: facilitation of vascular ingrowth, decreased propensity to incite inflammation, biologic inertness, resistance to infection, and ease of handling. Acellular dermal matrix possesses many of these properties and is utilized in reconstructing nasal soft tissue and skeletal support, tympanic membrane,
peri-orbital soft tissue, extra-oral and intraoral defects, oropharyngeal defects, dura mater, and soft-tissue deficits from parotidectomy. Furthermore, it is used to assist in preventing Frey syndrome following parotidectomy and surgical treatment of facial paralysis. The authors concluded that use of acellular dermal matrix for head and neck reconstruction has expanded exponentially and is validated in many studies. Moreover, they noted that further prospective RCTs are needed to further examine the effectiveness of acellular dermal matrix in head and neck reconstruction.

In a systematic review, Janis et al (2012) examined the benefits of acellular dermal matrices in abdominal wall reconstruction. The MEDLINE database was reviewed, including all publications as of December 31, 2011, using the search terms "dermal matrix" or "human dermis" or "porcine dermis" or "bovine dermis," applying the limits "human" and "English language". Prospective and retrospective clinical articles were identified. A total of 40 eligible articles were identified and included in this review; 35 of the studies were level IV; the remaining studies were level III. Acellular dermal matrix was used to reconstruct the abdominal wall in a wide range of clinical settings, including trauma, tumor resection, sepsis, and hernia repairs. The operative methods varied widely among clinical studies. While the heterogeneity of the patient populations and techniques limited interpretation of the data, concerns were identified regarding high rates of hernia recurrence with acellular dermal matrix use. The authors concluded that high-quality data derived from level I, II, and III studies are needed to determine the indications for acellular dermal matrix use and the optimal surgical techniques to maximize outcomes in abdominal wall reconstruction.

Ellis and Kulber (2012) reviewed the current literature on the use of acellular dermal matrix in forearm, wrist, and hand reconstruction. A comprehensive literature search was performed using the Cochrane Database of Systematic Reviews, MEDLINE, PubMed, and Web of Knowledge. Articles were categorized as acellular dermal matrix used in soft-tissue repair and in ligament reconstruction. Search terms included "acellular dermal matrix," "biologic dressing," "skin replacement," "dermal allograft," "AlloDerm," "FlexHD," "Permacol," and "Strattice". These were all cross-referenced with "forearm," "wrist," and "hand". Data extraction focused on indications, surgical techniques, clinical outcomes, and complications. Exclusion criteria included regeneration templates, neonatal foreskin, and review articles. More than 100 articles published between 1994 and 2011 were identified. Upon final review, 5 prospective case-control studies, 3 retrospective case-control studies, 4 case reports, 1 cross-sectional cohort, 1 prospective consecutive series, and 1 study type unknown were evaluated. Matrix was most commonly used in burn reconstruction. It has also been used in ligament and joint reconstruction for first carpometacarpal arthritis. One article illustrated the use of porcine matrix in basal joint arthritis, a practice that was abruptly terminated because of a concern over increased
infections. The authors concluded that the clinical indications for acellular dermal matrix have increased throughout the last 15 years. Hand surgeons have been cautious but diligent in developing alternative treatment options in hand reconstruction, with a focused effort to reduce donor-site morbidity. They stated that although acellular dermal matrices continue to find innovative uses to solve upper extremity surgical problems, more comparative prospective trials are needed.

**AmnioShield Amniotic Tissue Barrier**

AmnioShield amniotic tissue barrier (Alphatec Spine, Carlsbad, CA) is a amniotic membrane-based implantable barrier to prevent/reduce scar tissue formation. There is a lack of evidence regarding the effectiveness of the AmnioShield amniotic tissue barrier.

**Conexa Reconstructive Matrix**

Conexa reconstructive matrix (Tornier, Inc., Edna, MN) is a porcine dermis tissue substitute that is cleared through the 510(k) process as LifeCell Tissue Matrix (LTM) Surgical Mesh (LifeCell Corporation, Branchburg, NJ). According to the FDA (2008), the matrix is intended for the reinforcement of soft tissue repaired by sutures or suture anchors during tendon repair surgery including re-reinforcement of Achilles, biceps, patellar, quadriceps, rotator cuff, or other tendons. Indications for use also include the repair of body wall defects that require the use of reinforcing or bridging material to obtain the desired surgical outcome. The device is not intended to replace normal body structure or provide the full mechanical strength to support tendon repair of the Achilles, biceps, patellar, quadriceps, rotator cuff, or other tendons. Sutures, used to repair the tear, and sutures or bone anchors used to attach the tissue to the bone, provide biomechanical strength for the tendon repair. Based on the thickness of the matrix, this product is available as Conexa 100 and Conexa 200.

Conexa Reconstructive Tissue Matrix is an implantable orthopedic tissue graft used to reinforce orthopedic soft tissue repairs. It is made from porcine dermis processed to remove porcine cells and other cross-species contaminants, and sterilized. The Conexa Reconstructive Tissue Matrix is intended for the reinforcement of soft tissue repaired by sutures or suture anchors during tendon repair surgery and reinforcement for rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. Other indications for use include the repair of body wall defects which require the use of reinforcing or bridging material to obtain the desired surgical outcome. The manufacturer claims that Conexa supports a regenerative mechanism of action, instead of a “repair” mechanism of action (i.e. scar tissue formation). With repair mechanisms of action, the body will attempt to repair the graft site with scar tissue, resulting in weaker, less functional surgical outcomes. By providing an intact, undamaged, sterile extracellular matrix, Conexa acts as a host-
friendly biologic scaffold that supports attachment of the body's natural tissue regeneration mechanism to produce new tendon tissue and rapid population of new capillaries to provide blood flow and needed nutrition. Conexa also provides mechanical load sharing and reduces the stress on the repair site thereby reducing the chance of a re-tear or sub-optimal repair outcome. Conexa is supplied in a range of sizes from 2x4 cm to 5x10 cm. The size is selected by the surgeon depending on the repair size to be reinforced and may be cut or shaped as needed. Conexa is supplied in a terminally sterile pouch contained in an outer box. There is one Conexa unit per box. According to the manufacturer, only GraftJacket and Conexa have been validated in primate animal models in published peer-review tissue engineering literature to support a regenerative mechanism of action.

However, there is insufficient evidence to support the safety and effectiveness of Conexa as studies have primarily been in the form of individual case reports (Stover et al, 2009).

C-QUR™ Biosynthetic Mesh

C-QUR™ (Atrium Medical Corporation, Hudson, NH) biosynthetic mesh has been proposed for use in abdominal surgical repair procedures. Currently, there are no peer-review published studies available describing this product or its use in human subjects. Further investigation is needed to ascertain the clinical value of C-QUR™ biosynthetic mesh.

EpiFix Amniotic Membrane Allograft

EpiFix amniotic membrane allograft (MiMedx Group, Inc., Kennesaw, GA) is a biologic human amniotic membrane processed through Surgical Biologic's proprietary Purion® process, which combines cleaning, dehydration and sterilization to produce a safe, technically sterilized tissue allowing for storage at room temperature. It is used for the treatment of dermal wounds.

EpiFix is a multi-layer biologic dehydrated human amniotic membrane allograft comprised of an epithelial layer and two fibrous connective tissue layers specifically processed to be used for the repair or replacement of lost or damaged dermal tissue. It is prepared from human placenta. The processed allograft contains collagen types IV, V, and VII that promote cellular differentiation and adhesion. Usage includes on lay applications for, but not limited to, neuropathic ulcers, venous stasis ulcers, post-traumatic wounds and post-surgical wounds and pressure ulcers. According to the manufacturer, EpiFix provides a matrix for cellular migration/proliferation, provides a natural biological barrier, and is non-immunogenic. The manufacturer states that it also delivers well-known essential wound healing growth factors; delivers minimally...
manipulated extracellular matrix (ECM) proteins; provides unique anti-inflammatory cytokines, and contains tissue inhibitors of metallo-proteinases. Each allograft is packed in a hermetically sealed double peel pouch packaging in an outer box carton. According to the manufacturer, EpiFix differs from other products produced from human tissue based upon the derived source of the tissue allograft and allograft contents. Only EpiFix is composed of normal dehydrated human amniotic membrane (dHAM) and has no synthetic components. EpiFix has been used in burns, plastic surgery and wound care.

EpiFix Injectable is a minimally manipulated, dehydrated, non-viable cellular amniotic membrane allograft that preserves and delivers multiple extracellular matrix proteins, growth factors, cytokines and other specialty proteins present in amniotic tissue to help regenerate soft tissue (CMS, 2013). EpiFix Injectable is used in the treatment and management of chronic wounds. Usage includes injectable applications for neuropathic ulcers, venous stasis ulcers, post traumatic ulcers, post-surgical ulcers and pressure ulcers. It is particularly suited to deeply creviced, irregularly shaped or tunneling wounds. EpiFix Injectable is used for wound treatment, when it is necessary to replace or repair lost or damaged human collagen tissue. EpiFix Injectable can be injected in the wound site and hydrated as needed, or mixed with a fixed amount of normal saline solution to prepare a suspension for injection into the wound or areas of chronic inflammation. The size of the dosing used is determined based upon the size of the wound defect. EpiFix Injectable vials contain processed, dehydrated, sterilized amniotic membrane tissue grafts to be reconstituted to 0.5cc, 1.25cc and 2.0cc amounts.

There is limited evidence from well-controlled studies of the use of EpiFix amniotic membrane allograft in the treatment of wounds, with most of the evidence from a single investigator group, raising questions about the generalizability of findings. Although several studies have examined natural human amniotic membrane in wound healing, these studies would not be applicable to EpiFix, because the processing of the human amniotic membrane in preparation of the product may affect its performance. Thus, additional clinical outcome studies of EpiFix are needed to determine its performance in wound care.

Zelen et al (2013) reported on a randomized controlled trial of dehydrated human amniotic membrane (DHAM) allografts in adults with a diabetic foot ulcers. Subjects included 25 patients with diabetic foot ulcers of one month (4-weeks) duration or longer from a podiatry practice. Patients were excluded if they had large ulcers (greater than 25 cm2), Charcot foot, ulcer extending to the bone, clinical signs of infection, or inadequate circulation to the foot. Patients were randomized to receive "standard of care" (SOC) alone or standard care with the addition of DHAM. Standard care included the use of a silver containing dressing (Silvasorb gel and Aqacel AG) at the discretion of the attending
clinician and a compression dressing. Wound size reduction and rates of complete healing after 4 and 6 weeks were evaluated. Mean wound size reduction in the 12 patients in the SOC group was 20 percent at week 1, compared to a mean reduction in wound size of over 80 % in the 13 patients in the DHAM group. At 4 weeks, none of the subjects from the SOC group (0 %) was healed, whereas 10 of the 13 subjects in the DHAM group (77 %) had healed (p < 0.001). At 6 weeks, 1 of the 12 subjects from the SOC group (8 %) was healed and 12 of the 13 subjects in the DHAM group (92 %) were healed (p < 0.001). At 6 weeks, wounds were reduced by a mean of 1.8 % in the SOC group versus 98.4 % in the DHAM group (p < 0.001). No infections were reported in the DHAM group whereas 17 % of the SOC group had infections. Commenting on the results of this study, Lavery and Weir (2014) stated "[i]t has the best results that have ever been reported in any DFU study for the treatment group and probably the worst for the control group …".

Limitations of the study by Zelen et al (2013) included the lack of blinding of the investigators gathering data on wound size and other outcomes (such as through use of photographs). Other limitations include omission of certain important baseline variables and outcomes, and the lack of a guideline-supported protocol for standard of care that was sufficiently detailed to minimize variability. Other clinical studies of Epifix suffer from similar limitations.

A draft assessment of wound care products prepared for AHRQ judged this randomized controlled study by Zelen, et al. (2013) to be at moderate risk of bias.

Zelen et al (2013) reported on study of the micronized dehydrated amniotic membrane (mDHAM) where 45 patients were randomized to receive injection of 2 cc 0.5 % Marcaine plain, then either 1.25 cc saline (controls), 0.5 cc micronized dehydrated human amniotic membrane mDHAM, or 1.25 cc mDHAM. Follow-up visits occurred over 8 weeks to measure function, pain, and functional health and well-being. Zelen et al reported that significant improvement in plantar fasciitis symptoms was observed in patients receiving 0.5 cc or 1.25 cc mDHAM versus controls within 1 week of treatment and throughout the study period. At 1 week, AOFAS Hindfoot scores increased by a mean of 2.2 ± 17.4 points for controls versus 38.7 ± 11.4 points for those receiving 0.5 cc mDHAM (p < .001) and 33.7 ± 14.0 points for those receiving 1.25 cc mDHAM (p < .001). By week 8 AOFAS Hindfoot scores increased by a mean of 12.9 ± 16.9 points for controls versus 51.6 ± 10.1 and 53.3 ± 9.4 for those receiving 0.5 cc and 1.25 cc mDHAM, respectively (both p < .001). No significant difference in treatment response was observed in patients receiving 0.5 cc versus 1.25 cc mDHAM. Zelen et al concluded that, in patients with refractory plantar fasciitis, mDHAM is a viable treatment option.
In a retrospective case-series study, Forbes and Fetterolf (2012) demonstrated the use of dehydrated human amniotic membrane (dHAM) allografts in the treatment of wounds of various etiologies. Amniotic membrane was applied to a series of chronic wounds referred to a formal wound clinic for aggressive management, after prior, traditional treatment methods were found ineffective, over a period of 1 month. In each case, failure of traditional therapy was followed by placement of a dehydrated amniotic membrane allograft and the healing time course was documented with charted measurements. Wounds treated with the amniotic membrane allograft demonstrated improved healing, with a change in the healing trajectory from that previously noted. The authors concluded that dehydrated human amniotic membrane represented a potentially effective addition to existing wound care therapies, with further formal clinical studies indicated.

Sheikh et al (2014) stated that non-healing wounds present a significant social and economic burden. Chronic non-healing wounds are estimated to affect as many as 1 to 2 % of individuals during their lifetime, and account for billions of dollars of expense annually on both a national and global basis. These researchers described the use of a novel dehydrated amniotic membrane allograft (EpiFix®; MiMedx Group, Inc., Kennesaw, GA) for the treatment of chronic non-healing wounds. They described the results of EpiFix treatment in 4 patients who had not achieved wound closure with both conservative and advanced measures, and had been referred for a definitive plastic surgery procedure. Healing was observed in a variety of wounds with 1 to 3 applications of the dehydrated amniotic membrane material. The material was well-tolerated by patients. Healed wounds did not recur in long-term follow-up. The authors conclude that further investigation of the use of dehydrated amniotic membrane in broader application to various types of dermal wounds should be considered.

Zelen et al (2014) noted that diabetic foot ulcers (DFU) are notoriously slow to heal and even in cases where primary healing is achieved ulcers frequently recur. An optimal treatment for DFU would be one that supports both rapid and long-term healing. These investigators evaluated recurrence rates of DFU healed with use of dehydrated human amnion/chorion membrane (dHACM). A total of 22 patients with chronic DFU that healed with the use of dHACM were eligible for inclusion. All eligible patients had completed a single-center randomized clinical trial comparing rates of primary healing over a 12-week period with dHACM versus a standard regimen of care. Follow-up examinations were scheduled for 9 to 12 months after primary healing with dHACM. Subsequent evaluation of clinical records was made with IRB approval and patient consent. Eighteen of 22 eligible patients (81.8 %) returned for follow-up examination. Mean wound size prior to treatment with dHACM was 3.1 ± 3.8 cm2, median 1.7 cm2 (0.7, 13.5). Mean time to wound closure after dHACM initiation was 3.1 ± 2.8 weeks (median of 2.0 weeks, range of 1.0 to 9.0 weeks). At the 9 to 12 month follow-up visit 17 of 18 (94.4 %) wounds
treated with dHACM remained fully healed. The authors concluded that these findings supported the effectiveness of dHACM for treatment of DFU. The main drawbacks of this study included its retrospective study design and small sample size. Furthermore, 4 patients were lost to follow-up and the researchers were unaware of the status of their wound. They stated that larger studies are needed to confirm their findings.

Zelen and colleagues (2015) stated that advanced therapies such as bioengineered skin substitutes (BSS) and dHACM have been shown to promote healing of chronic diabetic ulcers. An interim analysis of data from 60 patients enrolled in a prospective, randomized, controlled, parallel group, multi-center clinical trial showed that dHACM (EpiFix, MiMedx Group Inc., Marietta, GA) is superior to standard wound care (SWC) and BSS (Apligraf, Organogenesis, Inc., Canton, MA) in achieving complete wound closure within 4 to 6 weeks. Rates and time to closure at a longer time interval and factors influencing outcomes remained unassessed; therefore, the study was continued in order to achieve at least 100 patients. With the larger cohort, these researchers compared clinical outcomes at 12 weeks in 100 patients with chronic lower extremity diabetic ulcers treated with weekly applications of Apligraf (n = 33), EpiFix (n = 32) or SWC (n = 35) with collagen-alginate dressing as controls. A Cox regression was performed to analyze the time to heal within 12 weeks, adjusting for all significant covariates. A Kaplan-Meier analysis was conducted to compare time-to-heal within 12 weeks for the 3 treatment groups. Clinical characteristics were well-matched across study groups. The proportion of wounds achieving complete closure within the 12-week study period were 73 % (24/33), 97 % (31/32), and 51 % (18/35) for Apligraf, EpiFix and SWC, respectively (adjusted p = 0.00019). Subjects treated with EpiFix had a very significant higher probability of their wounds healing [hazard ratio (HR: 5.66; adjusted p: 1.3 x 10−7] compared to SWC alone. No difference in probability of healing was observed for the Apligraf and SWC groups. Patients treated with Apligraf were less likely to heal than those treated with EpiFix [HR: 0.30; 95 % confidence interval (CI): 0.17 to 0.54; unadjusted p: 5.8 x 10−5]. Increased wound size and presence of hypertension were significant factors that influenced healing. Mean time-to-heal within 12 weeks was 47.9 days (95 % CI: 38.2 to 57.7) with Apligraf, 23.6 days (95 % CI: 17.0 to 30.2) with EpiFix group and 57.4 days (95 %CI: 48.2 to 66.6) with the SWC alone group (adjusted p = 3.2 x 10−7). Median number of grafts used per healed wound were 6 (range of 1 to 13) and 2.5 (range of 1 to 12) for the Apligraf and EpiFix groups, respectively. Median graft cost was $8918 (range of $1,486 to 19,323) per healed wound for the Apligraf group and $1,517 (range of $434 to 25,710) per healed wound in the EpiFix group (p < 0.0001). The authors concluded that these findings provided further evidence of the clinical and resource utilization superiority of EpiFix compared to Apligraf for the treatment of lower extremity diabetic wounds.
As noted by the authors, limitations of this study included: (i) patients were followed for only 1 week following complete healing, (ii) wound recidivism was not recorded, and (iii) the cost data were obtained from a CMS reimbursement schedule, and these do not reflect the actual cost of material across all clinical settings. They did not examine ancillary costs related to differences in product handling, storage and application procedures, which may have further impacted costs. Moreover, they stated that additional studies are needed to evaluate the recurrence rate over time.

Zelen, et al. (2016) continued the aformentioned in order to achieve at least 100 patients. With the larger cohort, the investigators compared clinical outcomes at 12 weeks in 100 patients with chronic lower extremity diabetic ulcers treated with weekly applications of Apligraf (n = 33), EpiFix (n = 32) or SWC (n = 35) with collagen-alginate dressing as controls. A Cox regression was performed to analyse the time to heal within 12 weeks, adjusting for all significant covariates. A Kaplan-Meier analysis was conducted to compare time-to-heal within 12 weeks for the three treatment groups. The investigators stated that clinical characteristics were well matched across study groups. The proportion of wounds achieving complete closure within the 12-week study period were 73% (24/33), 97% (31/32), and 51% (18/35) for Apligraf, EpiFix and SWC, respectively (adjusted P = 0·00019). Subjects treated with EpiFix had a significant higher probability of their wounds healing [hazard ratio (HR: 5·66; adjusted P: 1·3 x 10(-7) ] compared to SWC alone. No difference in probability of healing was observed for the Apligraf and SWC groups. Patients treated with Apligraf were less likely to heal than those treated with EpiFix [HR: 0·30; 95% confidence interval (CI): 0·17-0·54; unadjusted P: 5·8 x 10 (-5)]. Increased wound size and presence of hypertension were significant factors that influenced healing. Mean time-to-heal within 12 weeks was 47·9 days (95% CI: 38·2-57·7) with Apligraf, 23·6 days (95% CI: 17·0-30·2) with EpiFix group and 57·4 days (95%CI: 48·2-66·6) with the SWC alone group (adjusted P = 3·2 x 10(-7) ). Median number of grafts used per healed wound were six (range 1-13) and 2·5 (range 1-12) for the Apligraf and EpiFix groups, respectively.

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Zelen, et al. (2016) to be at low risk of bias.

In an in-vitro study, Massee et al (2016) evaluated PURION processed dehydrated human amnion/chorion membrane allografts (dHACM, EpiFix, MiMedx Group, Marietta, GA) for their ability to alter stem cell activity. Human bone marrow mesenchymal stem cells (BM-MSCs), adipose derived stem cells (ADSCs), and hematopoietic stem cells (HSCs) were treated with soluble extracts of dHACM tissue, and were evaluated for cellular proliferation, migration, and cytokine secretion. Stem cells were analyzed for cell number by DNA assay after 24 hours, closure of an acellular zone using microscopy over
3 days, and soluble cytokine production in the medium of treated stem cells was analyzed after 3 days using a multiplex ELISA array. Treatment with soluble extracts of dHACM tissue stimulated BM-MSCs, ADSCs, and HSCs to proliferate with a significant increase in cell number after 24 hours. dHACM treatment accelerated closure of an acellular zone by ADSCs and BM-MSCs after 3 days, compared to basal medium. BM-MSCs, ADSCs, and HSCs also modulated endogenous production of a number of various soluble signals, including regulators of inflammation, mitogenesis, and wound healing. dHACM treatment promoted increased proliferation and migration of ADSCs, BM-MSCs, and HSCs, along with modulation of secreted proteins from those cells. The authors concluded that dHACM may impact wound healing by amplifying host stem cell populations and modulating their responses in treated wound tissues. Moreover, they stated that “Additional studies will be required to further characterize stem cell responses to dHACM and how these results translate in vivo”.

Torabi et al (2016) developed a novel limb salvage technique using dHACM to generate granulation tissue over critical structures and then definitively closing the wound with split thickness skin grafts (STSG). Between November 5, 2014, and March 30, 2015, 7 patients underwent dHACM + STSG limb salvage. Demographics included 8 to 64 years of age, and 2 female and 5 male patients. Wounds included 2 with exposed tendons, 3 with exposed bone, and 2 with exposed bone and tendon; dHACM and STSG was successful in 6 of the 7 patients. None developed infection during dHACM treatment, STSG, and in the post-operative phase, even in the cases where initial antibiotic treatment was inadequate due to bacterial resistance. All wounds remain stably closed. The authors concluded that although a larger sample size is needed to fully evaluate this novel treatment modality, this early experience suggested dHACM þ STSG is a viable, low-cost alternative to free flap reconstruction. These investigators stated that future studies will include a randomized controlled trial (RCT), and will be aimed at optimizing patient selection, timing of treatment, and analyzing the cost utility of dHACM and STSG in comparison to free flap reconstruction in addition to understanding the biological response within the wounds.

Serena, et al. (2014) reported on a multicenter, randomized, controlled study to evaluate the safety and efficacy of one or two applications of Epifix dehydrated human amnion/chorion membrane allograft and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. The primary study outcome was the proportion of patients achieving 40% wound closure at 4 weeks. Of the 84 participants enrolled, 53 were randomized to receive allograft and 31 were randomized to the control group of multilayer compression therapy alone. At 4 weeks, 62% in the allograft group and 32% in the control group showed a greater than 40% wound closure (p = 0.005), thus showing a significant difference between the allograft-
treated groups and the multilayer compression therapy alone group at the 4-week surrogate endpoint. After 4 weeks, wounds treated with allograft had reduced in size a mean of 48.1% compared with 19.0% for controls. The investigators concluded that venous leg ulcers treated with allograft had a significant improvement in healing at 4 weeks compared with multilayer compression therapy alone.

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Serena, et al. (2014) to be at low risk of bias.

In a multi-center RCT, Bianchi and colleagues (2018) evaluated the efficacy of EpiFix allograft as an adjunct to multi-layer compression therapy for the treatment of non-healing full-thickness venous leg ulcers. These researchers randomly assigned 109 subjects to receive EpiFix and multi-layer compression (n = 52) or dressings and multi-layer compression therapy alone (n = 57). Patients were recruited from 15 centers around the USA and were followed-up for 16 weeks. The primary end-point of the study was defined as time to complete ulcer healing. Participants receiving weekly application of EpiFix and compression were significantly more likely to experience complete wound healing than those receiving standard wound care and compression (60 % versus 35 % at 12 weeks, p = 0.0128, and 71 % versus 44 % at 16 weeks, p = 0.0065). A Kaplan-Meier analysis was performed to compare the time-to-healing performance with or without EpiFix, showing a significantly improved time to healing using the allograft (log-rank p = 0.0110). Cox regression analysis showed that subjects treated with EpiFix had a significantly higher probability of complete healing within 12 weeks (HR: 2.26, 95 % CI: 1.25 to 4.10, p = 0.01) versus without EpiFix. The authors concluded that these findings confirmed the advantage of EpiFix allograft as an adjunct to multi-layer compression therapy for the treatment of non-healing, full-thickness venous leg ulcers.

The authors stated that these results may not be generalized to other amniotic membrane products seeing that scientific papers have been published describing differences among the products. They noted that it must also be recognized that all patients received a high level of care in a wound care center. For ethical reasons, per study protocol, patients receiving standard care were allowed to exit the study and receive advanced wound care treatments if their wound did not reduce by a minimum of 40 % within 8 weeks of study enrolment. Although these subjects were classified as non-healers in the final analysis due to their status at 8 weeks, they continued to be followed-up, with only 1 patient having complete healing at weeks 12 and 16. It should be noted that the study results remained unchanged and statistically significant even when these censored data were included. Moreover, this was an industry-sponsored study (it was funded by MiMedx Group).
A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Bianchi, et al. (2018) to be at low risk of bias.

Tettelbach et al (2019a) carried out a multi-center RCT at 14 wound care centers in the U.S. to confirm the efficacy of dHACM for the treatment of chronic lower extremity ulcers in persons with diabetes. Patients with a lower extremity ulcer of at least 4 weeks duration were entered into a 2-week study run-in phase and treated with alginate wound dressings and appropriate off-loading. Those with less than or equal to 25 % wound closure after run-in were randomly assigned to receive weekly dHACM application in addition to off-loading or standard of care (SOC) with alginate wound dressings, for 12 weeks. A total of 110 patients were included in the intent-to-treat (ITT) analysis, with n = 54 in the dHACM group and n = 56 in the no-dHACM group. Of the participants, 98 completed the study per protocol, with 47 receiving dHACM and 51 not receiving dHACM. The primary study outcome was percentage of study ulcers completely healed in 12 weeks, with both ITT and per-protocol participants receiving weekly dHACM significantly more likely to completely heal than those not receiving dHACM (ITT-70 % versus 50 %, p = 0.0338, per-protocol-81 % versus 55 %, p = 0.0093). A Kaplan-Meier analysis was performed to compare the time-to-healing performance with/without dHACM, showing a significantly improved time to healing with the use of allograft, log-rank p < 0.0187. Cox regression analysis showed that dHACM-treated subjects were more than twice as likely to heal completely within 12 weeks than no-dHACM subjects (hazard ratio [HR]: 2.15, 95 % confidence interval [CI]: 1.30 to 3.57, p = 0.003). At the final follow-up at 16 weeks, 95 % of dHACM-healed ulcers and 86 % of healed ulcers in the no-dHACM group remained closed. The authors concluded that these findings confirmed that dHACM is an effective treatment for lower extremity ulcers in a heterogeneous patient population.

The authors stated that an unfortunate weakness in any study of advanced wound care products compared with a “SOC group” is that the level of treatment provided as “SOC” was specified by study protocol and was generally of higher quality and more consistent than what may be provided outside a clinical trial setting, which may reduce the true effect size between treatment and control study arms. In a meta-analysis from 1999, standard “good” wound care consisted of wet-to-dry dressings and resulted in a healing rate of approximately 24 % after 12 weeks. In contemporary practice, a wider variety of more advanced dressings is used, and current “SOC” for treatment of lower extremity diabetic ulcers frequently consists of alginate dressings. In the present study, alginate dressings, absorbent non-adhesive hydro-polymer secondary dressings, and gauze were used in lieu of basic moist-to-dry dressings, which the authors believed increased the rates of healing in the SOC group and reduced the treatment effect size. A 12-week healing rate of 50 % with alginate dressings, double the rate expected with simple wet-to-
dry dressings, spoke to the overall influence of advanced dressings on rates of wound healing. Achieving 70 % healing within 12 weeks provided further evidence of the efficacy of dHACM compared with other advanced treatments. In a perfect world, all wounds could be adequately off-loaded at all times, and patients would be 100 % compliant with the use of the prescribed off-loading device. As in most other wound treatment studies, the inability to truly monitor off-loading compliance was a study weakness. In the present study, clinicians were allowed to use their judgement regarding the appropriate off-loading device to prescribe, including the use of full-contact casting and when off-loading was no longer needed once healing occurred. Given the variety of off-loading devices used, these researchers were unable to determine if the type of off-loading device influenced these findings. As no patients' wounds were off-loaded with full-contact casting, these investigators did not know if this would have improved treatment results in either study group. Variations in clinical recommendations for continued off-loading of healed wounds was not specified per study protocol, and it was unknown how this influenced the observed rates of wound recurrence. This was an industry-sponsored study; further studies with independent funding sources are needed to determine the clinical effectiveness of this therapy.

Brantley et al (2019) stated that pressure injuries (PIs; pressure ulcers) affect about 3 million adults in the U.S. and cost an estimated $11 billion dollars annually to treat. Prevention is most desirable, however, once a patient develops a pressure injury, the focus shifts to effective treatment and rapid closure to improve health outcomes. These researchers examined outcomes in 10 patients with Stage II and III PIs treated with dHACM allografts. All patients were treated with weekly application of dHACM plus standard wound care and followed for 8 weeks; 2 PIs were Stage II and 8 were Stage III. The average pressure injury size at dHACM initiation was 3.42 ± 1.76 cm2. After the 1st application of dHACM 7/10 (70 %) of PIs responded to treatment with a reduction in wound size. Within 2 weeks of dHACM initiation into the plan of care, 4/10 (40 %) of PIs had reduced in size by greater than 50 %. By week 4, 60 % of PIs (6/10) had reduced in size by greater than 50 %. Overall, during the 8 week evaluation period, 3 PIs healed completely and 9 of 10 PIs reduced in size. The authors concluded that dHACM allografts appeared to be a viable treatment option for Stage II and III PIs.

The authors stated that the drawbacks of this study were those inherent to any single-center product evaluation and any study on the treatment of pressure ulcers. Immobility, neurogenic bowel and bladder, poor nutrition, multiple co-morbidities, and care-giver preferences are common issues in patients developing pressure ulcers. These confounding factors made protocol design and data interpretation difficult when examining new treatments for PIs. In the present evaluation, treatment was frequently interrupted due to removal of dressings and allograft. These findings may have improved
if allograft material had been replaced immediately if removed. These researchers stated that although in the present study they only evaluated the use of dHACM in patients with Stage II and III PI, given their observations, it is plausible that similar benefits to wound healing may also occur in patients with Stage IV PI. They stated that more studies on the use of advanced technologies in these types of wounds is needed. This study was sponsored and funded by MiMedx Group.

On February 13, 2019, the Agency for Healthcare Research and Quality’s (AHRQ, 2019) Technology Assessment Program just posted a draft systematic review on “Skin Substitutes for Treating Chronic Wounds” for review. The draft noted that “We identified 74 commercially available skin substitutes and categorized them based on the Davison-Kolter classification system. Sixty-eight (92%) were categorized as acellular dermal substitutes, mostly replacements from human amniotic membranes and animal tissue sources. Three systematic reviews and 17 RCTs examined use of 13 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers and venous leg ulcers. Twenty-seven experimental ongoing clinical trials examined an additional 12 skin substitutes with similar classifications. Studies rarely reported clinical outcomes such as amputation, wound recurrence at least 2 weeks after treatment ended, and patient-related outcomes such as return to function, pain, exudate, and odor. The lack of studies examining the efficacy of most skin substitute products and the need for better-designed and reported studies providing more clinically relevant data in this field is this Technical Brief’s clearest implication”. This AHRQ review cited 4 studies for EpiFix (and all 4 are cited in CPB 0244); and none for EpiCord.

Epicord

EpiCord (Mimedx Group, Inc.) is a lyophilized, non-viable cellular umbilical cord allograft that provides a natural biological barrier and protective structure for wound healing environments. EpiCord is comprised of the protective elements of the umbilical cord with a thin amnion layer and a thicker Wharton Jelly mucopolysaccharide component. EpiCord provides an extracellular matrix (ECM) as a scaffold in the form of collagen types, fibronectin, laminins, and proteoglycans. This structure provides a natural wound covering and scaffold for cellular growth. According to the manufacturer, EpiCord is indicated for diabetic elderly patients who are affected by slow healing wounds. It is to be used in the treatment and management of chronic and acute wounds, burns as well as a natural biological barrier to protect tendons. EpiCord would be used in the treatment of a chronic leg ulcer that requires debridement, topical care and an allograft placement and dressing for proper management. EpiCord can be stored in ambient conditions.
In a prospective, multi-center, randomized-controlled, comparative parallel study, Tettelbach et al (2019b) examined the safety and effectiveness of dehydrated human umbilical cord allograft (EpiCord) compared with alginate wound dressings for the treatment of chronic, non-healing diabetic foot ulcers (DFU). This trial was conducted at 11 centers in the U.S. Individuals with a confirmed diagnosis of type 1 or type 2 diabetes presenting with a 1 to 15 cm² ulcer located below the ankle that had been persisting for at least 30 days were eligible for the 14-day study run-in phase. After 14 days of weekly debridement, moist wound therapy, and off-loading, those with less than or equal to 30% wound area reduction post-debridement (n = 155) were randomized in a 2:1 ratio to receive a weekly application of EpiCord (n = 101) or standardized therapy with alginate wound dressing, non-adherent silicone dressing, absorbent non-adhesive hydro-polymer secondary dressing, and gauze bandage roll (n = 54). All wounds continued to have appropriate off-loading during the treatment phase of the study. Study visits were conducted for 12 weeks. At each weekly visit, the DFU was cleaned and debrided as necessary, with the wound photographed pre- and post-debridement and measured before the application of treatment group-specific dressings. A follow-up visit was performed at week 16. The primary study end-point was the percentage of complete closure of the study ulcer within 12 weeks, as assessed by Silhouette camera. Data for randomized subjects meeting study inclusion criteria were included in an ITT analysis. Additional analysis was conducted on a group of subjects (n = 134) who completed the study per protocol (PP) (EpiCord, n = 86, alginate, n = 48) and for those subjects receiving adequate debridement (EpiCord, n = 67, alginate, n = 40); ITT analysis showed that DFUs treated with EpiCord were more likely to heal within 12 weeks than those receiving alginate dressings, 71 of 101 (70%) versus 26 of 54 (48%) for EpiCord and alginate dressings, respectively, p = 0.0089. Healing rates at 12 weeks for subjects treated PP were 70 of 86 (81%) for EpiCord-treated and 26 of 48 (54%) for alginate-treated DFUs, p = 0.0013. For those DFUs that received adequate debridement (n = 107, ITT population), 64 of 67 (96%) of the EpiCord-treated ulcers healed completely within 12 weeks, compared with 26 of 40 (65%) of adequately debrided alginate-treated ulcers, p < 0.0001; 75 subjects experienced at least 1 adverse event (AE), with a total of 160 AEs recorded. There were no AEs related to either EpiCord or alginate dressings. The authors concluded that the results of this 1st RCT on the use of EpiCord as a treatment for DFUs provided additional evidence of the safety and efficacy of dehydrated placental tissues.

The authors stated that although the study groups were well matched for traditional factors influencing healing, other circumstances, typically problematic in the diabetic population, that these researchers did not control for, such as nutrition, co-morbidities,
and polypharmacy, may have also influenced healing rates in the current study population. This was an industry-sponsored study; further studies with independent funding sources are needed to determine the clinical effectiveness of this novel therapy.

OrthoFlo

OrthoFlo is an amniotic fluid derived allograft used to “supplement the ability of existing synovial fluid to lubricate and protect” (MiMedx Group, Inc.) (CMS, 2017). OrthoFlo protects, reduces inflammation, lubricates and addresses pain of the joints. OrthoFlo is clinically intended for patients with joint pain due to disease or trauma, resulting in the reduction in lubricating properties of the synovial fluid. OrthoFlo is an amniotic fluid product that is optimally filtered to retain the natural macromolecular and physiologically active components of amniotic fluid, while removing low molecular weight by-products produced in utero. OrthoFlo is administered by a physician. It is injected in the joint with or without ultrasound guidance, as needed, to protect, lubricate, and reduce inflammation. Dosage is determined by the physician. OrthoFlo is supplied in single-use 0.5 mL, 1 mL, 2 mL, and 4 mL vials. MiMedx describes OrthoFlo as a Human Tissue Product for which FDA premarket approval is not required. While MiMedx’s packaging information describes OrthoFlo as an amniotic fluid derived product indicated for “homologous use”, the stated indication is supplementation of synovial fluid in the knee joint in order to cushion, lubricate and reduce inflammation.

Cytal (formerly Matristem)

According to the manufacturer, MatriStem/Cytal matrix products are composed of a porcine-derived extracellular matrix, also known as urinary bladder matrix. The primary advantage of MatriStem/Cytal products is that they maintain their natural collagen structure and components that are gradually incorporated within the patients' body while replacing the product with site-appropriate tissue. The result is constructively remodeled, site-specific tissue.

MatriStem/Cytal Burn Matrix, MatriStem/Cytal Micro Matrix, MatriStem/Cytal Surgical Matrix and MatriStem/Cytal Wound Matrix are made from a naturally occurring bioscaffold derived from porcine tissue, placed into a surgical site or wound. It is resorbed and replaced with new native tissue. The MatriStem/Cytal Surgical Matrix has been used for implantation to reinforce soft tissue where weakness exists (e.g., tissue and body wall Repair). The MatriStem/Cytal Wound Matrix comes in sheets or micronized particle forms, and has been used for chronic vascular ulcers, diabetic ulcers, draining wounds, partial and full-thickness wounds, podiatric pressure ulcers,
surgical wounds (donor sites/grafts, post-chemosurgery, post-laser surgery, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns and skin tears), tunneled/undermined wounds, and venous ulcers.

Cytal (formerly MatriStem) Wound Care Matrix is an extracellular matrix product derived from porcine urinary bladder tissue and designed to be replaced by native tissue in the wound (Snyder et al, 2012). MatriStem Wound Sheet (ACell, Inc., Columbia, MD) was cleared for marketing under the 510(k) process in October 2009 and “is intended for the management of wounds that including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds. The device is intended for one-time use”. MatriStem Wound Care Matrix was cleared for marketing under the 510(k) process in August 2010 (K112409) with MatriStem Wound Sheet as the predicate device and with the same indications.

MatriStem/Cytal wound micromatrix powder (Medline Industries, Inc., Mundelein, IL) is made from the extracellular matrix (ECM) material that naturally occurs in porcine bladders (pigs tissue has a collagen structure that is nearly identical to that of human tissue); that is why MatriStem/Cytal wound powder is sometimes known as pig powder. The powder keeps the wound from healing and as a result the body focuses on creating new cells. Its main mechanism has to do with the fact that the body doesn’t have to regenerate so much extracellular matrix on its own. Because the wound is covered in extracellular matrix there’s an increase of regenerative cells that are able to re-grow the tissue. MatriStem/Cytal MicroMatrix is a porcine-derived, naturally occurring non cross-linked, completely resorbable, acellular extracellular matrix derived from specific layers of porcine urinary bladder. MatriStem/Cytal MicroMatrix is made from the same material as the MatriStem/Cytal Wound Sheet, but in a micronized particle (powder) form. In this form, it is easier to apply when the wound has an irregular shape, under-mining edges or tunneling, or when shifting may cause the wound to lose contact with the dressing. The lyophilized micronized particles are applied topically to the surface of the wound to maintain and support a healing environment for wound management. MatriStem/Cytal contains a unique epithelial basement membrane which is known to be composed of several types of collagen, adhesion proteins, glycoproteins, and other elements of an extracellular matrix which all act synergistically in supporting natural tissue healing. MatriStem/Cytal triggers abundant new blood vessel formation and recruits numerous cell types to the site of the injury or wound. During the healing process, the device is degraded and completely resorbed, leaving new tissue where scar tissue would normally be expected. It is indicated for the management of wounds including: partial and full-
thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining wounds. MatriStem/Cytal MicroMatrix is supplied as 20 mg (5 ea) per box; 30 mg (5 ea.) per box; 60 mg (5 ea.) per box; 100 mg (1 ea.) per box; and 200 mg (1 ea.) per box. According to the manufacturer, existing codes do not adequately describe this product because of its unique combination of bioactive properties, especially its bimodal characteristic: one surface consists of an intact basement membrane which is especially conducive to epithelial and endothelial cell attachment, proliferation, and differentiation and is ideal for epithelial cell growth in many applications, which results in a more natural regeneration with little, if any, scar tissue formation. However, there is a lack of evidence regarding the effectiveness of the MatriStem/Cytal wound powder.

MatriStem/Cytal Wound Sheets are manufactured in multiple sizes of single layer lyophilized sheet configurations that are applied topically to the surface of the wound. MatriStem contains a unique epithelial basement membrane which is known to be composed of several types of collagen, adhesion proteins, glycoproteins, and other elements of an extracellular matrix which all act synergistically in supporting natural tissue healing. MatriStem/Cytal triggers abundant new blood vessel formation and recruits numerous cell types to the site of the injury or wound. During the healing process, the device is degraded and completely resorbed, leaving new tissue where scar tissue would normally be expected. It is indicated for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining wounds. MatriStem/Cytal wound sheets are supplied as: 3 cm x 3.5 cm (box of 5); 3 cm x 7 cm (box of 5); 7 cm x 10 cm (1 ea); 10 cm x 15 cm (box of 5); 10 cm x 15 cm (1 ea). The manufacturer states that this product has a unique combination of bioactive properties, especially its bimodal characteristic: one surface consists of an intact basement membrane which is especially conducive to epithelial and endothelial cell attachment, proliferation, and differentiation and is ideal for epithelial cell growth in many applications, which results in a more natural regeneration with little, if any, scar tissue formation.

MatriStem/Cytal Surgical Matrix is a porcine-derived, naturally occurring dehydrated extracellular matrix that maintains and supports a healing environment for wound management. MatriStem surgical devices are manufactured in various sizes of multi-layer dehydrated dry sheet configurations. When applied to a wound, these devices change the healing response, resulting in remodeled, functional, site specific tissue. MatriStem contains a unique epithelial basement membrane which is known to be composed of several types of collagen, adhesion proteins, glycoproteins, and other elements of an extracellular matrix which all act synergistically in supporting natural
tissue healing. MatriStem/Cytal triggers abundant new blood vessel formation and recruits numerous cell types to the site of the injury or wound. During the healing process, the device is degraded and completely resorbed, leaving new tissue where scar tissue would normally be expected. It is indicated for implantation to reinforce soft tissues. MatriStem/Cytal Surgical Matrix products are supplied as follows: surgical Matrix RS as (box of 5) 1.5 cm discs, 1 ea. 2 cm x 4 cm, 1 ea. 2 cm x 4 cm, 1 ea. 5 cm x 5 cm, 1 ea. 7 cm x 10 cm, 1 ea. 6 cm x 15 cm, 1 ea. 10 cm x 15 cm; Plastic Surgery Matrix as (box of 5) 1.5 cm discs, 1 ea. 4 cm x 12 cm, 1 ea. 6 cm x 15 cm, 1 ea. 7 cm x 10 cm, 1 ea. 10 cm x 15 cm; Plastic Surgery Matrix XS as 1 ea. 4 cm x 12 cm, 1 ea. 6 cm x 15 cm, 1 ea. 7 cm x 10 cm and 1 ea. 10 cm x 15 cm. According to the manufacturer, this product has a unique combination of bioactive properties, especially its bimodal characteristic: one surface consists of an intact basement membrane which is especially conducive to epithelial and endothelial cell attachment, proliferation, and differentiation and is ideal for epithelial cell growth in many applications, which results in a more natural regeneration with little, if any, scar tissue formation.

Cytal Burn Matrix (formerly MatriStem Burn Matrix) is a porcine-derived, naturally occurring dehydrated extracellular matrix, also known as urinary bladder matrix, that maintains and supports a healing environment for wound management. Cytal Burn Matrix is manufactured in multi-layer lyophilized (freeze-dried) sheet configurations. When applied to a wound, these devices changes the healing response, resulting in remodeled, functional, site specific tissue. According to the manufacturer, Cytal contains a unique epithelial basement membrane which is known to be composed of several types of collagen, adhesion proteins, glycoproteins, and other elements of an extracellular matrix which all act synergistically in supporting natural tissue healing. Cytal triggers abundant new blood vessel formation and recruits numerous cell types to the site of the injury or wound. During the healing process, the device is degraded and completely resorbed, leaving new tissue where scar tissue would normally be expected. The manufacturer states that it is indicated for the management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining wounds. Cytal Burn Matrix is supplied as: 7 cm x 10 cm fenestrated wound sheet, 1 ea; and 7 cm x 10 cm meshed wound sheet, 1 ea.; 3 cm x 3.5 cm (5/box) and (10/box); 3 cm x 7 cm (5/box and 10/box); 7 cm x 10 cm (1 ea. and 5/box); and 10 cm x 15 cm (1 ea. and 5/box). According to the requester, this product has a significant therapeutic distinction over similar products in that it offers the following characteristics: (i) naturally occurring, non-cross-linked extracellular matrix; completely resorbable; (ii) acellular; (iii) contains multiple naturally occurring growth factors; (iv) bimodal surface characteristic; (v) may reduce scar tissue formation; (vi) antimicrobial properties; (vii) lyophilized; and (viii) indicated in a complete range of wounds. MatriStem/Cytal
PSMX is a porcine-derived, lyophilized acellular extracellular matrix that maintains and supports a healing environment for wound management. It is indicated for the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining wounds. When applied to a wound, MatriStem/Cytal PSMX changes the healing response, resulting in remodeled, functional, site specific tissue. MatriStem/Cytal PSMX contains a unique epithelial basement membrane which is known to be composed of several types of collagen, adhesion proteins, glycoproteins, and other elements of an extracellular matrix which all act synergistically in supporting natural tissue healing. MatriStem/Cytal PSMX triggers abundant new blood vessel formation and recruits numerous cell types to the site of the injury or wound. During the healing process, the device is degraded and completely resorbed, leaving new tissue where scar tissue wound normally be expected. MatriStem/Cytal PSMX is supplied as follows: 5cm x 5cm, 4cm x 12 cm, 7cm x 10cm, 6cm x 15cm, 8cm x 16cm, and 10cm x 15cm. According to the manufacturer, MatriStem/Cytal PSMX is distinct from the other similar skin substitute products because it is naturally occurring, non-crosslinked, completely resorbable, acellular, and has bimodal surface characteristics and antibacterial properties.

MatriStem/Cytal Wound Matrix RS is a porcine-derived, lyophilized acellular extracellular matrix that maintains and supports a healing environment for wound management. It is indicated for the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining wounds. When applied to a wound, MatriStem/Cytal Wound Matrix RS changes the healing response, resulting in remodeled, functional, site specific tissue. MatriStem/Cytal Wound Matrix RS contains a unique epithelial basement membrane which is known to be composed of several types of collagen, adhesion proteins, glycoproteins, and other elements of an extracellular matrix which all act synergistically in supporting natural tissue healing. MatriStem/Cytal Wound Matrix RS triggers abundant new blood vessel formation and recruits numerous cell types to the site of the injury or wound. During the healing process, the device is degraded and completely resorbed, leaving new tissue where scar tissue wound normally be expected. MatriStem/Cytal Wound Matrix RS is supplied as follows: 1.5 cm disc (box of 5 each), 2cm x 4cm, 5cm x 5cm, 7cm x 10cm, 6cm x 15cm, 8cm x 16cm, and 10cm x 15cm. According to the manufacturer, MatriStem/Cytal Wound Matrix RS is distinct from the other similar skin substitute products because it is naturally occurring, non-crosslinked, completely resorbable, acellular, and has bimodal surface characteristics and antibacterial properties.
MatriStem/Cytal PSM is a porcine-derived, extracellular matrix that maintains and supports a healing environment for wound management. It is indicated for the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining wounds. When applied to a wound, MatriStem/Cytal PSM changes the healing response, resulting in remodeled, functional, site specific tissue. MatriStem/Cytal PSM contains a unique epithelial basement membrane which is known to be composed of several types of collagen, adhesion proteins, glycoproteins, and other elements of an extracellular matrix which all act synergistically in supporting natural tissue healing. MatriStem/Cytal PSM triggers abundant new blood vessel formation and recruits numerous cell types to the site of the injury or wound. During the healing process, the device is degraded and completely resorbed, leaving new tissue where scar tissue wound normally be expected. MatriStem/Cytal PSM is supplied as follows: 1.5cm disc (box of 5 each), 5cm x 5cm, 4cm x 12 cm, 7cm x 10cm, 6cm x 15cm, 7cm x 15cm, and 10cm x 15cm. According to the manufacturer, MatriStem/Cytal PSM is distinct from the other similar skin substitute products because it is naturally occurring, non-crosslinked, completely resorbable, acellular, and has bimodal surface characteristics and antibacterial properties.

Cytal Wound Matrix 3-Layer (Cytal 3L) and Cytal Wound Matrix 6-Layer (Cytal 6L) are generally intended for the management of wounds (both acute & chronic) including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor site/grafts, post-Mohs surgery, post laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, skin tears) and draining wounds (CMS, 2017). Cytal 3L and Cytal 6L are composed of animal derived, extracellular matrix, and are skin substitutes. They are comprised of naturally-occurring urinary bladder matrix (UBM), and maintain an intact epithelial basement membrane to maintain and support a healing environment through constructive remodeling. Cytal 3L and Cytal 6L are supplied in multi-layer single-use sheet configuration in sizes up to 10m x 15 cm. The devices are terminally sterilized using electron beam irradiation.

According to the manufacturer, Cytal 1 Layer; 2 Layer and burn products are intended for the management of wounds (both acute and chronic) (CMS, 2017). They are comprised of naturally-occurring urinary bladder matrix (UBM), and maintain an intact epithelial basement membrane to maintain and support a healing environment through constructive remodeling. These devices are cut to the desired size and applied directly to the wound bed by the treating clinician after removal of wound exudate and debris. They are intended for single use as they are applied and resorb into the patient's body. The manufacturer states that there is a significant functional therapeutic distinction between
Cytal 1 Layer and 2 Layer and Cytal Burn products, and Cytal 3 and 6 Layer products, on the basis of different manufacturing processes, (Cytal1, Cytal 2 and Cytal Burn) are freeze dried and lyophilized; whereas Cytal 3L and Cytal 6L are vacuum-pressed and have a fenestration pattern to aid in suturing. According to the manufacturer, "these difference result in functional and therapeutic distinctions."

Martinson and Martinson (2016) used Medicare claims data from 2011 to 2014 to identify beneficiaries with diabetes and foot ulcers. Patients treated with one of four types of skin substitute (Apligraf, Dermagraft, OASIS, and MatriStem) were identified. The skin substitutes were compared on episode length; amputation rate; skin substitute utilisation; and skin substitute costs. There were 13,193 skin substitute treatment episodes: Apligraf (HML) was used in 4926 (37.3%), Dermagraft (HSL) in 5530 (41.9%), OASIS (SIS) in 2458 (18.6%) and MatriStem (UBM) in 279 (2.1%). The percentage of DFUs that healed at 90 days were: UBM 62%; SIS 63%; HML 58%; and HSL 58%. Over the entire time, UBM was non-inferior to SIS (p<0.001), and either was significantly better than HML or HSL (p<0.005 in all four tests). HML was marginally superior to HSL (p=0.025 unadjusted for multiple testing). Medicare reimbursements for skin substitutes per DFU episode for UBM ($1435 in skin substitutes per episode) and SIS ($1901) appeared to be equivalent to each other, although non-inferiority tests were not significant. Both were less than HML ($5364) or HSL ($14,424) (p<0.0005 in all four tests). HML was less costly than HSL (p<0.0005). The authors concluded that various types of skin substitutes appear to be able to confer important benefits to both patients with DFUs and payers. Analysis of the four skin-substitute types resulted in a demonstration that UBM and SIS were associated with both shorter DFU episode lengths and lower payer reimbursements than HML and HSL, while HML was less costly than HSL but equivalent in healing. Limitations of this study include the fact that it is a retrospective observational study using administrative claims data.

Frykberg et al (2016) reported on an interim analysis of a prospective, multicenter clinical study is to assess the application of MatriStem MicroMatrix (MSMM) and MatriStem Wound Matrix (MSWM) (porcine urinary bladder derived extracellular matrix) compared with Dermagraft (DG) (human fibroblast-derived dermal substitute) for the management of non-healing diabetic foot ulcers (DFUs). The investigators conducted a randomized, multicenter study at thirteen centers throughout the US. It was designed to evaluate the incidence of ulcer closure, rate of ulcer healing, wound characteristics, patient quality of life, cost-effectiveness, and recurrence. Those subjects whose DFUs decreased in size by ≤30% or increased by ≤50% during the standard of care (SOC) phase were randomized into the treatment phase of the study. The study evaluated complete wound closure by eight weeks with weekly device application. A two-week post treatment SOC phase followed the treatment phase for any wounds that did not heal by the end of eight
weeks, and wound closure was also evaluated at the end of that period. Ulcer recurrence at 6 months post-treatment was evaluated in the subjects that showed wound healing by the end of the post-treatment SOC phase. Standard adjunctive therapy, including debridement, saline irrigation and foot off-loading, was provided to both arms during the four-week screening period, after which eligible subjects were randomised in a 1:1 ratio, to either the MatriStem (MS) or DG treatment arm. This study was developed to evaluate the hypothesis that the wound outcomes observed after wound management with MS were non-inferior to those of DG after eight weeks. The investigators reported on a planned interim results of this study after one half of the projected enrolment was completed. There were 95 subjects consented and entered into the SOC four-week screening phase of the trial and 56 were randomized into the treatment phase. At the planned interim analysis, there was a significantly lower cost per subject and significant improvement in patient quality of life for the subjects treated with MS compared with those managed with DG. However, there was not a statistically significant difference found during the analysis of the interim data between the two study groups for rate of wound healing or number of subjects with complete wound closure. The investigators concluded that the data from this interim analysis show that MSMM and MSWM provide results for healing DFUs that are similar to the results obtained for DG at a significant quality of life and economic advantage.

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Frykberg, et al. (2016) to be at moderate risk of bias.

Alvarez, et al. (2017) reported on a prospective, parallel, randomized, single-center study involving 17 subjects in an outpatient wound care center setting. Each subject with a DFU was randomized (2:1) to receive the Matristem urinary bladder wound matrix (UBM) plus offloading with a total contact cast (TCC) or standard care (nonadherent dressing plus TCC). All DFUs were on the plantar surface of the foot and all were Grade I-A according to the University of Texas Wound Classification System. A traditional TCC was used in all patients and consisted of a minimally padded, well-molded, and rigid (plaster plus fiberglass) construct that maintains contact with the entire plantar surface of the foot and lower leg. The endpoints of the study were wound healing at 12 and 16 weeks and ulcer recurrence at 1 year. Wound evaluations were performed weekly and wound surface area was measured by photo-digital planimetry. In the UBM group, the incidence of wound healing at 12 and 16 weeks was 90% and 100%, respectively, compared with 33% and 83.3% in the control (P = .062). The mean time to healing in the UBM-treated group was 62.4 days compared with 92.8 days in the control group (P = .031). The incidence of ulcer recurrence at 1 year was 10% (1/11) in the UBM-treated group and
50% (3/6) in the control. The authors concluded that the results of this interim analysis suggest treatment of DFUs with a UBM could significantly reduce the time to healing and improve the rate of recurrence.

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Alvarez, et al. (2017) to be at moderate risk of bias.

NuCel Liquid Wound Covering

NuCel liquid wound covering (Nutech Medical, Birmingham, AL) is derived from healthy living donors. It is an unique in-vivo liquid wound covering, providing a defensive barrier at the surgical site in situations where a patch covering is either inadequate or inconvenient. Mixed with patients’ own blood, NuCel is applied directly to the surgical site, offering surgeons the ability to spread the amniotic membrane over an irregular or larger area, including over large bone void fill constructs for spine fusion or large trauma repair. However, there is a lack of evidence regarding the effectiveness of the NuCel liquid wound covering.

FlexHD

FlexxHD is an acellular dermal matrix derived from human allograft skin, used for hernia repair and breast reconstruction.

FlexHD is a human allograft skin minimally processed to remove epidermal and dermal cells while providing the acellular matrix of the dermis (Snyder et al, 2012). It is processed using proprietary procedures developed by Musculoskeletal Transplant Foundation (MTF, Edison, NJ) to preserve and maintain the natural biomechanical, biochemical and matrix properties of the dermal graft. FlexHD is used to support cellular repopulation and vascularization in applications at the surgical site. It is indicated for use to replace damaged or inadequate integumental tissue. Ethicon promotes Flex HD for hernia repair and breast reconstruction. There is limited available published evidence on FlexHD prehydrated acellular dermal matrix. Primary studies included a retrospective medical record review of the use of FlexHD in tissue expander breast reconstruction (Rawlani et al, 2011) and an uncontrolled case series of the use of FlexHD in single-stage breast reconstruction (Rosenberg et al, 2011). Other studies reported on the use of both FlexHD and Alloderm human acellular dermal tissue matrix in breast reconstruction, but do not report detailed analysis of the comparative efficacy of these products (Topol et al, 2008; Cahan et al, 2011).

Miscellaneous

Isaacs et al (2008) compared a variety of potentially useful artificial and biological sealants applied to sutured nerve repairs to decrease gapping at the repaired site. A total of 57 fresh-frozen cadaveric nerve specimens were transected and repaired with two 8-0 nylon epineural sutures placed 180 degrees apart. The specimens were divided into 5 groups. Four groups received augmentation of the repair with application of either autologous fibrin glue, Tisseel fibrin glue, Evicel fibrin glue, or DuraSeal polyethylene glycol-based hydrogel sealant, and the 5th group had no glue. Each nerve construct was mounted in a servo-hydraulic materials testing machine and stretched at a constant 5 mm/min displacement rate until failure. A non-contact video analysis permitted normalization of stretch within the repair region. Statistical analysis was performed via analysis of variance followed by Tukey-Kramer post hoc pair-wise comparison when indicated. Resistance to gapping as measured through normalized stiffness (N/mm/mm) was greater for the Tisseel group, Evicel group, and DuraSeal group versus the no-glue group only. The stiffness of the autologous group approached significance versus the no-glue group. There were no significant differences in stiffness between any of the nerve glue groups. There was no statistical difference for the peak load at failure between any of the groups. The authors concluded that avoidance of gapping at the nerve repair site is crucial in achieving successful nerve regeneration. Commercially available tissue sealants (Tisseel, Evicel, and DuraSeal), when used to augment 2-suture nerve repairs, as in the authors' protocol, help prevent this initial gapping. None of the tissue sealants tested, however, increased the ultimate load to complete failure of the repair.

Avomentin

Ferguson et al (2009) assessed scar improvement with avotermín (recombinant, active, human TGFbeta3). In 3 double-blind, placebo-controlled studies, intra-dermal avotermín (concentrations ranging from 0.25 to 500 ng/100 microL per linear cm wound margin) was administered to both margins of 1 cm, full-thickness skin incisions, before wounding and 24 hrs later, in healthy men and women. Treatments (avotermín and placebo or standard wound care) were randomly allocated to wound sites by a computer generated randomization scheme, and within-participant controls compared avotermín versus placebo or standard wound care alone. Primary endpoints were visual assessment of scar formation at 6 months and 12 months after wounding in 2 studies, and from week 6 to month 7 after wounding in the 3rd. Investigators, participants, and scar assessors were blinded to treatment. Efficacy analyses were intention-to-treat. In 2 studies, avotermín 50 ng/100 microL per linear cm significantly improved median score on a 100 mm visual analog scale (VAS) by 5 mm (range of -2 to 14; \( p = 0.001 \)) at month 6 and 8 mm (-29 to 18; \( p = 0.0230 \)) at month 12. In the 3rd study, avotermín significantly improved total scar scores at all concentrations versus placebo (mean improvement: from 14.84 mm [95 % CI: 5.5 to 24.2] at 5 ng/100 microL per linear cm to 64.25 mm [49.4
to 79.1] at 500 ng/100 microL per linear cm). Nine [60 %] scars treated with avotermin 50 ng/100 microL per linear cm showed 25 % or less abnormal orientation of collagen fibres in the reticular dermis versus 5 [33 %] placebo scars. After only 6 weeks from wounding, avotermin 500 ng/100 microL per linear cm improved VAS score by 16.12 mm (95 % CI: 10.61 to 21.63). Adverse events at wound sites were similar for avotermin and controls. Erythema and edema were more frequent with avotermin than with placebo, but were transient and deemed to be consistent with normal wound healing. The authors concluded that avotermin has potential to provide an accelerated and permanent improvement in scarring.

**Amniotic Fluid Injection (e.g., Amniofix)**

Amniofix (MiMedx Group, Inc.) is a solubilized amniotic membrane for the purpose of growth factors. Amniotic fluid contains fibrinolytic agents, and there is evidence from animal models of the potential for amniotic fluid injection for corneal wound healing and for prevention of adhesion formation following orthopedic surgery. However, there is insufficient evidence (from human studies) to support the use of amniotic fluid injection for these indications. A controlled study is currently ongoing to evaluate the clinical effectiveness of AmnioFix in the reduction of the tenacity and frequency of soft tissue adhesions during the removal of segmental posterior lumbar instrumentation. In addition, a randomized controlled study of Amniofix in the treatment of recalcitrant plantar fasciitis is currently ongoing.

**BioDfactor Human Amnion Allograft**

BioDfactor human amnion allograft was developed as a liquid wound-covering product for use in-vivo to fill soft tissue defects or bone voids. It can be applied directly to the surgical site or mixed with patients’ own blood to provide an easy to use wound-covering.

Koike et al (2011) stated that human amniotic cells are a valuable source of functional cells that can be used in various fields, including regenerative medicine and tissue engineering. These researchers investigated the utility of human amniotic epithelial (hAE) cells as a new cell source for culturing stratified epithelium sheets for intra-oral grafting. Enzymatically isolated hAE cells were submerged in a serum-free, low-calcium-supplemented MCDB 153 medium without a feeder layer. The hAE cells were seeded onto a Millicell cell culture plate insert and cultured while submerged in a high-calcium medium for 4 days. Then, they were cultured at an air-liquid interface for 3 weeks. Cultures of hAE cells proliferated at the air-liquid interface. After 3 weeks, the hAE cells cultivated using the air-liquid interface method lead to almost 10 continuous layers of stratified epithelium without para-keratinization or keratinization. It confirmed
immunohistochemically that the presence of CK10/13 and Ki-67 positive cells were spread throughout almost all the epithelial layer, and that CK19 positive cells were expressed throughout the entire epithelial layer in the cultured hAE cell sheets. Cultured hAE cells sheets showed a staining pattern similar to that of uncultured oral mucosa: ZO-1 and occludin were located in the intercellular junctions throughout all the epithelial layers. It was suggested that the hAE sheets consisted of highly-active proliferating cells and undifferentiated cells, and had a barrier function. The authors concluded that these findings suggested that hAE cells may be a promising cell source for the development of stratified epithelium allograft sheets using a human cell strain.

Gutierrez-Moreno et al (2011) analyzed the literature on the safety and effectiveness of amniotic membrane grafting and compared the cost of currently available grafts (autografts, amniotic membrane grafts, and biocompatible skin substitutes) to promote tissue repair in venous ulcers. A systematic review of the literature on the use of amniotic membrane grafts for the treatment of venous ulcers was performed up to 2010. A cost-minimization analysis of direct healthcare costs was then performed (at 3 and 6 months). A sensitivity analysis was performed to confirm the stability of the results. Only 1 study addressing safety and effectiveness was identified. The cost-minimization analysis showed that autografts are always the least-expensive option (€ 1,053 compared with € 1,825 for amniotic membrane grafts and € 5,767 for biocompatible skin grafts). At 6 months, however, amniotic membrane grafts would have cost € 6,765 less than the use of biocompatible skin substitutes. The authors concluded that despite having excellent therapeutic potential for the re-epithelialization of venous ulcers that do not respond to conventional treatment, amniotic membrane transplant remains an experimental therapy. Autograft is the most efficient treatment but amniotic membrane graft is less expensive than the use of biocompatible skin substitutes.

Fibrin Sealant for Breast Reconstruction

The use of fibrin sealant has been proposed as a means of preventing seroma formation following breast cancer surgery. Carless and Henry (2006) performed a systematic review of RCTs to examine the effectiveness of fibrin sealants in reducing post-operative drainage and seroma formation after breast cancer surgery. Studies were identified by computer searches of Medline, Embase, the Cochrane Central Register of Controlled Trials and manufacturer websites (to June 2005), and bibliographic searches of published articles. Trials were eligible for inclusion if they reported data on post-operative drainage and the number of patients who developed a seroma. A total of 11 trials met the criteria for inclusion. In general, the trials were small and of poor methodological quality. Fibrin sealant did not reduce the rate of post-operative seroma (relative risk 1.14, 95 % CI: 0.88 to 1.46), the volume of drainage (weighted mean difference - 117.7, 95 % CI: - 259.2 to 23.8 ml), or the length of hospital stay (weighted
mean difference - 0.38, 95 % CI: - 1.58 to 0.83 days). The authors concluded that the current evidence does not support the use of fibrin sealant in breast cancer surgery to reduce post-operative drainage or seroma formation.

Cipolla et al (2010) evaluated the effectiveness of fibrin glue in the prevention of seroma formation after axillary lymphadenectomy. A total of 159 breast cancer patients about to undergo quadrantectomy or mastectomy plus axillary lymphadenectomy were enrolled in the study and randomized into 2 groups: (i) fibrin glue spray applied to the axillary fossa plus placement of closed suction drainage were used in 80 patients (group A), and (ii) placement of closed suction drainage was only used in 79 patients (group B). Patients in group A showed a slight advantage with regard to the mean duration of axillary drainage placement (4.5 +/- 1.3 days in group A versus 5.1 +/- 1.6 days in group B) and number of seroma aspirations (6.3 +/- 1.1 in group A versus 6.7 +/- 1.2 in group B). No statistically significant differences were observed between the 2 groups of patients regarding the mean volume of total axillary drainage and of total seroma volume. The authors concluded that the use of fibrin glue does not prevent seroma formation and does not reduce seroma magnitude and duration.

Llewellyn-Bennett et al (2012) noted that latissimus dorsi (LD) flap procedures comprise 50 % of breast reconstructions in the United Kingdom. They are frequently complicated by seroma formation. In a randomized study, these researchers investigated the effect of fibrin sealant (Tisseel) on total seroma volumes from the breast, axilla and back (donor site) after LD breast reconstruction. Secondary outcomes were specific back seroma volumes together with incidence and severity of wound complications. Consecutive women undergoing implant-assisted or extended autologous LD flap reconstruction were randomized to either standard care or application of fibrin sealant to the donor-site chest wall. All participants were blinded for the study duration but assessors were only partially blinded. Non-parametric methods were used for analysis. A total of 107 women were included (sealant = 54, control = 53). Overall, back seroma volumes were high, with no significant differences between control and sealant groups over 3 months. Fibrin sealant failed to reduce in-situ back drainage volumes in the 10 days after surgery, and did not affect the rate or volume of seromas following drain removal. The authors concluded that the findings of this randomized study, which was powered for size effect, failed to show any benefit from fibrin sealant in minimizing back seromas after LD procedures.

CellerateRx

CellerateRX activated type 1 collagen powder is composed of collagen fragments approximately 1/100th the size of the native collagen molecule. The product is intended to deliver the benefits of collagen immediately to the wound site in a variety of types of wounds. Newman, et al. (2008) reported on their experience with CellerateRx
activated type I collagen in the treatment of recalcitrant wounds in the diabetic population resulting from minor trauma and/or venous stasis disease. The authors reported on two middle-aged diabetic male patients with lower extremity wounds refractory to conservative wound care who were treated with CellerateRx (activated, fragmented, and nonintact type I collagen) in a gel and powder form. The authors stated that both patients had complete resolution of recalcitrant wounds in 6 to 7 weeks. The authors concluded that wound resolution was evident when using the authors' practice protocol, which includes the application of activated collagen. The authors stated that the inherent properties of type I collagen may contribute to a more rapid healing process.

**Mediskin**

Mediskin is frozen irradiated porcine xenograft with a dermal and epidermal layer. It has been used for partial-thickness skin ulcerations and abrasions. Other applications may include temporary covering for full-thickness skin loss, toxic epidemal necrolysis (TEN) and meshed autograft protection.

Mediskin is a frozen irradiated porcine-derived de-cellularized fetal skin product with a dermal and epidermal layer. Mediskin a frozen irradiated porcine xenograft that has a shelf life of 24 months. It may reduce pain, protein, and fluid loss, provide a barrier to external contamination and a moist wound healing site, and protect underlying tissue in the treatment of burns, abrasions, donor sites, decubitus and chronic vascular ulcers. It also provides an optimal environment for wound healing. Mediskin may also be used as temporary wound cover. It can be used on any person except those who have a known sensitivity to porcine products, on patients with histories of multiple serum allergies, or on wounds with large amounts of eschar. As the wound heals, Mediskin will naturally slough off. It is supplied in rolls (3" wide by 12, 24 or 48" long) and is also supplied in 7" x 18" sheets and patches of 3"x4" and 2"x2". According to the manufacturer, the product differs from others as it is a porcine xenograft, temporary skin substitute. There are few published studies addressing the use of Mediskin for wound treatment. The use of porcine-derived decellularized fetal skin products (e.g., Mediskin®) has not been established since there are currently no published studies addressing the use of Mediskin®.

**Parietex Composite (PCO) Mesh**

Parietex™ Composite (PCO) mesh has a resorbable collagen barrier on one side to limit visceral attachments and a 3-D polyester knit structure on the other to promote tissue ingrowth and ease of use. There is a lack of evidence regarding the clinical value of the Parietex Composite Mesh in the treatment of genito-urinary (e.g., uterine or vaginal vault) prolapse.

On July 13, 2011, the FDA issued a statement that serious complications are not rare with the use of surgical mesh in trans-vaginal repair of pelvic organ prolapse. The FDA reviewed the literature from 1996 to 2011 to evaluate safety and effectiveness and found surgical mesh in the trans-vaginal repair of pelvic organ prolapse does not improve symptoms or quality of life more than non-mesh repair. The review found that the most common complication was erosion of the mesh through the vagina, which can take multiple surgeries to repair and can be debilitating in some women. Mesh contraction was also reported, which causes vaginal shortening, tightening, and pain. In addition, the FDA’s update stated that "Both mesh erosion and mesh contraction may lead to severe pelvic pain, painful sexual intercourse or an inability to engage in sexual intercourse. Also, men may experience irritation and pain to the penis during sexual intercourse when the mesh is exposed in mesh erosion".

Alloskin

Alloskin (Allosource, Centennial, OH) is a specialty allograft derived from epidermal and dermal cadaveric tissue and designed for wound care (Snyder, et al., 2012). Alloskin is a 1:1 meshed, biological cadaveric dermis, which is decellularized and further processed to provide an acellular tissue allograft (CMS, 2013). These products have been used in acute and chronic wound therapy.

Alloskin AC allograft is a natural skin replacement that can be used as a scaffold for regeneration of tissue through revascularization and remodeling into the host tissue to achieve wound closure of partial or full-thickness wounds due to tissue loss from burns, trauma and chronic wounds, such as venous and arterial ulcers, diabetic foot ulcers and pressure ulcers (CMS, 2013). Alloskin AC tissue allograft is surgically applied and secured to the skin by the anchoring method chosen by the surgeon (sutures, staples, adhesive glue, etc.). Alloskin AC is supplied 4cmx4cm/16cm² and 5cmx5cm/25cm². There is a similar human cadaver acellular product, Graftjacket. Alloskin AC is processed differently than Graftjacket. After epidermal layer is removed by chemical delamination, the resulting dermal product is low-dose, e-beam irradiated to preserve the graft in a shelf-stable format. E-beam sterilization is considered a gentler method of sterilization than gamma irradiation for delicate collagen matrices.

AlloSkin RT human allograft is a meshed, biologic wound covering comprised of human cadaveric dermis. It is low-dose, e-beam irradiated, allowing its use in clinical settings where there is no access to a cryo-rated freezer. AlloSkin RT is for homologous use and is used clinically as a temporary skin replacement for closure of partial or full-thickness wounds due to burns, trauma or chronic wounds, such as venous and arterial ulcers, neuropathic diabetic ulcers and pressure ulcers. AlloSkin is surgically applied and secured to the skin by anchoring method chosen by the surgeon (sutures, staples,
adhesive glue, etc.). The allograft sloughs in 7-14 days as granulation of the wound bed proceeds, and might be reapplied to provide a skin replacement that is intended to help promote wound healing by protection of the injured tissues and supporting final closure of the wound. The manufacturer states that Alloskin is processed differently than similar products.

Moravveg et al (2012) reported on 14 patients with severe third-degree burns treated with Alloskin from June 2009 until December 2010 as the sample for this study. After debridement and wound excision, meshed split thickness skin graft was used to cover the entire wound. Alloskin (allogen fibroblasts cultured on a combination of silicone and glycosaminoglycan) was applied on one side and petroleum jelly-impregnated gauze (Iran Polymer and Petrochemical Institute) was applied on the other. The healing time, scar formation, and pigmentation score were assessed for the patients. All analyses were undertaken with SPSS 17 software. The authors stated that Alloskin demonstrated good properties compared to petroleum jelly-impregnated gauze. The average healing time and hypertrophic scar formation were significantly different between the two groups. In addition, the skin pigmentation score in the alloskin group was closer to normal. The authors stated that Alloskin grafting may be a useful method to reduce healing time and scar size and may require less autologous split thickness skin grafts in extensive burns where a high percentage of skin is burned and there is a lack of available donor sites.

**Allomax**

Allomax is an allograft made from donated human skin consisting of epidermal and dermal layers. AlloMax is a dry sheet of sterile, human dermis for use in repairing abdominal wall wounds, hernia repair, multi-layer surgical wounds/openings and other damaged tissue. It has also been used for repair of chest wall defects and breast reconstruction. According to the manufacturer, when hydrated and placed in contact with healthy well vascularized tissue, the graft supports cell in-growth and revascularization, allowing the body to remodel the graft and over time close the wound. In breast reconstruction, it closes the space between the pectoralis muscle and the chest wall. For hernia repair, AlloMax is used to repair complex abdominal wall wounds. Often multiple pieces of AlloMax are sutured together to repair an abdominal wall wound or defect. AlloMax is supplied in an individualized sterile pouch in a variety of sizes. According to the manufacturer, there are significant differences in product attributes even among similar products.

A 2012 review was conducted on the history of use of acellular dermal matrices in breast reconstructive surgery (Cheng and St. Cyr, 2012). The authors stated that a paucity of data exists to directly compare AlloDerm®, DermaMatrix®, Strattice™, Permacol™,
DermACELL, FlexHD®, SurgiMend®, and AlloMax™ for use in breast reconstruction. They found that most studies related to hernia repair and concluded that an ideal acellular dermal matrix product is still unavailable.

**AlloPatch**

AlloPatchHD is an acellular human dermis derived from human allograft skin minimally processed to remove epidermal and dermal cells. It is processed using proprietary procedures developed by Musculoskeletal Transplant Foundation (MTF, Edison, NJ) to preserve and maintain the natural biomechanical, biochemical and matrix properties of the dermal graft. AlloPatchHD is used to support cellular repopulation and vascularization in applications at the surgical site. According to the manufacturer, this unique product is indicated for use to replace damaged or inadequate integumental tissue. Allopatch HD is designed to provide an extracellular matrix (ECM) scaffold for tendon augmentation (Snyder et al, 2012).

AlloPatch Pliable (MTF, Edison, NJ) is a preparation of a reticular cut of human dermis aseptically processed to preserve the native tissue and retain the standard amount of collagens and elastins normally present. It requires no rehydration or refrigeration prior to use and can be stored at ambient temperature. This dermis differs from many of the other human dermal matrices available that are derived from a more superficial cut of the dermis, which contains both papillary and reticular portions of the dermis. The HR-ADM comes in size-specific grafts as small as 1.5 cm × 1.5 cm to minimize wastage and can be trimmed to fit the wound.

Zelen et al (2017a) compared clinical outcomes of AlloPatch Pliable, a novel, open-structure human reticular acellular dermis matrix (HR-ADM), to facilitate wound closure in non-healing diabetic foot ulcers (DFUs) versus DFUs treated with standard of care (SOC). Following a 2-week screening period in which DFUs were treated with offloading and moist wound care, patients were randomised to either SOC alone or HR-ADM plus SOC applied weekly for up to 12 weeks. At 6 weeks, the primary outcome time, 65% of the HR-ADM-treated DFUs healed (13/20) compared with 5% (1/20) of DFUs that received SOC alone. At 12 weeks, the proportions of DFUs healed were 80% and 20%, respectively. Mean time to heal within 12 weeks was 40 days for the HR-ADM group compared with 77 days for the SOC group. There was no incidence of increased adverse or serious adverse events between groups or any adverse events related to the graft. Mean and median graft costs to closure per healed wound in the HR-ADM group were $1475 and $963, respectively. The authors stated that strengths of the study include comprehensive SOC, satisfactory allocation concealment, an ITT analysis, adequate statistical power based on sample size and appropriate adjustment for multiple statistical testing and reporting according to CONSORT guidelines. Limitations of this investigation...
include lack of blinding from the patient's and investigator's perspective, an absence of exact tissue-level exposure measurement and reporting for each wound (e.g. Wagner grading), although each wound was evaluated to ensure that no wound reached greater than Wagner 2. There is also extensive right censoring for analyses at 12 weeks because of the decision to exit patients from the study whose wounds did not reduce in area by at least 50% after 6 weeks of either treatment regimen.

Zelen et al (2017b) retrospectively reviewed healing in patients with DFUs that failed the standard of care (SOC) treatment from a previous prospective randomized, controlled trial (RCT). That trial compared the efficacy of AlloPatch Pliable human reticular acellular dermal matrices (HR-ADMs) with the SOC. Of the 16 out of 20 patients who did not heal in the SOC group, 12 were eligible for crossover treatment with the HR-ADM. The authors studied the rate of complete healing in that specific cohort after 12 weeks of crossover treatment. Of the 12 patients who were eligible for the HR-ADM, 10 (83%) achieved complete wound healing, with a mean healing time of 21 days to closure. The corresponding wound area reduction was from 1.7 cm² to 0.6 cm². The mean product cost to closure was $800/patient.

The relatively small sample of this study and its extension raise questions about the generalizability of the findings. In addition to the limitations mentioned by the authors, the method of blinding in the randomized controlled trial also introduced the potential for bias. Adjudicators were blinded to patient study group assignments, but the protocol does not say that the adjudicators were blinded to the investigators assessment of healing.

Dasgupta and colleagues (2016) hypothesized that a novel human reticular ADM (HR-ADM; AlloPatch Pliable) when aseptically processed would have a more open uniform structure with retention of biological components known to facilitate wound healing. The reticular and papillary layers were compared through histology and scanning electron microscopy. Biomechanical properties were assessed through tensile testing. The impact of aseptic processing was evaluated by comparing unprocessed with processed reticular grafts. In-vitro cell culture on fibroblasts and endothelial cells were performed to showcase functional cell activities on HR-ADMs. Aseptically processed HR-ADMs have an open, interconnected uniform scaffold with preserved collagens, elastin, glycosaminoglycans, and hyaluronic acid. HR-ADMs had significantly lowered ultimate tensile strength and Young's modulus versus the papillary layer, with a higher percentage elongation at break, providing graft flexibility. These preserved biological components facilitated fibroblast and endothelial cell attachment, cell infiltration, and new matrix synthesis (collagen IV, fibronectin, von Willebrand factor), which support granulation and angiogenic activities. The authors concluded that the novel HR-ADMs provided an open, interconnected scaffold with native dermal mechanical and biological properties.
Furthermore, aseptic processing retained key extracellular matrix elements in an organized framework and supported functional activities of fibroblasts and endothelial cells. Moreover, they stated that further in-vitro studies are needed to characterize the cell behavior and functionality of these biologically and mechanically stable novel reticular dermal grafts in a chronic setting.

Zelen et al (2018) noted that aseptically processed human reticular acellular dermal matrix (HR-ADM) has been previously shown to improve wound closure in 40 diabetic patients with non-healing foot ulcers. The study was extended to 40 additional patients (80 in total) to validate and extend the original findings. The entire cohort of 80 patients underwent appropriate off-loading and SOC during a 2-week screening period and, after meeting eligibility criteria, were randomized to receive weekly applications of HR-ADM plus SOC or SOC alone for up to 12 weeks. The primary outcome was the proportion of wounds closed at 6 weeks; 68 % (27/40) in the HR-ADM group were completely healed at 6 weeks compared with 15 % (6/40) in the SOC group. The proportions of wounds healed at 12 weeks were 80 % (34/40) and 30 % (12/40), respectively. The mean time to heal within 12 weeks was 38 days for the HR-ADM group and 72 days for the SOC group. There was no incidence of increased adverse or serious adverse events (AEs) between groups or any graft-related AEs. The mean and median HR-ADM product costs at 12 weeks were $1,200 and $680, respectively. The authors concluded that HR-ADM was clinically superior to SOC, was cost-effective relative to other comparable treatment modalities, and was an effective treatment for chronic non-healing DFUs.

The authors stated that drawbacks of this study included the fact that it was an open study that did not blind the patient or the investigator to the intervention allocated because blinding was not feasible (although reviewers were blinded to the type of treatment in their evaluation of wound closure). It was also limited in ulcer size and depth, in that there was no tendon, capsule, muscle, or bone exposure, which is frequently observed in complex ulcers presenting to the wound clinic. These investigators stated that future trials may assess the use of HR-ADM on deeper wounds and more medically complex patient populations as frequently seen in the “real-world” population.

A draft assessment of wound care products prepared for AHRQ judged this randomized controlled study by Zelen, et al. (2018) to be at moderate risk of bias.

ArthroFlex

According to the manufacturer, ArthroFlex (FlexGraft) is a unique decellularized human skin allograft product indicated for the treatment of chronic wounds, such as diabetic foot ulcers and large surgical wounds. Arthroflex contains both collagen and elastin which
provide structural support for resilience, a compliment of growth factors to assist healing, as well as multiple cytokines that assist in epithelialization and modulate the proliferation and differentiation of epithelium, and finally fully developed extracellular matrix which allows for infiltration of recipient cells. The extracellular matrix stimulates epithelialization from the wound periphery and from remnant epidermal appendages when placed in contact with the wound. The manufacturer states that Arthroflex provides a physiological barrier that decreases water loss, electrolytes, proteins and heat from the wound bed and creates a mechanical barrier that reduces environmental microbiological contamination. Arthroflex is applied directly to the wound or ulcer and secured to the site in one of several ways, including the use of sutures, staples, or skin adhesive strips. It is currently provided with a thickness of 1.26 mm to 1.75 mm and two scaffold sizes: 35 mm x 35 mm and 40 mm x 70 mm. The manufacturer states that they are likely to provide additional product sizes and thicknesses in the future. Arthroflex decellularized dermis patch has also been used in Achilles tendon repair and shoulder reconstruction. Available peer-reviewed published medical literature on Arthroflex has focused on its biomechanical properties (Ehsan et al, 2012; Beitzel et al, 2012).

DermACELL

DermACELL is an acellular regenerative human dermal allograft procured and processed from donated human tissue. DermACELL is used to provide a physiological and mechanical barrier that reduces environmental contamination and assists in promotion of granulation tissue and epithelialization for any topical or surgical wound. It is sutured topically to wounds, such as chronic non-healing wounds or partial and full thickness burns, and is sutured surgically to muscle flaps or other connective tissue for indications such as closing of complicated ventral/incisional hernias, breast reconstruction, temporal defects, tendon and ligament damage, and in guided tissue regeneration in oral applications. As an allograft collagen scaffold, DermACELL supports a patient's own cellular in-growth, resulting in tissue regeneration. DermACELL is supplied as one packaged allograft in various sizes, from 4 to 96 square centimeters and from 0.2-0.4 mm thick.

DermACELL, DermACELL AWM, DermACELL AWM Porous (LifeNet Health) "are decellularized human dermal allografts" indicated for use in "chronic non-healing wounds such as diabetic and venous leg ulcers, acute burns, breast reconstruction and other associated soft tissue injuries" (CMS, 2019). The grafts comes in various sizes, from 4 to 320 square centimeters and from 0.2 - 3.5 mm thick.

DermaCELL is provided by the Skin and Wound Allograft Institute, which is a wholly owned subsidiary of LifeNet Health (Virginia Beach, VA) (Snyder et al, 2012). The company believes that its MatraCell processing technology creates a readily available, extracellular matrix that then provides a collagen scaffold to support cell ingrowth.

There is limited published evidence in the peer-reviewed medical literature on DermACELL (Chen et al, 2012; Capito et al, 2012).

Walters et al (2016) reported on an interim analysis of a multicenter study involving 168 patients who were randomized into DermACELL, conventional care, and Graftjacket treatment arms in a 2:2:1 ratio. Patients in the acellular dermal matrix groups received either 1 or 2 applications of the graft at the discretion of the investigator. Weekly follow-up visits were conducted until the ulcer healed or the endpoint was reached. At the primary endpoint of 12 weeks, there was a nonsignificant trend in the proportion of completely healing ulcers in the DermACELL arm than in the conventional care arm and the Graftjacket arm (52.8% versus 41.1% and 39.1%, respectively, NS). By 16 weeks, the DermACELL arm had a significantly higher proportion of completely healed ulcers than the conventional care arm (67.9% vs 48.1%; P = .0385) and a nonsignificant trend toward greater healing than in the Graftjacket arm (67.9% vs 47.8%; P = .1149). Contrary to prior studies of Graftjacket, in this study sponsored by the manufacturers of DermACELL, there was no evidence of efficacy of Graftjacket compared to conventional treatment; the rates of complete healing and mean percent reduction in wound area from baseline with Graftjacket was neither clinically or significantly different than with conventional treatment. The DermACELL arm also exhibited a nonsignificant greater reduction in wound area at 16 weeks than the conventional care arm (91.4% vs 80.3%; P = .0791) and the Graftjacket arm (91.4% vs 73.5%; P = .0762). There was a nonsignificant trend in reduction of wound area at 16 weeks in the conventional care arm than in the Graftjacket arm. There was no clinically or statistically significant difference in mean number of weeks to complete wound closure in the DermACELL arm (8.6 weeks) than in the conventional care arm (8.7 weeks) and the Graftjacket arm (8.6 weeks). The authors reported that the proportion of severe adverse events and the proportion of overall early withdrawals were similar among the 3 groups based on relative population size (P ≥ .05). Limitations of the study include its open label nature and the lack of a run-in period. The study report did not specify whether the persons who were assigned to conventional care were treated according to widely accepted, evidence-based clinical guidelines. There were a significant number of dropouts (18 of 71 in the DermACELL group, 13 of 69 in the conventional care arm, and 5 of 28 in the Graftjacket arm, and intention to treat analysis was not reported.
In a prospective RCT, Cazzel and colleagues (2017) compared the safety and efficacy of a human acellular dermal matrix (ADM), D-ADM, with a conventional care arm and an active comparator human ADM arm, GJ-ADM, for the treatment of chronic diabetic foot ulcers. The study enrolled 168 diabetic foot ulcer subjects in 13 centers across 9 states. Subjects in the ADM arms received 1 application but could receive 1 additional application of ADM if deemed necessary. Screen failures and early withdrawals left 53 subjects in the D-ADM arm, 56 in the conventional care arm, and 23 in the GJ-ADM arm (2:2:1 ratio). Subjects were followed through 24 weeks with major end-points at weeks 12, 16, and 24. Single application D-ADM subjects showed significantly greater wound closure rates than conventional care at all 3 end-points while all applications D-ADM displayed a significantly higher healing rate than conventional care at week 16 and week 24. GJ-ADM did not show a significantly greater healing rate over conventional care at any of these time-points. A blinded, 3rd party adjudicator analyzed healing at week 12 and expressed "strong" agreement ($\kappa = 0.837$). Closed ulcers in the single application D-ADM arm remained healed at a significantly greater rate than the conventional care arm at 4 weeks post-termination (100 % versus 86.7 %; p = 0.0435). There was no significant difference between GJ-ADM and conventional care for healed wounds remaining closed. Single application D-ADM demonstrated significantly greater average percent wound area reduction than conventional care for weeks 2 to 24 while single application GJ-ADM showed significantly greater wound area reduction over conventional care for weeks 4 to 6, 9, and 11 to 12. The authors concluded that D-ADM demonstrated significantly greater wound healing, larger wound area reduction, and a better capability of keeping healed wounds closed than conventional care in the treatment of chronic DFUs.

The authors stated that although this study utilized stringent criteria for evaluation, the lack of information surrounding additional applications of human ADMs in the literature proved challenging for study design. This resulted in the study being erroneously powered using healing rates reported in other human ADM studies that reported only a single application of product with a 12 week follow-up period. Although the single application wound healing rate shown in this study was significantly better than conventional care throughout, the healing rate for all subjects did not become statistically significant until week 15 even though the percent wound area reduction was statistically significant from week . This study provided a very detailed analysis of healing rates and it should be noted that multiple probability tests were applied to this data set without correcting related probabilities. While some may consider this a source of probability bias, more recent views have found this acceptable. Elucidating the effect of a second application on the overall wound environment and its ability to heal was not considered during protocol development. Furthermore, since additional applications of ADMs were allowed at investigator discretion and a few of these wounds healed quickly thereafter,
more second applications may have occurred than were necessary. Criteria for the timing of second applications for ADMs were not standardized and were an area of consideration for additional research. The results of the logistic regression analysis indicated that baseline wound area size should be a focal point of further research.

Additionally, although wound depth was collected at each visit, these data were not used as the Silhouette System had difficulty reliably determining depth. It appeared that the depth measurements may have changed depending on the angle or distance of the camera. However, investigators used a ruler to measure wound depth to determine if a subject passed the inclusion criteria so there was no concern about the accuracy of the screening process. It should be noted that in contrast to the unreliable depth measurements, the Silhouette system was extremely accurate in measuring the wound area. Furthermore, the outlined area image was double-checked for every subject at each visit to ensure the wound area was accurately measured. Another weakness of this study was that the investigators were not blinded to the treatment type when assessing wound closure. However, this was mitigated by the use of the Aranz laser system which eliminated the bias in measuring wound area reduction. Additionally, a blinded, third-party adjudicator assessed healed wounds and those close to healing by 12 weeks follow-up. The adjudicator expressed “strong” agreement with investigator designations and found an additional 2 healed wounds for D-ADM, 1 healed wound for GJ-ADM, and no change for conventional care subjects. These additional healed wounds were conservatively not included in the data analysis; but were evidence that there was no investigator bias in favor of D-ADM specifically or ADMs in general. Another disadvantage mentioned previously was the possibility of an artificially lowered healing rate for as many as 9 D-ADM wounds due to the stricter definition of healing applied in this study. The different definitions in healing should be taken into account when comparing this study with older literature, but this study may provide a benchmark for healed rates as more published studies transition to the new AHRQ guidelines for determining the healed status of wounds.

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Cazzel, et al. (2017) to be at low risk of bias.

Cazell (2019) stated that VLUs are often chronic and difficult to treat, which makes alternative options to conventional care necessary to improve ulcer healing rates. While human ADMs have shown promise in treating DFUs, no comparative studies have been published regarding VLU treatment. In a multi-center, randomized, controlled, open-label trial, these researchers evaluated the safety and efficacy of D-ADM compared with conventional wound care management in patients with chronic ulcers of the lower extremity. Patients were randomly assigned to receive either D-ADM or standard of care (control) in a 2:1 ratio. Treatment began at week 0 and wounds were evaluated on a
weekly basis until wound closure was observed or the patient completed 24 weekly follow-up visits. A total of 18 patients were included in the D-ADM arm and 10 patients in the control arm. There was a strong trend of reduction in percent wound area for D-ADM patients with an average reduction of 59.6 % at 24 weeks versus 8.1 % at 24 weeks for control patients. In addition, healed ulcers in the D-ADM arm remained closed at a substantially higher rate after termination than healed ulcers in the control. The authors concluded that this exploratory study demonstrated D-ADM increased healing rates and reduction in wound size compared to conventional care. The D-ADM also presented a favorable profile compared to the published literature on HSE, which can require several applications. These researchers stated that these early results support the use of D-ADM for treating chronic VLUs; and further larger prospective, RCTs are needed to better assess its place in clinical practice.

The authors stated that this pilot study had several limitations. The small patient population (n = 18 in the D-ADM group) and unbalanced proportion between the 2 groups (2:1) ensured a low probability of achieving statistical significance. However, as a pilot study, the purpose was to explore the potential for therapeutic benefits from using D-ADM in patients with VLUs, an area with scarce information, and achieving statistical significance was not expected. Accordingly, the larger proportion of D-ADM patients provided a better understanding of its therapeutic effects and safety profile, both of which are critical information for use in designing future trials. Another limitation of this study was the lack of criteria for investigators to follow as to when a 2nd application would be appropriate. Such formal guidelines do not exist with this new material and was left to individual clinician discretion. Finally, although the lack of blinding for study investigators would be considered a limitation, an independent adjudicator blinded to treatment type evaluated the healing status of all wounds as a secondary check to prevent bias. The kappa score of 0.923 indicated very good inter-rater reliability between the study investigators and the blinded, independent adjudicator. Furthermore, the adjudicator scored 1 additional wound treated with D-ADM as healed that the study investigators scored as unhealed, suggesting investigator bias was not an issue despite the lack of blinding.

Repriza

Repriza is a prehydrated, ready-to-use, acellular dermal matrix derived from human allograft tissue. It is intended for implantation during plastic and reconstructive surgeries wherever an acellular dermal matrix may be used. For example, it may be used to support implants in a defined pocket such as in breast reconstruction, and abdominal wall reconstruction procedures. Repriza can also be used in a range of applications to augment soft tissue irregularities and for implantation in irregularities such as a depression over the nasal bridge. Repriza is a "surgical implant" and "would have no
other use outside the surgical setting*. The scaffold is gradually integrated with, and ultimately replaced by the body's own tissue. The quantity of product used varies based upon surgical application, individual patient circumstances, and the dimensions of the surgical site. Repriza is supplied sterile and ready to use in two sizes: 4 x 12 cm and 6 x 16 cm. Custom sizes and thicknesses are available upon request. According to the manufacturer, Repriza is used in the same indications and same manner as Alloderm and Graft Jacket; however, there is a significant difference in the cost of the materials.

**Memoderm**

MemoDerm (Memometal, Inc., Memphis, TN) is a sterile acellular dermal allograft derived from aseptically processed cadaveric human skin tissue that is terminally sterilized (Snyder et al, 2012). It is intended for the repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument. It has been used for repairs (e.g., rotator cuff) and wounds (e.g., chronic diabetic ulcer). The allograft acts as a scaffold of collagen and elastin fibers that are preserved during the process that renders the allograft acellular. During the granulation phase of the wound repair/regeneration cycle, the matrix of intact collagen network and preserved vascular channels in MemoDerm acts as a scaffold to facilitate angiogenesis and migration of growth factors that stimulate cell migration. When applied to wounds, MemoDerm has been shown to become vascularized and incorporated into the wound bed and provide an effective means for wound closure. MemoDerm is supplied freeze-dried and must be rehydrated prior to use. Once rehydrated, the allograft can be applied topically to the wound and secured by suturing and stapling to the skin surrounding the wound.

**Matrix HD**

Matrix HD (RTI Biologics, Alachua, FL) is a human dermal allograft restricted to homologous use for wound care; protection, reinforcement or covering of soft tissue in horizontal and vertical augmentation procedures. Matrix HD is sterile dehydrated acellular dermis from donated human tissue. The allograft provides a natural collagen scaffold skin substitute to support the body's regenerative processes. Matrix HD is typically used in conjunction with a chronic wound care management regime for the treatment of diabetic ulcers, charcot foot ulcers, venous ulcers, trauma wounds, pressure sore/ulcers, partial and full thickness wounds, and surgical wounds. Once the wound bed is prepared, the graft is placed and secured with sutures. Two allografts may be applied, one on top of the other, for optimal healing results. Matrix HD is supplied in patient specific sizes, ranging from 2 x 3 cm to 10 x 10 cm, so that the surgeon can utilize the amount of tissue needed. The size is selected by the surgeon depending on the size of the wound.
BioCleanse

BioCleanse processed human allograft tendons are used in various areas of the body to repair, replace or reconstruct the native tendon or ligament. The tendon is surgically implanted into the body to recreate the normal anatomy and restore basic function. It can be used to repair anterior cruciate ligaments, posterior cruciate ligaments, medial collateral ligaments, lateral collateral ligaments, posterior lateral corner, medial patella femoral ligament, Achilles tendons, biceps, acromioclavicular joints, lateral ankle stabilizations, lunar collateral ligaments and any soft tissue repair augmentation. By using BioCleanse tendons instead of an autograft, the surgeon may minimize operating time and eliminate second-site donor morbidity. BioCleanse tendons are restricted to homologous use for the repair, replacement or reconstruction of musculoskeletal defects by a qualified healthcare professional.

Strattice

Strattice Reconstructive Tissue Matrix is a reconstructive tissue matrix (surgical mesh) that supports tissue regeneration. It is derived from porcine dermis and undergoes non-damaging proprietary processing that removes cells and significantly reduces the key component believed to play a major role in the xenogeneic rejection response. Strattice is used by surgeons as a surgically implanted soft tissue patch to reinforce a patient's soft tissue where weakness exists, and for the surgical repair of damaged or ruptured soft tissue, such as in hernia repair, open abdominal repairs and in breast reconstruction, post mastectomy. Once implanted, Strattice promotes rapid revascularization [cell repopulation and white cell migration] and provides for management and strong repair of partial and full thickness wounds; pressure ulcers; venous ulcers; diabetic ulcer; chronic vascular ulcers; tunneled/undermined wounds; surgical wounds; trauma wounds; draining wounds; or other bleeding surface wounds. Strattice is available to physicians in 2 versions: pliable and firm, in various sizes: Pliable: 5 cm x 16 cm and 8 cm x 16 cm, and Firm: 6 cm x 16 cm, 10 cm x 16 cm, 16 cm x 20 cm, 20 cm x 20 cm, and 20 cm x 25 cm. The physician will determine the most appropriate size and version to be used based on each individual patient case.

The use of Strattice porcine-derived decellularized collagen products has been proposed for use in various surgical procedures and in the treatment of dermal wounds. Currently, there is insufficient evidence to allow for proper evaluation regarding the effectiveness of this technology.

Unite Biomatrix


08/27/2019
Unite Biomatrix (Synovis Orthopedic and Woundcare, Inc.) is a wound biomodulating decellularized extracellular matrix (ECM) that is sourced from equine pericardium (Snyder, et al., 2012). Unite Biomatrix is a non-reconstituted collagen dressing used to maintain the wound bed in the healing phase thereby allowing for health granulation tissue and wound closure. Unite Biomatrix is indicated for local management of moderately to heavily exuding wounds. Unite Biomatrix was cleared by the FDA in 2011 based upon a 510(k) "For the management of moderately to severely exuding wounds, including: partial and full thickness wounds, draining wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (e.g., abrasions, lacerations, partial thickness [second-degree] burns, skin tears), surgical wounds (e.g., donor sites/grafts, post-laser surgery, post-Mohs surgery, podiatric wounds, dehisced surgical incisions)."

It is applied to the debrided wound bed without promoting an inflammatory response, while maintaining integrity as the wound heals. To apply, cut the rinsed Unite Biomatrix to a size slightly larger than the outline of the wound area and secure in place by sutures or staples. As healing occurs, sections of the matrix may gradually peel and may be removed during dressing changes. Additional Unite Biomatrix may be applied to discrete areas of the wound that have not yet healed satisfactorily. Unite Biomatrix is packaged in a chemical solution and is available pre-fenestrated or non-fenestrated. Unite Biomatrix differs from other products in that it is composed of decellularized equine pericardial implants. The use of equine-derived decellularized collagen products (e.g., OrthADAPT™ and Unite™) has not been established as shown by the lack of evidence on the subject.

OrthADAPT

OrthADAPT Bioimplant is a highly organized Type 1 collagen scaffold derived from Equine Pericardium used as a scaffold for soft tissue repair and reinforcement. OrthADAPT Bioimplant is intended to be used for implantation to reinforce the repair or reconstruction of soft tissues, including the reinforcement of soft tissues repaired by sutures or suture anchors during surgical repair. The inherent properties of this xenograft provide support to challenging tendon repairs in both sports medicine and lower extremity surgical repairs, such as reinforcement of rotator cuff, patellar, Achilles, biceps, quadriceps, or other tendons. The use of equine-derived decellularized collagen products (e.g., OrthADAPT™ and Unite™) has not been established as shown by the lack of evidence on the subject.

Talymed
Talymed (Marine Polymer Technologies, Inc., Danvers, MA) is a sterile advanced wound matrix comprised of shortened fibers of poly-N-acetylglucosamine, isolated from microalgae (Snyder, et al., 2012). Talymed is indicated for the management of wounds including: diabetic ulcers, venous ulcers, pressure wounds, ulcers caused by mixed vascular etiologies, full thickness and partial thickness wounds, second degree burns, surgical wounds, traumatic wounds healing by secondary intention, chronic vascular ulcers and dehisced surgical wounds and bleeding surface wounds, abrasions and lacerations. Talymed is placed on the open wound and covered with a transparent dressing. New wound matrix can be reapplied as necessary. Talymed™ is provided as a 5 x 5 cm and 10 x 10 cm patch that should be cut to fit wound size. According to the manufacturer, Talymed is similar to Oasis Wound Matrix, Integra Flowable Wound Matrix, and PriMatrix Dermal Repair Scaffold, but is created from a different source and has a different mechanism of action.

Talymed was cleared for marketing under the 510(k) process (K102002) in July 2010 for “the management of wounds including: diabetic ulcers; venous ulcers; pressure wounds; ulcers caused by mixed vascular etiologies; full thickness and partial thickness wounds; second degree burns; surgical wounds-donor sites/grafts, post-Mohs surgery, post laser surgery, and other bleeding surface wounds; abrasions, lacerations; traumatic wounds healing by secondary intention; chronic vascular ulcers; dehisced surgical wounds.”

Hankins et al (2012) evaluated in terms of number needed to treat (NNT), the comparative clinical and cost efficacy of targeted advanced wound care matrices (AWCMs) as adjuncts to compression therapy for the treatment of chronic venous leg ulcers (VLUs) from the U.S. health care system (payer) perspective. A review of published articles (from the earliest available Medline publication date to June 1, 2011) identified randomized controlled trials (RCTs) evaluating complete wound closure rates for up to 24 weeks in patients with VLUs treated with targeted AWCMs (Apligraf, Oasis, or Talymed) plus compression therapy compared with compression therapy alone. The most favorable estimates of product efficacy (i.e., those that were statistically significant compared with compression therapy) were used. These included statistically adjusted results for Apligraf as reported in the product insert and the biweekly application for Talymed. Based on the reported efficacy of targeted AWCMs, these researchers calculated the NNT to achieve 1 additional treatment success (i.e., complete wound closure) over that which was achieved with standard therapy alone; 95 % CIs were estimated using the Wilson score method proposed by Newcombe. Cost efficacy, defined as the incremental cost per additional successfully treated patient, was then calculated by multiplying the NNT associated with each treatment by the product acquisition cost per treated VLU episode. One study for each of 3 targeted AWCMs (Apligraf [n = 130 treatment, n = 110 control]; Oasis Wound Matrix [n = 62 treatment, n =
58 control]; and Talymed [n = 22 treatment, n = 20 control]) met inclusion criteria. Study
designs and wound characteristics varied. Average VLU sizes were 1 cm², 10 to 12
cm², and 10 to 13 cm² in the studies of Apligraf, Oasis, and Talymed, respectively.
Ulcer duration exceeded 12 months for 50 % of patients in the Apligraf study and was at
least 7 months for 47 % of patients in the Oasis study; patients with ulcers exceeding 6
months were excluded from the study of Talymed. Length of follow-up was 24 weeks for
Apligraf, 12 weeks for Oasis, and 20 weeks for Talymed. NNT point estimates of clinical
efficacy were 2 for Talymed, 5 for Oasis, and 6 for Apligraf; 95 % CIs ranged from 2 to 8
for Talymed, 3 to 24 for Apligraf, and 3 to 39 for Oasis. Incremental costs (95 % CIs) per
additional successfully treated patient were $1,600 ($1,600 to $6,400) for Talymed,
$3,150 ($1,890 to $24,570) for Oasis, and $29,952 ($14,976 to $119,808) for Apligraf.
The authors concluded that the most expensive AWCM for the treatment of VLUs did not
appear to provide the greatest comparative clinical or cost efficacy. Conclusions must be
tempered by the small number of available studies (n = 3), variability in trial duration
(from 12 to 24 weeks) and baseline wound characteristics, and limitations in study
quality. Given the high prevalence, economic burden, and substantial disability of VLUs,
and the wide variation in costs for AWCMs, payers need more high-quality head-to-head
comparisons to guide coverage and reimbursement determinations for these products.

Endoform

Endoform Dermal Template (Mesynthes, Ltd., North Attleboro, MA, and Wellington, New
Zealand) is a non-reconstituted, acellular, collagen, single-use wound matrix dressing
derived from ovine forestomach. It is indicated for in the treatment of partial and full-
thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular
ulcers, tunneled/undermined wounds, surgical wounds, trauma wounds, and draining
wounds (Snyder, et al., 2012).

EndoForm Dermal Template is an extracellular matrix derived from ovine forestomach.
According to the company Web site, “Endoform is a proprietary biomaterial containing a
rich and complex mix of important biological extracellular matrix (ECM) molecules,
including structural (collagens I, III, IV & elastin) and adhesive proteins (fibronectin and
laminin), glycosaminoglycans (heparin sulfate and hyaluronic acid) and growth factors
(FGF2 & TGFβ).”

EndoForm Dermal Template was cleared for marketing under the 510(k) process in
January 2010 for “single use in the treatment of the following wounds: partial and full-
thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular
ulcers; tunneled/undermined wounds; surgical wounds (donor sites/grafts, post-Mohs
surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions,
lacerations, second-degree burns, and skin tears); draining wounds.”

Endoform Dermal Template is a wound dressing primarily composed of ovine collagen and is supplied as a sterile intact, perforated or meshed sheet ranging in size from 9 cm² to 400 cm². Endoform is supplied sterile and is intended for single use in the treatment of wounds. Endoform is cut to fit the shape of the wound, placed on the wound bed, rehydrated with sterile saline and covered. When rehydrated, Endoform transforms into a soft conforming sheet which is naturally incorporates into the wound over time. The dressing can be left in place for 5 - 7 days. Endoform is sold in boxes of 10 dressings each and has a 2 year shelf-life. Endoform does not require physician fixation. Because of its simplicity, a patient at home can perform a dressing change once a treatment plan has been established.

There is a lack of peer-reviewed published evidence on Endoform collagen wound dressing.

**Duraseal**

DuraSeal Xact is a synthetic, absorbable hydrogel used for dural sealing to prevent cerebral spinal fluid (CSF) leaks of the dura mater. It is indicated as an adjunct to sutures for repair in spine surgery. DuraSeal Xact is sprayed onto a target tissue site as a two-component liquid system through an applicator attached to two syringes. During application, the two liquids mix and react to form a flexible, absorbable hydrogel suitable for sealing the dura mater. DuraSeal Xact is supplied as a kit containing two pre-filled syringes, a powder vial, and an applicator. The powder vial contains PEG, which is reconstituted by the first syringe to create a PEG ester solution. The second syringe contains a trilysine amine solution polymerization to form a biocompatible absorbable hydrogel.

**Dermaspan**

DermaSpan is an acellular dermal matrix derived from aseptically processed cadaveric human allograft skin tissue. It is used for the repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument. The allograft acts as a scaffold to facilitate angiogenesis and migration of growth factors that stimulate cell migration. The collagen scaffold of DermaSpan facilitates the recellularization and revascularization of the host tissue. DermaSpan is applied to the patient's surgical site and secured by suturing. It may be applied for up to two applications. According to the applicant, when applied to the wound, DermaSpan has been shown to become vascularized and incorporated into the wound bed and to provide an effective means for wound closure. DermaSpan is supplied freeze-dried, with one side covered by a layer of N-Terface membrane backing enclosed inside a Tyvek inner pouch. The allograft and inner pouch are then enclosed in a secondary outer Poly-foil pouch and
sterilized. Approximate allograft dimensions, thicknesses and expiration date are indicated on the labeling. There is a lack of peer-reviewed published clinical evidence supporting the use of Dermaspan.

Integuply

Integuply is an acellular human dermis derived from aseptically processed human allograft skin tissue. It is indicated for the repair or replacement of damaged or inadequate integumental tissue or for other homologous uses of human integument. Integuply is typically used in conjunction with a chronic wound care management regimen for the treatment of diabetic ulcers, charcot foot ulcers, venous ulcers, trauma wounds, pressure ulcers, pressure ulcers, partial and full thickness wounds, and surgical wounds. When applied to wounds, Integuply becomes vascularized and incorporated into the wound bed to provide an effective means of wound closure. The matrix and preserved vascular channels in Integuply acts as a scaffold to facilitate angiogenesis and migration of growth factors that stimulate cell migration. Integuply is applied topically to the wound site and secured by suturing or stapling to the skin surrounding the wound. Typically only one application is needed. It can be meshed or non-meshed. Integuply is supplied in 38 different sizing and thickness configurations and is packaged freeze dried.

Promogran

Promogran Matrix Wound Dressing (Ethicon) is a sterile primary dressing comprised of freeze-dried composite of 55 percent collagen and 45 percent oxidized regenerated cellulose. It is intended to bind and protect the functionality of growth factors, such as platelet-derived growth factors (PDGR) in hostile proteolytic environments. Promogran Matrix wound dressing is indicated for the management of exuding wounds including: diabetic ulcers, venous ulcers, ulcers caused by mixed vascular etiologies, full thickness and partial thickness wounds, donor sites and other bleeding surface wounds, abrasions, traumatic wound healing by secondary intention, and dehisced surgical wounds.

Duragen Plus

DuraGen Plus Dural Regeneration Matrix is an absorbable implant for repair of dural defects. It is a soft, white, pliable, nonfriable porous collagen matrix. DuraGen Plus is supplied as sterile, non-pyrogenic, for single use.

DermaMatrix
DermaMatrix tissue is an allograft derived from donated human skin. To minimize inflammation or rejection at the surgical site, the epidermis and all viable dermal cells are removed while the original dermal collagen matrix is maintained. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation (MTF) and is available through Synthes CMF. Published peer-reviewed evidence for DermaMatrix has focused on its use in breast reconstruction. It is used for the replacement of damaged or inadequate integumental tissue or for the repair, reinforcement or supplemental support of soft tissue defects. According to the manufacturer, clinical applications include, but are not limited to the following: facial applications, including soft tissue defects, nasal reconstruction and septal perforation, parotidectomy; intraoral applications, including cleft palate repair, oral resurfacing, vestibuloplasty; radial forearm free flap repair; breast reconstruction postmastectomy; and abdominal wall repair. Peer-reviewed published evidence for DermaMatrix has focused primarily on its use in breast reconstruction. There is limited peer-reviewed published evidence supporting its use for other applications (Capito, et al., 2012; Athavale, et al., 2012; Kathju, et al., 2011; Lee, et al., 2010).

DermaMatrix (formerly InteXen) Porcine Dermal Matrix is pyrogen free, porcine dermis. It has been used in treatment of hernias where the connective tissue has ruptured or for implantation to reinforce soft tissues in urological, gynecological and gastroenterological anatomy.

Grafix

Grafix Core and Grafix Prime are extracellular matrix containing growth factors for acute and chronic wounds, including diabetic foot ulcers and burns.

Grafix Core is an allograft containing endogenous mesenchymal stem cells indicated for the treatment of deep chronic wounds, limb salvage procedures, tendon repair and burns. Grafix Prime is an allograft containing endogenous mesenchymal stem cells indicated for upper epithelial layer chronic wounds and burns.

Grafix CORE is an allograft derived from human chorionic placental tissue “intended” for patients with acute and chronic wounds including, but not limited to, diabetic foot ulcers, venous stasis ulcers and pressure ulcers that have not responded to standard of care therapy. Grafix CORE has one layer (a thick stromal layer), a collagen rich membrane, mesenchymal stem cells (MSCs), and anti-inflammatory cytokines and regenerative growth factors. The thick stromal layer of Grafix CORE has been used in wounds with exposed bone and tendon to help promote granulation of deep tissue. The collagen matrix provides a physiological microenvironment for cells and proteins to promote cellular adhesion and migration in addition to supporting growth factor function. Cytokines
and growth factors, epidermal growth factor and transforming growth factor-beta3 in Grafix CORE mediate integral events such as angiogenesis, cell recruitment and proliferation. Once thawed and rinsed, Grafix CORE is applied to the wound and covered with a standard, non-adherent dressing. Additional applications are used as needed with frequency ranging from every 7-14 days until the wound is closed. Grafix CORE is supplied as a cryopreserved membrane mounted on nitrocellulose paper and is available in 2 sizes; 2cm x 2cm and 5cm x 5cm. According to the manufacturer, the presence of MSCs in Grafix distinguishes it from all other skin substitutes.

Grafix PRIME is an allograft derived from the amniotic membrane of human placental tissue used for the management of acute and chronic wounds including, but not limited to, diabetic foot ulcers, venous stasis ulcers and pressure ulcers that have not responded to standard of care therapy. Additional uses include burns, adhesion barriers, and Mohs procedures. Grafix PRIME has two layers (epithelial layer and stromal layer) and is comprised of a collagen rich membrane, mesenchymal stem cells, and anti-inflammatory cytokines and regenerative growth factors. The collagen matrix provides a physiological microenvironment for cells and proteins to promote cellular adhesion and migration in addition to supporting growth factor function. Cytokines and growth factors, epidermal growth factor and transforming growth factor-beta3 in Grafix PRIME mediate integral events such as angiogenesis, cell recruitment and proliferation. Once thawed and rinsed, Grafix PRIME is applied to the wound and covered with a standard, non-adherent dressing. Additional applications are used as needed with frequency ranging from every 7-14 days for up to 12 weeks or until the wound is closed. Grafix PRIME is supplied as a cryopreserved membrane mounted on nitrocellulose paper and is available in 3 sizes; 2cm x 2cm and 5cm x 5cm, and 7.5cm x 15cm. According to the manufacturer, the presence of mesenchymal stem cells in Grafix distinguishes it from all other skin substitutes. Mesenchymal stem cells coordinate the tissue repair process through down regulation of inflammation, by stimulating blood vessel formation (angiogenesis), and by supporting fibroblast and epithelial cells resulting in rapid wound closure.

As part of an agreement with the FDA, Grafix is indicated as a "wound cover" for the treatment of acute and chronic wounds. The manufacturer has announced its intent to submit a Biologics License Application to support clinical indications for Grafix.

The functionality, clinical use, and patient population of GrafixPL CORE is the same as Grafix CORE (CMS, 2017). GrafixPL CORE is a lyopreserved chorion-derived placental membrane retaining the extracellular matrix, growth factors, and endogenous viable cells of the native tissue. The product functions as a protective barrier supporting the repair of
acute and chronic wounds. GraplixPL Core is available in 3 sizes: 16 mm disc, 2 cm x 3 cm, and 5 cm x 5 cm. GraplixPL CORE is applied directly to the wound on a weekly basis for up to 12 weeks or until the wound is closed, the same as Grafix CORE.

GraplixPL Prime is a placental tissue allograft categorized as a skin substitute and intended for homologous use as a wound cover (CMS, 2017). It is a three-dimensional matrix, designed for application directly to acute and chronic wounds, including but not limited to diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), pressure ulcers, surgical wounds, burns, dehisced wounds, and wounds with exposed tendon, bone, and/or muscle by acting as a wound cover or barrier. It is applied directly to the wound weekly for up to 12 weeks or until the wound is closed. Grafix PL Prime is supplied as a lyopreserved amnion-derived placental membrane between two pieces of plastic mesh backing, packaged in a sealed foil pouch. It is available in 3 sizes: 16mm disc, 2cm X 3cm, and 5 cm X 5 cm.

In a randomized, controlled study, Lavery et al (2014) compared the efficacy of Grafix Prime, a human viable wound matrix (hVWM) (n = 50), to standard wound care (n = 47) to heal diabetic foot ulcers (DFUs). Subjects included adults with type 1 or type 2 diabetes who have foot ulcers that were present for at least 1 month (4 weeks) and no longer than 1 year (52 weeks). Excluded were subjects with large ulcers (greater than 15 cm²), infection, inadequate circulation to the foot, and exposed muscle, tendon, bone or joint capsule. Wounds in both groups received standard wound care that included surgical debridement, off-loading and non-adherent dressings. The wound dressing was petroleum impregnated gauze (Adaptic) and either saline moistened gauze or an adhesive hydrocellular foam (Allevyn) for moderately draining wounds. The primary endpoint was the proportion of patients with complete wound closure by 12 weeks. Wound closure was independently confirmed via a central wound core laboratory with 2 blinded wound care experts who reviewed all wounds via digitized acetate tracing and photography. Secondary end-points included the time to wound closure, adverse events and wound closure in the crossover phase. The proportion of patients who achieved complete wound closure was significantly higher in patients who received Grafix (62 %) compared with controls (21 %, p = 0·0001). The median time to healing was 42 days in Grafix patients compared with 69·5 days in controls (p = 0·019). There were fewer Grafix patients with adverse events (44 % versus 66 %, p = 0·031) and fewer Grafix patients with wound-related infections (18 % versus 36·2 %, p = 0·044). Among the study subjects that healed, ulcers remained closed in 82·1 % of patients (23 of 28 patients) in the Grafix group versus 70 % (7 of 10 patients) in the control group (p = 0·419).

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Lavery et al. (2014) to be at low risk of bias.
Fryberg et al (2017) reported the results of a prospective, multicenter, open-label, single-arm clinical trial to establish clinical outcomes when Grafix Prime viable cryopreserved human placental membrane (vCHPM) is applied weekly to complex diabetic foot ulcers (DFUs) with exposed deep structures. Patients with type 1 or type 2 diabetes and a complex DFU extending through the dermis with evidence of exposed muscle, tendon, fascia, bone and/or joint capsule were eligible for inclusion. Of the 31 patients enrolled, 27 completed the study. The mean wound area was 14·6 cm², and mean duration was 7·5 months. For patients completing the protocol, the primary endpoint, 100% wound granulation by week 16, was met by 96·3% of patients in a mean of 6·8 weeks. Complete wound closure occurred in 59·3% (mean 9·1 weeks). The 4-week percent area reduction was 54·3%. There were no product-related adverse events. Four patients (13%) withdrew, two (6·5%) for non-compliance and two (6·5%) for surgical intervention.

Limitations of the study include a lack of a well-defined guideline-supported standard of care that includes nutritional support and blood glucose control. Certain baseline measurements necessary for evaluation (wound culture, nutrition, lymphocyte count) relevant to comparison of treatment and control groups were not reported, as were certain important outcomes (rate of secondary amputation at 4 to 6 months). Additional studies are needed to compare Grafix to advanced wound care dressings.

Ananian, et al. (2018) analyzed clinical outcomes and product cost between GrafixPrime viable cryopreserved placental membrane (vCPM) and Dermagraft human fibroblast-derived dermal substitute (hFDS) for the treatment of chronic diabetic foot ulcers in a prospective, multicenter, single-blind study. The outcomes of 62 patients were analyzed: 31 patients in the vCPM treatment group and 31 patients in the hFDS treatment group. Utilizing a non-inferiority trial design and the established treatment regimen of 8 applications for hFDS, the investigators demonstrated that vCPM was not inferior to hFDS for the proportion of patients achieving complete wound closure (9.68, 90% CI: [10.67, 28.94]). However, preliminary findings show that vCPM may have better outcomes for wounds ≤ 5 cm²: 81.3% (13/16) of wounds in the vCPM group vs. 37.5% (6/16) of wounds in the hFDS group reached complete closure at the end of treatment (p = 0.0118).

A draft assessment of wound care products prepared for AHRQ (2019) judged this randomized controlled study by Ananian, et al. (2018) to be at moderate risk of bias.

Stravix and StravixPL

According to the manufacturer, Osiris Therapeutics, Inc., Grafix Prime, GrafixPL Prime and Stravix/StravixPL are similar in that both placental tissue allografts indicated for use on wound repair for the following indications: diabetic foot ulcer, venous leg ulcers,
pressure ulcers, dehisced surgical wounds, burns, acute surgical wounds, pyoderma gangrenosum, and epidermolysis bullosa, including complex wounds with exposed bone, tendon and hardware, and chronic recalcitrant wounds of various etiologies in peripheral arterial disease (PAD). Specifically, Stravix/StraviPL are used for deeper wounds in higher risk patients and the wounds located in areas subject to high shear force. The quantity and size of the product used will vary based upon wound size and physician recommendation. Stravix/StraviPL are approximately 10 times thicker than Grafix Prime and GrafixPL Prime and dosing recommendation is weekly for up to 12 weeks or until the wound is closed.

ENDURAGen

ENDURAGen Dermal Collagen implants are an acellular dermal matrix composed of cross-linked porcine dermal collagen. ENDURAGen Collagen Implant is a biomaterial made of a patented collagen matrix that has a structural architecture similar to human tissue which provides a scaffold for fibroblast infiltration and vascularization. The enzymatic digestion and cross-linking manufacturing process is intended to make ENDURAGen Implants resistant to breakdown and absorption, allowing for a durable repair or reconstruction for soft tissue contouring and/or reinforcement procedures.

The ENDURAGen Collagen Implant was cleared as substantially equivalent to Permacol, originally approved by the U.S. Food and Drug Administration on January 17, 2002. ENDURAGen Collagen Implants are specifically indicated for soft tissue reinforcement, augmentation, and repair in plastic and reconstructive surgery of the head and face. The ENDURAGen Biomaterial is a sterile, off-white, moist, durable, flexible flat sheet of cross-linked porcine dermal collagen and elastin fibers. The flexible material is intended to conform to anatomical shapes. ENDURAGen Implants are prehydrated and supplied in sterile sealed packets.

Peer-reviewed published evidence for the use of ENDURAGen is limited to case reports, small case series, and evaluations of its biomechanical properties (Wu et al, 2011; McCord et al, 2008; Cillo et al, 2007; Vural et al, 2006; Ibrahim et al, 2013).

In 2008, McCord and group reported their experience using a new acellular porcine dermal graft (Enduragen) in 129 eyelids. A retrospective chart review was performed that included every case in which Enduragen was used by the two primary authors in the upper or lower eyelid. Patient demographics, type of procedure performed, and complications were reviewed. A total of 69 patients and a total of 129 eyelids were included in the study. Eight procedures were spacers in the upper lid, 104 were for spacers in the lower lid, and 17 were for lateral canthal reinforcement. Twenty-two procedures were in primary cases and 47 were in eyelids for secondary reconstructions,
for a total of 69 patients. There were 13 eyelid complications, for a complication rate of 10%. Nine cases required surgical revision, and there were 4 cases of infection, all of which were successfully treated with oral and topical antibiotics. According to the authors, Enduragen has proved to be a very satisfactory substitute for ear cartilage and fascia in eyelid surgery in both reconstructive and primary eyelid cases. It seems to be far superior to other commercially available tissue substitutes because of its predictability of structure and robust behavior. All problems that were encountered in this series seemed to be related more to technical errors than to any deficiency in or reaction to the Enduragen. The increased strength, rigidity, and durability give support to the lids comparable to that obtained with autogenous ear cartilage and fascia.

### Puros

Puros Dermis Allograft Tissue Matrix (Zimmer Dental) is a natural biological matrix designed for soft tissue augmentation, periodontal/peri-implant soft tissue management, and guided tissue regeneration procedures (Snyder et al, 2012). The tissue is treated using the Tutoplast sterilization procedure to kill bacteria, destroy cells, remove prions, and reduce potential tissue rejection. The manufacturer's Web site does not specifically state if Puros Dermis is derived from human tissue, although this may be implied. Puros Dermis does not have 510(k) clearance or premarket approval, suggesting that this is a human-derived tissue product.

### Suprathel

Suprathel (Polymedics Innovations GmbH, Denkendorf, Germany) is a synthetic, biocompatible, and absorbable skin substitute made from polymers of lactic acid (Snyder et al, 2012). Suprathel is a composed entirely of synthetic materials, including a tripolymer of polyactide, trimethylene carbonate and ε-caprolactone. It is an alloplastic, absorbable “skin substitute” with properties similar to the skin. It is highly permeable to oxygen and water vapor, providing a particularly favorable environment for wound healing. Suprathel is used for epidermal and dermal wounds, such as split skin graft donor sites and partial thickness burns. Suprathel may also be used for partial and full thickness wounds. The Suprathel membrane is applied once to a clean débrided wound surface and then breaks down during the healing process. According to the manufacturer, the products of Suprathel degradation stimulate the healing process by increasing angiogenesis and rebuilding the dermis. The acidification of the wound bed by breakdown products is also supposed to have a bactericidal effect. Suprathel is fully malleable at room temperature, and becomes more pliable at body temperature. Suprathel Wound and Burn Dressing was cleared for marketing under the 510(k) process in May 2009 for “temporary coverage of noninfected skin defects, such as superficial wounds, under sterile conditions. The dressing is intended to maintain a moist
wound healing environment. A moist wound healing environment allows autolytic débridement. The Suprathel Wound and Burn Dressing is used in the management of: Partial and full thickness wounds; Pressure (stage I and IV) and venous ulcers; Ulcers caused by mixed vascular etiologies; venous stasis and diabetic ulcers; 1st and 2nd degree burns; Partial thickness burns; cuts and abrasions; acute wounds; trauma wounds; surgical wounds; superficial wounds; grafted wounds and donor sites."

Depending on the wound size, the appropriate square centimeters of the Suprathel membrane(s) shall be applied. A protective gauze should be applied over Suprathel on areas subject to mechanical stress, such as the extremities and the dorsal side of the torso. This protective dressing should comprise a fatty gauze and absorbent gauze. Suprathel, together with the gauze, shall remain unchanged until wound healing is completed. If Suprathel remains longer on the skin, it will be absorbed completely in approximately 60 days, without irritation to the upper epithelial layers. Suprathel is available in four sizes: 5 x 5 cm; 9 x 10 cm; 18 x 10 cm; and 18 x 23 cm square sheet membranes. Suprathel is also available in hand-shaped pads that can be used on the flexor and/or exterior side of the hand.

Epidex

Epidex (Euroderm AG, Baden-Dättwil, Switzerland) is a skin product generated from keratinocytes from the patient’s hair follicles. Epidermal sheets are created with silicone membrane support. Euroderm AG seems to be strictly a European company (Snyder et al, 2012). None of its skin products seem to be sold in the United States and it has no listing with FDA.

Matriderm

Matriderm (Dr. Suwelack Skin and Health Care AG) is a collagen-elastin matrix designed to support dermal regeneration after severe skin injuries. The matrix provides a structure for the invasion of native cells to regenerate the dermis. After placement, Matriderm is covered with a very thin, split-thickness, skin graft. The company Web site promotes Matriderm for treating severe burn injuries (Snyder et al, 2012). This product does not seem to be available in the United States and is not listed on the FDA Web site. A company called Suwelack Matrix Systems, Inc., Stony Brook, NY, USA, was established in 2005 but does not have any products listed on the FDA Web site.

LiquidGen
Skye LiquidGen is an allograft tissue matrix for use as an in vivo wound covering to fill tissue defects or localized areas of inflammation. According to the manufacturer, LiquidGen can be applied directly to the surgical site, mixed with patients own blood or used with other carriers to cover or fill soft tissue defects. LiquidGen is cryopreserved, and can be stored for up to 2 years. There are a lack of published clinical studies of the effectiveness of LiquidGen.

**EPIFLO Transdermal Continuous Oxygen Therapy [TCOT] for Wound Healing**

According to Ogenix, Inc., (Beachwood, OH), EPIFLO transdermal continuous oxygen therapy (TCOT) is an FDA-cleared, 3-ounce, 24/7 oxygen therapy that effectively treats many chronic wounds (e.g., burns, diabetic foot ulcers, pressure sores, surgical wounds, and venous stasis ulcers). EPIFLO is designed to deliver oxygen directly to a wound. Unlike negative pressure wound therapy and hyperbaric chambers, chronic wound patients who receive EPIFLO do not have to endure dozens of treatment visits, each lasting upwards of 90 minutes, nor tolerate being tethered to a vacuum pump. EPIFLO is small enough to fit inside one’s pocket; thus it is portable. In this regard, EPIFLO is not hyperbaric oxygen therapy.

Banks and Ho (2008) examined the effectiveness of the EpiFLO device as an adjunct treatment modality in chronic wound management. This study included 3 men with spinal cord injury (SCI), who each presented with a stage IV pressure ulcer in the pelvic region. They were treated with the EpiFLO device as an adjunct therapy. In Case 1, the patient was monitored for 9 weeks, whereas in Cases 2 and 3, the patients were monitored for 5 weeks. Healing was determined on a weekly basis by wound dimensions and volume, which were compared before and after the intervention. Comparison of pre- and post-treatment outcome measurements showed significant improvement with EpiFLO in each case. The authors concluded that EpiFLO seems to have had a positive effect on the healing rate of chronic pressure ulcers in individuals with SCI. The findings of this small case-series study need to be validated by well-designed studies.

Bakri and colleagues (2008) tested the hypothesis that local transdermal delivery of oxygen improves oxygenation in sternotomy wounds after cardiac surgery; the secondary hypothesis was that supplemental inspired oxygen improves sternal wound PsqO(2). After undergoing cardiopulmonary bypass, a total of 30 patients randomly received: (i) 2 EpiFlo oxygen generators that provided oxygen at 6 ml/hr into an occlusive wound dressing, or (ii) identical-appearing inactive generators. PsqO(2) and temperature were measured in the wound approximately 5-mm below the skin surface. PsqO(2) and arterial oxygen (Pao(2)) were measured 1 hr after intensive care unit admission (Fio(2) = 60 %) and on the 1st and 2nd post-operative mornings at Fio(2) of both 30 % and 50 % in random order. Data from 4 patients were excluded for technical reasons. Patient
characteristics were similar in each group, as were type of surgery and peri-operative management. Increasing Fio(2) from 30 % to 50 % improved Pao(2) from 99 [84 to 116] to 149 [128 to 174] mm Hg (p < 0.001, mean [95 % CI]) and sternal wound PsqO(2) from 23 [16 to 33] to 27 [19 to 38] mm Hg (p < 0.001). In contrast, local oxygen delivery did not improve tissue oxygenation: 24 [14 to 41] versus 25 [16 to 41] mm Hg (p = 0.88.

The authors concluded that additional inspired oxygen improved Pao(2) and sternal wound PsqO(2) after cardiopulmonary bypass surgery, and may, consequently, reduce infection risk. However, oxygen insufflated locally into an occlusive dressing did not improve wound PsqO(2) and, therefore, does not appear to be useful clinically in cardiac surgery patients to reduce sternal wound infections.

Schreml et al (2010) noted that oxygen is a pre-requisite for successful wound healing due to the increased demand for reparative processes such as cell proliferation, bacterial defense, angiogenesis and collagen synthesis. The author stated that even though the role of oxygen in wound healing is not yet completely understood, many experimental and clinical observations have shown wound healing to be impaired under hypoxia. However, this review did not provide any clinical data to support the use of TCOT for wound healing.

In a prospective, controlled study, Blackman et al (2010) (i) examined the clinical efficacy of a pressurized topical oxygen therapy (TWO(2)) device in outpatients (n = 28) with severe diabetic foot ulcers (DFU) referred for care to a community wound care clinic; and (ii) evaluated ulcer reoccurrence rates after 24 months. A total of 17 patients received TWO(2) 5 times per week (60-min treatment, pressure cycles between 5 and 50 mb) and 11 selected a silver-containing dressing changed at least twice per week (control). Patient demographics did not differ between treatment groups, but wounds in the treatment group were more severe, perhaps as a result of selection bias. Ulcer duration was longer in the treatment (mean of 6.1 months, SD 5.8) than in the control group (mean of 3.2 months, SD 0.4) and mean baseline wound area was 4.1 cm2 (SD 4.3) in the treatment and 1.4 cm2 (SD 0.6) in the control group (p = 0.02). Fourteen of 17 ulcers (82.4 %) in the treatment group and 5 of 11 ulcers (45.5 %) in the control group healed after a median of 56 and 93 days, respectively (p = 0.04). No adverse events were observed and there was no re-occurrence at the ulcer site after 24 months’ follow-up in either group. The authors noted that although the absence of randomization and blinding may have under- or over-estimated the treatment effect of either group, the significant differences in treatment outcomes confirmed the potential benefits of TWO(2) in the management of difficult-to-heal DFUs. Moreover, they stated that clinical efficacy and cost-effectiveness studies as well as studies to elucidate the mechanisms of action of TWO(2) are needed.
In a pilot study, Woo et al (2012) evaluated the effectiveness of TCOT on chronic wound healing in 9 patients. After 4 weeks of treatment, mean wound surface area and wound infection check-list scores were significantly reduced. Signs of bacterial damage were also reduced. The authors concluded that findings from this study suggested TCOT may be beneficial in promoting chronic wound healing. These preliminary findings from a small pilot study need to be validated by well-designed studies.

Also, an UpToDate review on “Basic principles of wound management” (Armstrong and Meyr, 2013) does not mention the use of transdermal continuous oxygen therapy as a therapeutic option.

**Gore Bio-A Fistula Plug**

An anal fistula is a small channel or tunnel between the anal canal and the surrounding skin that most commonly develops after an anal abscess bursts, creating an opening. Gore BIO-A Fistula Plugs is a synthetic bioabsorbable scaffold used in sphincter-preserving anal fistula repair.

In a retrospective review of a database of patient records, Heydari et al (2013) evaluated the safety and effectiveness of the use of a new synthetic fistula plug made of bioabsorbable polymers in the treatment of crypto-glandular anal fistulas. A total of 48 patients (39 men and 9 women; mean age of 49.9 years) with 49 fistulas were treated with the synthetic plug between November 2009 and March 2012. Types of fistula were as follows: 24 superficial trans-sphincteric, 18 medium trans-sphincteric, 5 deep trans-sphincteric, and 1 medium inter-sphincteric. The fistula tract was cleaned by using curettage, and a synthetic plug was sized to fit the tract and inserted. A draining seton was used pre-operatively in 1 patient. Main outcome measures were complete closure of the fistula, with no discharge/residual fistula (verified by endo-anal ultrasonography), perineal pain level (assessed with a visual analog scale), and fecal continence. Follow-up was conducted at 1 week and 1, 3, 6, and 12 months post-operatively. The overall healing rate was 69.3 % (34/49 fistulas, 33/48 patients); 8 patients (24.2 %) had healing by 3 months after surgery, 21 patients (63.6 %) had healed by 6 months, and 4 patients (12.1 %) had healed by 12 months. By 3 months, no patient had perineal pain or fecal incontinence. No plug became dislodged, and no patient had the onset of anal stenosis, bleeding, local infection, or any other complication. The authors concluded that in patients with crypto-glandular anal fistulas, the use of a bioabsorbable synthetic plug provided a high rate of healing without causing fecal incontinence or other major adverse effects. Moreover, they stated that larger and randomized studies of this treatment are needed. Major drawbacks of this study included small number of patients and the retrospective non-randomized nature of the study.
Allowrap

Allowrap DS or Dry are a double-sided epithelial layer human amniotic membrane. It has been used as an onlay and/or wrapping tissue applications following surgical repair.

AlloWrap DS and AlloWrap Dry consist of human amniotic membrane that has been processed using a proprietary technology, and is designed with two layers of amniotic tissue with the epithelial layers facing outward (CMS, 2014). AlloWrap DS tissue allograft is surgically applied to the skin. Most wounds respond with one application of AlloWrap DS; however it can be reapplied if needed. AlloWrap DS is supplied in the following sizes: 2cm x 2cm; 2cm x 4cm; 4cm x 4cm; and 4cm x 8cm. AlloWrap Dry tissue is surgically applied to the skin and is supplied in a range of sizes: 1 x 1cm; 1 x 2cm; 1.5 x 2cm; 1 x 4cm; 2 x 2cm; 2 x 4cm; 4 x 4cm; 6 x 6cm; and 4 x 8cm. It can be used in a variety of procedures as a wound cover or barrier.

AmnioBand and Guardian

AmnioBand and Guardian are human tissue allografts made of donated placental membrane (CMS, 2014). The allograft is comprised of native human amnion and chorion. The amnion and the chorion together create a membrane in which the amnion serves as a covering epithelium. The membrane is hydrophilic and can be used in a hydrated or dehydrated state. Although marketed under two different brand names, the products are identical. AmnioBand and Guardian are allograft membrane coverings intended for interior or exterior wounds including use as a covering for the surgical site. Usage includes various wounds and ulcers and other soft tissue defects. Both AmnioBand and Guardian are processed and packaged under aseptic conditions, and are available in the same 5 sizes: 2x2 cm, 3x4 cm, 3x8 cm, 4x4 cm, and 4x6 cm.

According to the manufacturer Musculoskeletal Transplant Foundation, AmnioBand Viable is a placental matrix derived from human donated amnion membranes originating from the inner lining of the placenta. AmnioBand Viable is intended for internal and external tissue defects, including acute, chronic, and surgically-created wounds. It is used as a natural wound scaffold to support the body’s inherent ability to restore and remodel tissue through components that have been preserved in the native tissue. AmnioBand Viable contains biological extracellular matrix proteins, cytokines, growth factors, and viable endogenous cells that work to support host tissue remodeling. This provides a barrier to infections and helps to maintain a moist wound environment for healing. AmnioBand Viable is supplied in 2 cm x 2 cm and 5 cm x 5 cm sizes.
According to the manufacturer, AmnioBand SL is a dehydrated single amnion layer matrix derived from human donated amnion membranes originating from the inner lining of the placenta. It is indicated for patients who present with chronic wounds caused by diabetes, obesity, COPD, obstructed blood flow and other underlying conditions. AmnioBand SL is a minimally processed human allograft which retains the structural properties of the amnion extracellular matrix. The resulting dehydrated allograft serves as a wound scaffold. AmnioBand SL contains growth factors and cytokines that support the membrane’s native function to promote cell proliferation and tissue remodeling during the wound healing phase. AmnioBand SL is available in rectangular and circular shapes ranging from 0.79 square centimeter to 49 square centimeters.

According to the Musculoskeletal Transplant Foundation, AmnioBand Particulate is derived from human donated amnion membrane originating from the inner lining of the placenta. AmnioBand Particulate is an allograft membrane scaffold for wounds, including use as a scaffold for a surgical site. It is a lyophilized placental matrix in particulate form, aseptically processed to preserve the tissue’s natural cytokines and tissue matrix. AmnioBand Particulate is intended to be used as a wound care scaffold for the replacement of damaged or inadequate integumental tissue, such as diabetic foot ulcers, venous leg ulcers, pressure ulcers, or for other homologous use, particularly irregularly-shaped or crevassing wounds. AmnioBand Particulate is available in a variety of masses, ranging from 40mg to 160mg.

Didomenico et al (2016) compared AmnioBand (MTF, Edison, NJ) aseptically processed dehydrated human amnion and chorion allograft (dHACA) versus standard of care (SOC) in facilitating wound closure in nonhealing DFUs. Patients with DFUs treated with SOC (off-loading, appropriate debridement, and moist wound care) after a 2-week screening period were randomized to either SOC or wound-size-specific dHACA applied weekly for up to 12 weeks plus SOC. Primary endpoint was the percentage of wounds healed at 6 weeks between groups. At 6 weeks, 70% (14/20) of the dHACA-treated DFUs healed compared with 15% (3/20) treated with SOC alone. Furthermore, at 12 weeks, 85% (17/20) of the DFUs in the dHACA group healed compared with 25% (5/20) in the SOC group, with a corresponding mean time to heal of 36 and 70 days, respectively. At 12 weeks, the mean number of grafts used per healed wound for the dHACA group was 3.8 (median 3.0), and mean cost of the tissue to heal a DFU was $1400. The mean wastage at 12 weeks was 40%. One adverse event and 1 serious adverse event occurred in the dHACA group; neither was graft related. Three adverse events and 1 serious adverse event occurred in the SOC group.
The drawbacks of this study included the lack of blinding (patient and investigator) and lack of a soft-tissue matrices comparator. Future studies may consider comparing different amniotic tissue forms and allowing wounds of greater severity or depth. In addition, withdrawal of patients whose wounds did not reduce in area by at least 50 % after 6 weeks of either treatment regimen -- done to ensure patient safety -- resulted in high right censoring for analyses at 12 weeks. Another issue in regard to inclusion/exclusion criteria was the use of ABI as one means of evaluating distal perfusion. Diabetic patients' calcification of lower extremity arteries can falsely elevate readings, with values often exceeding 1.3. In most instances, such high readings would have automatically caused a screen failure, and this might have resulted in a more biased population, which was why Doppler studies were performed on the entire cohort for evaluation of biphasic flow in the study extremities. Finally, although the cost analysis was based upon publically available data (mean sales price per cm² and published studies), a preferred, full health economic analysis of dHACA was beyond the scope of this trial.

A draft assessment of wound care products prepared for AHRQ judged this randomized controlled study by DiDomenico, et al. (2016) to be at moderate risk of bias.

DiDomenico and associates (2017) noted that in a recently published, prospective RCT comparing aseptically processed dHACA to SOC, 85 % wound closure rates were reported in the dHACA-arm while only 25 % of patients in the SOC-arm healed. In a retrospective cross-over study, these researchers evaluated the effectiveness of dHACA in those patients that failed to respond to the SOC treatments and who exited the original study after failing up to 12 weeks of SOC treatment. Patients with non-healing wounds from the SOC-arm after exit from the original study were offered weekly adjunctive applications of dHACA (AmnioBand) for up to 12 weeks. The primary end-point was the proportion of wounds completely healed at 12 weeks; secondary end-points included the difference in wound area from baseline to the end of study and the percentage area reduction (PAR). A total of 11 patients were eligible to participate; wounds for 9 of the 11 patients healed (82 %). The mean wound area decreased from 1.7 cm² to 0.2 cm² (p = 0.0005), with a corresponding mean PAR of 92 %. Of the 2 wounds that failed to heal, 1 DFU decreased in area by 91 % and the other by 26 %. The authors concluded that the results of this cross-over study supported the conclusions of the original RCT, which determined that aseptically processed dHACA was an effective means to treat recalcitrant DFUs. Moreover, they stated that further comparative investigations and studies of more complex wounds will further clarify which patients will most benefit from this technology.
The main drawbacks of this study were its retrospective nature, small sample size (n = 11), and the fact that patients were not required to follow-up since they were seen as regular wound patients in the clinic and were under no obligation to return and receive the complimentary graft. In addition, a comprehensive economic analysis was also beyond the scope of this study.

DiDomenico et al (2018) stated that amnion and chorion allografts have shown great promise in healing diabetic foot ulcers (DFUs). Results from an interim analysis of 40 patients have demonstrated the accelerated healing ability of a novel aseptically processed, dehydrated human amnion and chorion allograft (dHACA). These investigators reported on the full trial results of 80 patients where dHACA was compared with standard of care (SOC) in achieving wound closure in non-healing DFUs. After a 2-week screening period, during which patients with DFUs were unsuccessfully treated with SOC, patients were randomized to either SOC alone or SOC with dHACA applied weekly for up to 12 weeks. At 12 weeks, 85 % (34/40) of the dHACA-treated DFUs healed, compared with 33 % (13/40) treated with SOC alone. Mean time to heal within 12 weeks was significantly faster for the dHACA-treated group compared with SOC, 37 days versus 67 days in the SOC group (p = 0.000006). Mean number of grafts used per healed wound during the same time period was 4.0, and mean cost of the tissue to heal a DFU was $1,771. The authors concluded that aseptically processed dHACA healed DFUs significantly faster than SOC at 12 weeks. These researchers stated that future trials of dHACA should consider a comparative arm using an advanced skin substitute for greater evidence and may even permit wounds of greater severity or depth. Patients with a higher proportion of serious co-morbidities may also be considered in order to enhance representation of a more “real-world” scenario.

The authors noted that the main drawback of this study was withdrawing patients at 6 weeks rather than continuing through 12 weeks of treatment if clinicians judged that their wounds were not sufficiently responding to treatment in order to ensure patient safety and permit other treatment pathways.

Additional clinical studies involving larger numbers of patients from a variety of clinical settings are necessary to establish the effectiveness and safety of AmnioBand.

Dermapure

DermaPure is a single layer decellularized dermal allograft derived from split thickness grafts harvested from human cadaver tissue donors. DermaPure is used for the treatment of acute and chronic wounds such as diabetic foot ulcers, venous stasis ulcers, and additional wounds that are refractory to more conservative care (CMS, 2014).
DermaPure is derived from split thickness grafts harvested from cadaveric human tissue donors. DermaPure is supplied in the following allograft sizes: 2x3cm, 3x4cm, and 4x6cm.

Dermavest

Dermavest is a particularized, decellularized human placental connective tissue extracellular matrix intended to replace or supplement damaged or inadequate integumental tissue (skin substitute) and re-stabilize a debrided wound (CMS, 2014). Dermavest is comprised of a different source of human connective tissue than the other products. It has up to 5 times more (mg) human connective tissue matrix per square cm. It is supplied as a single dehydrated, 2x3cm sterile pad.

Biovance

Biovance is a decellularized dehydrated human amniotic membrane (DDHAM) used in the repair or replacement of damaged or lost soft tissue (CMS, 2014). This allograft is derived from the placental amnion and includes epithelial and stromal components that provide a collagen-rich extracellular matrix. In addition to the natural scaffold being a physical conduit for infiltrating cells, Biovance contains extracellular proteins such as elastin, fibronectin, proteoglycans, glycosaminoglycans, and laminins important in extracellular matrix strength, cell attraction, and migration. Biovance is sterilized and available in 4 sizes: 1x2 cm, 2x3 cm, 4x4 cm and 6x6 cm.

NeoxFlo

NeoxFlo cryopreserved human amniotic membrane and umbilical cord product in particulate form obtained from donated human placental tissue (CMS, 2014). It is intended to be used as a wound covering for dermal ulcers and defects such as diabetic ulcers, to replace or supplement damaged or inadequate integumental tissue. NeoxFlo can be prepared by the physician as a suspension with normal saline for topical application or applied in dry form topically. It is especially intended for use in difficult to reach wounds that are either irregularly shaped or tunneled. Neox Flo it is supplied in a single-use vial in 3 different doses: 25 mg, 50 mg and 100 mg. The typical chronic wound patient will receive an average of 1 to 2 applications of NeoxFlo to facilitate healing. The dosage depends on the wound size.

ClarixFlo
ClarixFlo is a cryopreserved biological particulate amniotic membrane and umbilical cord product derived from human placental tissue (CMS, 2014). It is intended to facilitate replacement or supplement damaged or inadequate integumental tissue. ClarixFlo is supplied in a single-use vial in three different doses: 25 mg, 50 mg and 100 mg. It is prepared by the physician as a suspension with normal saline for injection into the tissue. The typical patient will receive 1 treatment of ClarixFlo to facilitate healing. Dosing is dependent upon the size of the damaged or inadequate integumental tissue.

Neox 100 and CLARIX 100

NEOX 100 (Amniox Medical, Inc.) is a cryopreserved skin graft substitute comprised of human amniotic membrane and umbilical cord used as a wound covering in chronic non-healing dermal wounds, such as diabetic foot and venous leg ulcers, to modulate inflammation and encourage healing (CMS, 2014). NEOX 100 is supplied in 3 different sizes: 2x2 cm, 4.0x4.0 cm, and 7.0x7.0 cm. NEOX 100 is a quick-peel matrix administered by placing the appropriately sized product to completely cover the wound bed after debridement, and is secured to the wound edges using sutures or surgical staples, at the discretion of the physician.

CLARIX 100 is cryopreserved human amniotic membrane, umbilical cord and additional proteins used as a surgical wrap or barrier, quick-peel matrix. CLARIX 100 is comprised of human amniotic tissue that contains biology which modulates inflammation and permits rapid regenerative healing of surgical wounds (CMS, 2017). CLARIX 100 differs from NEOX in that rather than being used as a wound covering for dermal ulcers and defects, and CLARIX 100 is a surgical covering, wrap, or barrier to modulate inflammation and promote healing. It is supplied as a single use graft in differing sizes, and stored at 80 degrees C to 4 degrees C. The dosage per administration depends on the size of the surgical site; the graft is placed to completely cover the site, and is secured using sutures or surgical staples, at the discretion of the physician. The grafts are supplied cryopreserved in a sealed foil pouch.

NEOX Cord and Clarix Cord

NEOX 1k (Amniox Medical, Inc.) is a non-implantable cryopreserved biological skin graft substitute comprised of human amniotic membrane retrieved from electively donated umbilical cords (CMS, 2013). NEOX 1k is used as a wound covering in chronic non-healing dermal wounds, ulcers and defects, such as diabetic ulcers, to modulate inflammation and encourage healing. It is supplied as a single-use graft in 4 different sizes: 1.5x1.5 cm; 2.5x2.5 cm; 4.0x3.0 cm; 6.0x3.0 cm. NEOX 1k is administered by
placing the appropriately sized product to completely cover the wound bed after debridement, and is secured to the wound edges using sutures or surgical staples, at the discretion of the physician.

Clarix Cord 1K is cryopreserved human amniotic membrane, umbilical cord and additional proteins, used as a surgical wrap or barrier, 1 mm thick form.

NEOX CORD RT and CLARIX CORD 1K are also non-implantable biological products used for wound healing and surgical coverings (CMS, 2017). NEOX CORD 1K is the updated brand name for NEOX 1K, the same product. NEOX CORD RT is similar to NEOX CORD 1K, but it is terminally sterilized in addition to the NEOX CORD 1K aseptic process. CLARIX CORD 1K is identical to NEOX CORD 1K, but it was used as a surgical covering, wrap, or barrier. NEOX CORD RT and CLARIX CORD 1K are supplied as single-use grafts in sizes ranging from 2.0 cm² to 24.0 cm². The graft is placed to completely cover the site, and is secured using sutures or surgical staples.

Revitalon

Revitalon is a human tissue allograft made of donated amniotic membrane derived from the inner lining of donated placenta. Revitalon can be used as a covering for full-thickness wounds, damaged membranes, and as a dressing for burns. It is comprised of native human amnion and chorion consisting of collagen types I, III, IV, V, VI, laminin, fibronectin, nidogen, and proteoglycans. The amnion is comprised of five layers of collagen and fibronectin and is tough, transparent, nerve-free, and nonvascular. Revitalon allografts are supplied in a single-sized package and provided in the following sizes: 1 cm round dot, 2x2 cm, 4x4 cm, and 4x6 cm.

Marigen

Marigen is an omega 3, acellular, dermal extracellular matrix xenograft made from fish (piscine) dermis (CMS, 2014). Marigen contains natural insoluble proteins such as collagen as well as proteoglycans, glycosaminoglycans, and fibronectin. These provide a scaffold for revascularization and repopulation by the patient's cells for wound healing. Marigen is used as a wound covering and wound matrix for full-thickness wounds and burns, or as a covering for damaged membranes. It is supplied in the following sizes: 3x3.5cm, 3x7cm, and 7x10cm.

Affinity
Affinity, amniotic fluid membrane allograft, is minimally processed for clinical use in wound repair and healing (CMS, 2014). Affinity is comprised of the amniotic epithelial layer, the amniotic basement membrane, and the amniotic stroma. This membrane contains (1) collagen types III, IV, laminin and proteoglycans; (2) cross-linked hyaluronic acid; (3) trophic proteins; (4) growth factors; (5) Tissue Inhibitors of Matrix metallo-proteinases (TIMPs); and (6) multipotential cells. Affinity is intended to be applied as an on-lay graft for acute and chronic wounds, including, but not limited to, neuropathic ulcers, venous stasis ulcers, pressure ulcers, burns, post-traumatic wounds and post-surgical wounds. The product will be sterilely packaged for single-use and available in the following size: 2.5 x 2.5 cm.

Nushield

Nushield is an allograft produced from human placental membrane and includes the amniotic epithelial layer, the amniotic basement membrane, the amniotic stroma, the chorionic basement membrane, and the chorionic stroma. This membrane contains (1) collagen types III, IV, laminin and proteoglycans; (2) cross-linked hyaluronic acid; (3) trophic proteins; (4) growth factors; (5) Tissue Inhibitors of Matrix metallo-proteinases (TIMPs); and (6) multipotential cells. Nushield is intended to be applied as an on-lay graft for acute and chronic wounds, including, but not limited to, neuropathic ulcers, venous stasis ulcers, pressure ulcers, burns, post-traumatic wounds and post-surgical wounds. It is also used as a wound covering and as a barrier for the protection of tendons, nerves and dura. The product will be sterilely packaged for single-use and available in the following sizes: 2x3 cm, 4x4 cm, and 6x6 cm. Nushield will also be expandable (meshed) form.

Architect ECM and Architect PX

Architect Extracellular Matrix (ECM) is a medical device comprised almost entirely of type I collagen that has been stabilized and sterilized for ease of use and enhance durability as a wound dressing. It is made from equine pericardium and utilized a patented collagen stabilizing technology called “BriDGE” that supports rapid healing by: not promoting an inflammatory response; serving as a temporary matrix that provides a platform for cell migration; helping to optimize the wound-healing environment; and facilitating cellular activity. The manufacturers of Architect state that it is "the only equine pericardium sourced ECM wound dressing available on the US market since the withdrawal of Synovis' Unite Biomatrix in June, 2012." It is used for partial or full-thickness wounds such as diabetic foot ulcers, second-degree burns and venous leg ulcers.
Architect PX is a partially stabilized extracellular matrix (ECM) comprised of equine pericardium that is indicated for the local management of moderately to heavy exuding wounds (CMS, 2014). By partially stabilizing its equine pericardium ECM, Architect PX can maintain its natural ECM tissue regeneration properties longer on the wound.

The manufacturer claims that “this “partially” stabilized extracellular matrix more quickly adheres to the wound bed than Architect, thereby fitting more closely into established wound care protocol”. Products that adhere more slowly may require more provider training to achieve optimal results. Architect PX can limit the inflammatory response, thereby enabling the ECM components to support tissue regeneration longer during the healing process. Architect PX is also engineered to provide structural and functional proteins which can stimulate and support tissue regeneration for a longer duration than non-stabilized products.

**Excellagen**

According to the manufacturer, Excellagen (pharmaceutically formulated bovine full length fibrillin collagen gel 2.6%) is indicated for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/graft, post-Moh’s surgery, post laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second degree burns and skin tears) and draining wounds (CMS, 2013). It is applied immediately following wound debridement. It is an acellular biological modulator designed for platelet activation (when applied to debrided wounds and in the presence of a small influx of blood), resulting in the localized release of platelet-derived growth factors that are essential to wound healing. Excellagen also provides a substrate and scaffold for chemotaxis, cellular adhesion, migration, and proliferation to promote granulation tissue growth. Excellagen is supplied as a sterile gel in a package of 4 ready-to-use 1 mL glass syringes with fill volume of 0.5cc.

**AmnioExCel and BioDExCel**

AmnioExCel (also marketed under trade name BioDExCel) is a sterile, resorbable, noncrosslinked dehydrated human amnion membrane allograft composed of an epithelial layer and a stromal layer specifically processed for repair or replacement of lost or damaged dermal tissue (CMS, 2013). The product contains collagen and extracellular substrates to include growth factors, connective proteins, and cytokines that support and promote angiogenesis, tissue granulation and epithelialization for the repair and replacement of injured tissue. The collagen in the allograft provides an extracellular matrix which acts as a natural scaffold for cellular attachment and a structural tissue matrix that facilitates cell migration and proliferation for tissue repair and regeneration. The natural composition of the amniotic membrane extracellular matrix is preserved.
without cross-linkage, thereby providing improved graft incorporation by the body. Usage includes, but is not limited to, allograft application to wounds including traumatic injuries, burns or surgical wounds; complex, chronic and acute wounds, such as diabetic ulcers, venous and arterial ulcers, pressure ulcers or cutaneous ulcers; wounds with exposed tendon, muscle, bone or other vital structures and other soft tissue defects. Both AmnioExCel and BioDExCel are steriley packaged for single use and each product is available in the same 5 sizes: 1.5 x 2 cm; 2 x 3 cm; 2 x 6 cm; 4 x 4 cm; and 4 x 8 cm.

In a prospective, open-label, randomized, parallel group clinical trial, Snyder et al (2016) evaluated dehydrated amniotic membrane allograft (DAMA) (AmnioExCel, Derma Sciences Inc., Princeton, NJ) plus SOC compared to SOC alone for the closure of chronic DFUs. This study was implemented at 8 clinical sites in the U.S. Eligibility criteria included adults with type 1 or type 2 diabetes mellitus who have 1 or more ulcers with a Wagner classification of grade 1 or superficial 2 measuring between 1 cm2 and 25 cm2 in area, presenting for more than 1 month with no signs of infection/osteomyelitis; ankle-brachial index (ABI) greater than 0.7; HbA1c Less than 12 %; and serum creatinine less than 3.0 mg/dL. Eligible subjects were randomized (1:1) to receive either SOC alone (n = 14) or DAMA+SOC (n = 15) until wound closure or 6 weeks, whichever occurred first. The end-point was the proportion of subjects with complete wound closure (defined as complete re-epithelialization without drainage or need for dressings). A total of 35 % of subjects in the DAMA+SOC cohort achieved complete wound closure at or before week 6, compared with 0 % of the SOC alone cohort (intent-to-treat population, p = 0.017). There was a more robust response noted in the per protocol population, with 45.5 % of subjects in the DAMA+SOC cohort achieving complete wound closure, while 0 % of SOC-alone subjects achieved complete closure (p = 0.0083). No treatment-related adverse events were reported. The authors concluded that these findings suggested DAMA is safe and effective in the management of DFUs, but additional research is needed.

A draft assessment of wound care products prepared for AHRQ judged this randomized controlled study by Snyder, et al. (2016) to be at moderate risk of bias.

**BioDfence**

BioDfence is a sterile human placental-derived amniotic tissue based allograft that is procured from live, healthy donors during childbirth. BioDfence is composed of an epithelial layer and a stromal layer specifically processed for the repair and replacement of lost or damaged dermal tissue or the prohibition of adhesion formation (CMS, 2013). This allograft contains collagens and extracellular substrates to include growth factors, connective proteins, and cytokines that preserve planes of tissue while inhibiting incorporation of the vital structure(s) into the overlying developing tissue. The collagen
acts as a scaffold for cellular attachment and a structural tissue matrix that facilitates cell migration and proliferation. This product was initially used in the acute care inpatient setting in connection with neurosurgical, orthopedic and spine surgical procedures. BioDfence is also being used in individual wound care cases. The dehydrated (and the hydrated) human amnion allografts are intended for the repair or replacement of lost or damaged dermal tissue. Usage includes, but is not limited to, allograft application to wounds including: traumatic injuries, burns, Mohs procedures or surgical wounds; complex chronic and acute wounds, such as diabetic ulcers venous and arterial leg ulcers, pressure ulcers or cutaneous ulcers; wounds with exposed vital structures, e.g., tendon, bone, blood vessels; and other soft tissue defects. The product also provides adhesion barrier properties when necessary. In neurosurgery, it provided a structural barrier between the dura and surrounding soft tissue using a sutureless technique. BioDfence is packaged for single use in 7 sizes: 1.5 x 2cm; 2 x 3 cm; 2 x 6 cm; 4 x 4 cm; 4 x 8 cm; 10 x 10 cm; and 15 x 15 cm. According to the manufacturer, the differences between BioDfence and BioDfence Dryflex (see below) are as follows: BioDfence DryFlex is dehydrated, making it less sticky, and a better choice for use with instrumentation. BioDfence is hydrated, which makes it a bit sticky and glue may not be needed, which may make it easier to use for procedures such as on corneal defects.

Both BioDfence DryFlex and BioDfence have a cross-linked basement membrane which is not penetrable and becomes a biologic barrier. It is placed over exposed vital structures, such as nerves, blood vessels or other tissues to protect them and keep them intact.

BioDfence DryFlex

BioDfence DryFlex is a sterile allograft derived from amniotic membrane that is procured from live, healthy donors during child birth and comes fully hydrated or dehydrated. It is used as a structural barrier between the dura and surrounding soft tissue using a suture-less technique.

BioDfence DryFlex is a human placental-derived amniotic tissue based allograft composed of an epithelial layer and a stromal layer specifically processed for the repair and replacement of lost or damaged dermal tissue or the prohibition of adhesion formation (CMS, 2013). This allograft contains collagens and extracellular substrates to include growth factors, connective proteins, and cytokines that preserve planes of tissue while inhibiting incorporation of the vital structure(s) into the overlying developing tissue. The collagen acts as a scaffold for cellular attachment and a structural tissue matrix that facilitates cell migration and proliferation. While this product was initially used in the acute care inpatient setting in connection with neurosurgical, orthopedic and spine surgical procedures, physicians and surgeons are now using it in individual wound care cases. The dehydrated (and the hydrated) human amnion allografts are intended for the repair of...
or replacement of lost or damaged dermal tissue. Usage includes, but is not limited to, allograft application to wounds including: traumatic injuries, burns Mohs procedures or surgical wounds; complex chronic and acute wounds, such as diabetic ulcers venous and arterial leg ulcers, pressure ulcers or cutaneous ulcers; wounds with exposed vital structures, e.g., tendon, bone, blood vessels; and other soft tissue defects. The product also provides adhesion barrier properties when necessary. BioDfence DryFlex is packaged for single use in 5 sizes: 1.5 x 2 cm; 2 x 3 cm; 2 x 6 cm; 4 x 4 cm; and 4 x 8 cm. The differences between BioDfence Dryflex and BioDfence are as follows: BioDfence DryFlex is dehydrated, making it a better choice for use with instrumentation. BioDfence is hydrated, which may not be needed, which may make it easier to use for procedures such as on corneal defects. Both products have a cross-linked basement membrane which is not penetrable and becomes a biologic barrier. It is placed over exposed vital structures, such as nerves, blood vessels or other tissues to protect them and keep them intact.

AmnioMatrix and BioDMatrix

AmnioMatrix and BioDMatrix are a viable human multipotential placental cryopreserved allografts composed of morselized amniotic membrane and amniotic fluid components recovered from the same human donor (CMS, 2013). The amniotic membrane is separated from the placenta and morselized into particulate form, then combined with amniotic fluid components to form the allograft. The processing method is intended to preserve the structural properties of the collagen; growth factors; inherent cellular materials and matrix present in the tissue to create a micro-scaffold to be used to aid in the wound healing process. AmnioMatrix (also to be marketed under the trade name BioDMatrix) is intended for the treatment of wounds, including but not limited to surgical wounds, burns or traumatic injury; and chronic and acute wound conditions. The allograft is also used to augment the local treatment of soft tissue defects for the supportive treatment of wound-associated bone defects. The product may be mixed with normal saline for application to surgical sites and open, complex or chronic wounds or mixed with the recipient's blood to fill soft tissue defects and wound-associated bone defects. AmnioMatrix is cryopreserved and supplied in injectable form in sterile vials. It is available in 4 sizes: small (0.25 cc); medium (0.50 cc); large (1.0 cc); and extra-large (3.0 cc).

XCM Biologic Tissue Matrix

XCM Biologic Tissue Matrix is a sterile, non-cross-linked 3-D matrix derived from porcine dermis. It provides a support structure for cellular migration and as such the matrix is incorporated into the surrounding tissue. It is “indicated for use in general surgical procedures for the reinforcement and repair of soft tissue where weakness exists including, but not limited to: defect of the thoracic wall, suture line reinforcement,
muscle flap reinforcement; urogynecological surgical reinforcement including but not limited to, rectal and vaginal prolapse, reconstruction of the pelvic floor, hernia repair; soft tissue reconstructive procedures including plastic and reconstructive surgical application, and for reinforcement of the soft tissues, which are repaired by suture or suture anchors, including but not limited to, rotator cuff, patellar, Achilles, biceps, quadriceps and other tendons." XCM Biologic Tissue Matrix is supplied sterile (hydrated) in a foil liner pouch. It does not require refrigeration, or any preparation before use.

Xelma

Xelma is an extracellular matrix (ECM) protein to provide cell adhesion proteins in order to initiate healing in hard-to-heal wounds.

XWrap Dry or Hydro Plus

XWrapDry or Hydro is a resorbable, chorion-free, human amnion allograft, used as a covering for soft tissue defects and wounds.

Repriza

Repriza is a prehydrated, ready-to-use acellular dermal matrix graft prepared from human skin allograft intended for use in a single application (CMS, 2013). It is used as a skin substitute in the treatment of various types of wounds including burns, chronic ulcers, and surgical wounds. In addition to its use as a skin substitute, Repriza may also be used as an implant during plastic and reconstructive surgeries wherever an acellular dermal matrix may be used. For example, it may be used for augmentation of soft tissue irregularities and to support implants in a defined pocket such as in breast reconstruction, and abdominal wall reconstruction procedures. The quantity and size of product used varies based upon surgical application, individual patient circumstances, and the dimensions of the wound or surgical site. It is available in standard sizes with custom sizes and thicknesses available upon request. Repriza is used in the same indications and the same manner as both Alloderm and Graft Jacket. However, there is a significant difference in cost of the materials (CMS, 2013). In addition, Repriza is sterile, hydrated and ready to use on opening its package without soaking or washing and it may be stored at ambient temperature. It has no “sidedness”, so either side may be approximated to tissues of the wound or burn.

TenSIX
TenSIX is an acellular dermal matrix with natural histomorphology preserved. TenSIX is derived from aseptically processed cadaveric human skin tissue that is terminally sterilized. It is made from human donor skin, which undergoes a process that removes the epidermis and dermal cells, thereby creating an acellular dermis. "Human cadaveric dermal tissue" is referred to as acellular dermal allograft. TenSIX acts as a scaffold to facilitate angiogenesis and migration of growth factors that stimulate cell migration. Once rehydrated, the allograft can be applied topically to the wound and secured in the preferred manner of choice by the physician. Typically this is accomplished by the suturing or stapling the allograft to the skin surrounding the wound. TenSIX allograft tissue is to be used for the repair or replacement of damaged or inadequate integumental tissue or for the other homologous of human integument. It is used in women and tendon coverage. Most notably, it will be used for wounds resulting from chronic diabetic foot ulcers.

**FortaDerm and FortaDerm Antimicrobial**

FortaDerm is a single-layer fenestrated sheet of porcine collagen. FortaDerm is a skin substitute intended for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. It is supplied dry in sheet form in sizes ranging from 5x5 cm to 12x36 cm. FortaDerm is packaged in sterile, sealed single pouches and is administered by surgically applying and fixing it to a wound using sutures or other fixation method. FortaDerm is used similarly to other collagen wound dressings.

FortaDerm Antimicrobial PHMB is a sterile single-use sheet dressing made of collagen matrix and is coated with polyhexamethylene biguanide hydrochloride (PHMB) (CMS, 2014). It is intended for the management of wounds and as an effective barrier to resist microbial colonization within the dressings and reduce microbes penetrating through the dressing. It is supplied dry in sheet form in sizes ranging from 4x4 cm to 12x36 cm. FortaDerm Antimicrobial PHMB is packaged in sterile, sealed single pouches.

FortaDerm Antimicrobial PHMB Wound Dressing is a skin substitute designed for use on acute and chronic, partial and full-thickness wounds. It is surgically applied and fixed to a wound using sutures or other fixation method based on the size of the wound being treated.

**Alloskin/ AlloSkin RT**
Alloskin is allograft derived from epidermal and dermal human cadaver skin that has been preserved. It is regulated by the FDA as human tissue for transplantation (CMS, 2010). It is used in acute and chronic wound therapy.

Adherus

Adherus™ is made of 2 components that form a gel when they are combined. The gel is applied after the surgeon closes a dural incision. The gel acts as a thin, elastic barrier intended to prevent CSF from leaking until the dura tissue has properly healed on its own. The gel is then absorbed by the body over several months and excreted or removed from the body through the urine.

BioDRestore™ Elemental Tissue Matrix

The BioDRestore Elemental Tissue Matrix is a morialized, flowable tissue allograft derived from amniotic tissues.

Bio-ConneKt Wound Matrix

Bio-ConneKt Wound Matrix (MLM Biologics) is a bioengineered skin substitute derived from equine Type I collagen (CMS, 2015). Bio-ConneKt is intended for management of moderately to heavily exuding wounds, including partial and full thickness wounds, draining & tunneling wounds, pressure sores/ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds, and surgical wounds. The product is placed directly into the wound site and incorporates into the wound, as the wound heals.

Bio-ConneKt is supplied in 4 different sizes: 6 cm x 7 cm, 5 cm x 5 cm, 3 cm x 3 cm, and 2 cm x 2 cm. It comes in a double pouch package and in a final outer cardboard envelope. The product is trimmed to a size slightly larger than the outline of the wound, then affixed to the wound and covered with a standard, non-adherent surgical dressing.

AmnioPro Membrane

AmnioPro Membrane (Human Regenerative Technologies, LLC) is a human amniotic tissue allograft consisting of dehydrated and decellularized human amniotic membrane that has been processed with proprietary HydraTek technology. AmnioPro thin membrane is designed as a single layer wound covering for common wounds, and AmnioPro thick membrane is designed as a thicker single layer wound covering for deeper wounds where tissue bulk is required. It is intended to be used as a wound
covering and is surgically applied to the skin in the treatment of chronic acute and surgical wounds. Both products are available in the following sizes: 1x1cm, 1x2cm, 2x2cm, 2x4cm, 4x4cm, 4x6cm, and 4x8cm.

**AmnioPro Flow**

AmnioPro Flow (Human Regenerative Technologies, LLC) is a human placental tissue matrix consisting of decellularized particulate placental connective tissue matrix intended to replace or supplement damaged or inadequate integument. AmnioPro Flow is ideal for use in difficult to reach, irregularly shaped or tunneled wounds. Typically one application is applied per wound; however it may be reapplied if necessary. AmnioPro Flow is supplied in the following sizes: 0.5cc, 1.0cc, 1.5cc, and 2.0cc vials.

**Helicoll**

Helicoll (EnColl Corporation) is a bovine collagen acellular dermal matrix. Helicoll is a semi-occlusive, self-adhering and sterilized Type-1 collagen sheet for wound treatments, second degree burns, and chronic ulcers. It is indicated for use as a topical collagen wound dressing, and topical wound management including partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (abrasions, lacerations, second-degree burns, skin tears, and for surgical wounds, donor sites/grafts, post-Mohs’ surgery, post-laser surgery, podiatric, wound dehiscence).

Biodegradable collagen dressings are derived from animal tissues; they maintain a moist environment that promotes healing and the formation of granulation tissue. Helicoll is individually packaged and intended as a single application for an individual patient. Product should be trimmed to size prior to contact with the patient. It is supplied in a multiple sizes ranging from 2x2 to 6x26 square inches.

**Keramatrix**

Keramatrix (Keraplast Technologies, LLC) is an open-cell wound dressing comprised of freeze-dried acellular, animal-derived keratin protein. Keramatrix provides a biocompatible cell-growth substrate or scaffold for growth of new tissue in three dimensions and is resorbed into the developing tissue. When a wound occurs, the epithelium is lost and thus the keratin based skin structure is also lost; keramatrix substitutes the outer layer of the skin by introducing a replacement keratin-based structure. When placed in the wound bed it provides a cell-growth-friendly structure for tissue regeneration and maintains moist wound healing environment. Through interaction with enzymes in the healing wound, Keramatrix is degraded to a gel which is resorbed.
Keramatrix is indicated for the patient population with the following types of chronic wounds: pressure ulcers, venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers and donor sites and grafts. It is supplied in various sizes.

According to the manufacturer, Keramatrix is significantly different than “standard care” wound products because of Keramatrix’ combination of moist wound healing, growth-friendly structure and resorption into the wound, causing minimal disturbance to developing tissue.

AmnioStrip

AmnioStrip is comprised of placental tissue designed for use in protecting a wide variety of wounds, while simultaneously creating an environment conducive to the regeneration of healthy tissue. This tissue supposedly improves outcome in wound management. However, there is a lack of evidence regarding its clinical effectiveness.

WoundEx

According to the manufacturer, Human Regenerative Technologies, LLC., WoundEx consists of placental connective tissue matrix intended to replace or supplement damaged or inadequate connective tissue (CMS, 2017). WoundEx membrane allograft consists of dehydrated and decellularized human amniotic membrane that has been processed with proprietary HydraTek technology. "WoundEx Thin Membrane is designed as a single layer wound covering for common wounds, and WoundEx Thick Membrane is designed as a thicker single layer wound covering, for deeper wounds where more tissue bulk is required." WoundEx membrane is intended to be used as a wound covering in the treatment of chronic and acute wounds. Both the thin and thick membranes are supplied in the following sizes: 1 x 1 cm; 2 x 2 cm; 2 x 4 cm; 4 x 4 cm; 4 x 6 cm and 4 x 8 cm. WoundEx is stored at ambient temperature and has a 5-year shelf life.

WoundEx Flow

WoundEx Flow (Skye Biologics) consists of placental connective tissue matrix intended to replace or supplement damaged or inadequate connective tissue (CMS, 2017). WoundEx membrane allograft consists of dehydrated and decellularized human amniotic membrane that has been processed with proprietary HydraTek technology. WoundEx Flow is supplied in single use: 0.5cc, 1.0 cc, 1.5 cc, 2.0 vials. WoundEx Flow is stored at ambient temperature and has a 5-year shelf life.

Avance Nerve Garaf
Avance Nerve Graft is a processed, decedecellularized nerve allograft, used as an alternative to nerve conduits for nerve repair procedures.

**Cortiva Allograft Dermis**

Cortiva Allograft Dermis is a noncrosslinked acellular porcine dermal matrix, used for soft tissue repair procedures such as hernia repair.

**FloGraft**

FloGraft is a cryopreserved liquid, injectable amniotic fluid-derived allograft used in soft tissue repair.

**Fortiva Porcine Dermis**

Fortiva Porcine Dermis is a non-crosslinked porcine dermis, designed to act as a scaffold that allows for neovascularization and reincorporation with the individual's own tissue. It is used in soft tissue repair procedures such as hernia repair.

**CorMatrix ECM**

CorMatrix ECM is an acellular biomaterial ((porcine small intestine submucosa processed to remove cells) the remaining ECM is composed of structural proteins such as collagen, elastin, etc. It supports cardiac repairs and gradually replace tissue as it is remodeled, leaving no foreign material behind.

**DuraMatrix**

DuraMatrix is a dura substitute matrix membrane engineered from purified type I collagen, used for onlay or sutured implantation.

**BioFix**

The BioFix Allograft Membrane and Allograft Membrane-Plus are dehydrated, decellularized amniotic membranes, intended for homologous use as a wound covering. The BioFix Allograft Flow is intended for homologous use as a wound covering or connective tissue matrix. The BioFix Membrane is about 45 µm thick. The BioFix Membrane-Plus is about 200 µm thick. Each membrane is offered in the following sizes: 2x4 cm, 4x4 cm, 4x6 cm, and 4x8 cm. The BioFix Flow is offered in 0.5 cc, 1.0 cc, and 2.0 cc.
FlowerPatch

FlowerPatch is dehydrated amniotic membrane allograft processed from human amniotic tissues.

Willett et al (2014) assessed the effectiveness of micronized dehydrated human amnion/chorion membrane (μ-dHACM) as a disease-modifying intervention in a rat model of osteoarthritis (OA). It was hypothesized that intra-articular injection of μ-dHACM would attenuate OA progression. Lewis rats underwent medial meniscal transection (MMT) surgery to induce OA; 24 hours post-surgery, μ-dHACM or saline was injected intra-articularly into the rat joint. Naïve rats also received μ-dHACM injections. Microstructural changes in the tibial articular cartilage were assessed using equilibrium partitioning of an ionic contrast agent (EPIC-μCT) at 21 days post-surgery. The joint was also evaluated histologically and synovial fluid was analyzed for inflammatory markers at 3 and 21 days post-surgery. There was no measured baseline effect of μ-dHACM on cartilage in naïve animals. Histological staining of treated joints showed presence of μ-dHACM in the synovium along with local hyper-cellularity at 3 and 21 days post-surgery. In MMT animals, development of cartilage lesions at 21 days was prevented and number of partial erosions was significantly reduced by treatment with μ-dHACM. EPIC-μCT analysis quantitatively showed that μ-dHACM reduced proteoglycan loss in MMT animals. The authors concluded that μ-dHACM was rapidly sequestered in the synovial membrane following intra-articular injection and attenuated cartilage degradation in a rat OA model. They stated that these data suggested that intra-articular delivery of μ-dHACM may have a therapeutic effect on OA development.

Placental Tissue Matrix Allograft

Lullove (2015) stated that damaged connective tissue commonly leads to lower extremity injuries. These injuries can result in inflammation, reduced mobility, and chronic pain. Conservative treatment may include orthotics, offloading the injury, physical therapy, and/or NSAIDs. If conservative treatment fails, surgical intervention may be required. Even after successful surgery, these procedures often result in reduced joint mobility and tendon or ligament strength. A novel flowable tissue matrix allograft, derived from human placental connective tissue, has recently been made available for minimally invasive treatment of damaged or inadequate tissue (PX50®, Human Regenerative Technologies LLC, Redondo Beach, CA). Based on the universal role of connective tissue in the body, and its reported anti-microbial, anti-adhesive, and anti-inflammatory properties, these researchers assessed the effects of using this placental tissue matrix in the treatment of a series of lower extremity injuries. In this pilot study, 9 of 10 patients reported pain levels of 2 or less by week 4 using the VAS pain scale. They stated that this short-term
pilot study showed that injectable, flowable amniotic allografts can be used for orthopedic sports injuries of the lower extremities. The findings of this small (n = 10), pilot study need to be validated by well-designed studies.

Schneider et al (2016) noted that biomaterials based on decellularized tissues are increasingly attracting attention as functional alternatives to other natural or synthetic materials. However, a source of non-cadaver human allograft material would be favorable. These researchers established a decellularization method of vascular tissue from cryo-preserved human placenta chorionic plate starting with an initial freeze-thaw step followed by a series of chemical treatments applied with a custom-made perfusion system. This novel pulsatile perfusion set-up enabled us to successfully decellularize the vascular tissue with lower concentrations of chemicals and shorter exposure times compared to a non-perfusion process. The decellularization procedure described here led to the preservation of the native extracellular matrix architecture and the removal of cells. Quantitative analysis revealed no significant changes in collagen content and a retained glycosaminoglycan content of approximately 29 %. In strain-to-failure tests, the decellularized grafts showed similar mechanical behavior compared to native controls. In addition, the mechanical values for ultimate tensile strength and stiffness were in an acceptable range for in-vivo applications. Furthermore, biocompatibility of the decellularized tissue and its re-cellularization ability to serve as an adequate substratum for upcoming re-cellularization strategies using primary human umbilical vein endothelial cells (HUVECs) was demonstrated. HUVECs cultured on the decellularized placenta vessel matrix performed endothelialization and maintained phenotypical characteristics and cell specific expression patterns. Overall, the decellularized human placenta vessels can be a versatile tool for experimental studies on vascularization and as potent graft material for future in-vivo applications. These investigators stated that in the US alone more than 1 million vascular grafts are needed in clinical practice every year. Despite severe disadvantages, such as donor site morbidity, autologous grafting from the patient's own arteries or veins is regarded as the gold standard for vascular tissue repair. Besides, strategies based on synthetic or natural materials have shown limited success. Tissue engineering approaches based on decellularized tissues are regarded as a promising alternative to clinically used treatments to overcome the observed limitations. However, a source for supply of non-cadaver human allograft material would be favorable. The authors established a decellularization method of vascular tissue from the human placenta chorionic plate, a suitable human tissue source of consistent quality. The decellularized human placenta vessels can be a potent graft material for future in-vivo applications and furthermore might be a versatile tool for experimental studies on vascularization.

Cook Medical Anal Fistula Plug
Filgate et al (2015) stated that enteric fistulas are a recognized complication of various diseases and surgical interventions. Non-operative medical management will result in closure of 60 to 70% of all fistulas over a 6- to 8-week period, those that fail non-operative management will require operative intervention if they are to close. These investigators presented a series of upper gastrointestinal (GI) fistula managed with endoscopic intervention and insertion of biological fistula plug over a 3-year period across 3 Hospitals, both public and private, in Western Australia. Over a 3-year period, 14 patients were referred for treatment of acute or persistent fore-gut fistulas. All fistulas were managed with endoscopic intervention and insertion of a porcine small intestine sub-mucosa plug (Biodesign Cook medical Inc., Bloomington, IN). No patients with fistula were excluded. Data were collected on patient demographics and underlying diagnosis. The biological plugs were deployed using 3 different endoscopic techniques (direct deployment via the endoscope, catheter-assisted endoscopic deployment, or a pull through via a guide wire using a rendezvous technique). Patients with fore-gut fistula were treated using biological plugs. The age of the fistulas treated ranged from 14 days to 3 years. The fistulas were predominantly gastric in origin (8 cases); 3 esophageal, 1 gastro-pleural-bronchial, and 2 jejunal fistulas were also managed using this technique.

Of the 14 fistulas treated using this method, 13 resolved following the treatment. Median time to closure of the fistula was 2 days (range of 1 to 120 days); 3 patients required more than 1 intervention to complete closure. The authors concluded that biological plugs offered a further option for management of the traditionally difficult foregut fistula, without major morbidity associated with other treatment modalities. It is limited to the ability to deploy the plug endoscopically. This was a small study (n = 14); and it did not entail the use of anal fistula plug.

Viaflow and Viaflow C Flowable Placental Tissue Matrices

Viaflow and Viaflow C Flowable Placental Tissue Matrices are pre-mixed, tissue matrix allografts, processed from human placental tissues. The fluid tissue combination contains collagens, growth factors, and other key biologic components.

- 2 configurations available: Ambient temperature (Viaflow) and Cryopreserved (Viaflow C)
- 5-year shelf life at ambient temperature (Viaflow)
- 5-year shelf life at -40°C (Viaflow)
- Flowable through a 23-G needle
- Target defects quickly and precisely
- Easily mixable with carriers.
The placental extracellular matrix (ECM) supports healing by modulating correct tissue reconstruction rather than scar tissue formation. This ECM includes growth factors, fibronectin, laminin, hyaluronic acid, proteoglycans, and other proteins.

Lullove (2015) noted that damaged connective tissue commonly leads to lower extremity injuries. These injuries can result in inflammation, reduced mobility, and chronic pain. Conservative treatment may include orthotics, off-loading the injury, physical therapy, and/or non-steroidal anti-inflammatory drugs (NSAIDs). If conservative treatment fails, surgical intervention may be required. Even after successful surgery, these procedures often result in reduced joint mobility and tendon or ligament strength. A novel flowable tissue matrix allograft, derived from human placental connective tissue, has recently been made available for minimally invasive treatment of damaged or inadequate tissue (PX50®, Human Regenerative Technologies LLC, Redondo Beach, CA). Based on the universal role of connective tissue in the body, and its reported anti-microbial, anti-adhesive, and anti-inflammatory properties, these researchers assessed the effects of using this placental tissue matrix in the treatment of a series of lower extremity injuries. In this pilot study, 9 of 10 patients reported pain levels of 2 or less by week 4 using the visual analog scale (VAS) pain scale. This short-term pilot study showed that injectable, flowable amniotic allografts can be used for orthopedic sports injuries of the lower extremities. Moreover, they stated that further research would be needed to compare the use of amniotic allograft tissue injections versus corticosteroid injections head-to-head, and further larger studies, including randomized controlled trials, may elucidate the reasons for these differences.

TruSkin

According to the manufacturer Orsis Therapeutics Inc., TruSkin is a split-thickness cryopreserved human skin allograft, intended for the replacement or reconstruction of inadequate or damaged integumental tissue. The manufacturer states that TruSkin, an advanced skin substitute, is an easy-to-use, off-the-shelf alternative to fresh skin allograft. TruSkin addresses biological deficiencies in the wound, assists in epithelialization, and aids in preserving surrounding tissue. The key differentiating feature of TruSkin from all other preserved skin allografts is the proprietary processing, which retains all components of fresh skin in their native state, including: collagen-rich skin Extracellular Matrix (ECM), endogenous bioactive factors, and endogenous living skin cells. The applicant claims that TruSkin is indicated for patients with acute and chronic wounds, who have limited treatment options and are at great risk for wound-related morbidities and mortality. TruSkin offers patients an alternative to invasive procedures, including autologous skin grafting or limb amputation. The quantity and size of the
product used will vary based upon wound size and physician recommendation. Application of TruSkin is recommended weekly or bi-weekly for up to 12 weeks or until the wound is closed. TruSkin is supplied as a graft in two sizes: 32 cm² and 8 cm².

Artacent

According to the manufacturer Tides Medical, Artacent Wound is a dual-layer human amniotic membrane graft used for acute and chronic wound applications (CMS, 2019). It is derived from the submucosa of donated human placenta. It consists of collagen layers, including basement membrane and stromal matrix. Its dual layer and bilateral application improves handling, while its unique design permits easy manipulation and placement onto the wound bed. The manufacturer claims that Artacent Wound contains essential growth factors “shown to stimulate wound healing”. Artacent Wound is “intended for treatment of acute and chronic wounds such as diabetic ulcers, venous stasis ulcers, burns, and additional wounds that are refractory to more conservative care.” Artacent Wound is applied to the wound bed following wound preparation. Absorbable/non-absorbable suture material and/or tissue adhesives may be used to apply the graft to the site, if necessary. Artacent Artacent Wound is supplied in the following sizes: 1 cm x 1 cm, 2 cm x 2 cm, 2 cm x 3 cm, 4 cm x 4 cm, 4 cm x 6 cm, 4 cm x 8 cm, 10 mm disk, and 16 mm disk.

Artacent Cord

According to Tides Medical, Artacent Cord human umbilical cord is “a wound healing patch that is comprised of the umbilical cord.” “It is intended for the treatment of acute and chronic wounds such as diabetic ulcers, venous stasis ulcers, burns, and additional wounds that are refractory to more conservative care.” Artacent Cord is applied to the wound bed following wound preparation. Absorbable/non-absorbable suture material and/or tissue adhesives may be used to apply the graft to the site, if necessary. Once applied the allograft can hydrated with sterile saline or other sterile solution, if needed.

Cygnus

According to the manufacturer Vivex Biomedical, Inc., CYGNUS is an amniotic tissue allograft with innate regenerative capability to support healing without adhesion or scar formation (CMS, 2016). It is used most often to treat acute wounds, chronic wounds, and burns, and it can serve as an adhesion barrier to keep potentially adherent surfaces apart. CYGNUS is a dried human amnion membrane allograft composed of a single layer of epithelial cells, a basement membrane, and an avascular connective tissue matrix. It is a minimally manipulated, dried non-viable cellular amniotic membrane allograft that
preserves and delivers multiple extracellular matrix proteins, growth factors, cytokines, and other specialty proteins present in amniotic tissue to help regenerate soft tissue. CYGNUS is supplied in a variety of sizes, ranging from 1 cm x 2 cm to 7 cm x 7 cm.

Interfyl

According to the manufacturer Alliqua Biomedical, Inc., Interfyl is a decellularized and dehydrated placental disc (chorionic plate) derived extracellular matrix (ECM). Its connective-tissue matrix (CTM) serves as a scaffold for recipient cells in the wound to regenerate soft tissue. Because it is not cross-linked and does not contain cells, Interfyl reduces the likelihood of immunogenic and inflammatory responses as compared to other HCT/Ps, thereby minimizing inflammation and scarring. Interfyl is intended for use as the replacement or supplementation of damaged or inadequate integumental tissue by providing support for the body’s normal healing processes. Indications for Interfyl include treatment of deep dermal wounds, irregularly-shaped and tunneling wounds, augmentation of deficient/inadequate soft tissue, and the repair of small surgical defects. Interfyl is supplied as single-dose flowable product syringes containing 250 mg in 1.5 mL, and as particulate product in vials containing 50 mg and 100 mg.

PuraPly

According to the manufacturer Organogenesis, Inc., PuraPly Antimicrobial Wound Matrix (PuraPly AM) and Puraply Wound Matrix (PuraPly) is a single-layer fenestrated sheet of porcine collagen. PuraPly Am is a double-layer fenestrated and cross-linked sheet of porcine collagen, coated with polyhexamethylene biguanide hydrochloride (PHMB) to resist microbial colonization and reduce microbial penetration within the matrix. The two products are prescribed by a physician or other qualified health care professional and indicated for the management of wounds. They are typically administered in an outpatient setting but may be administered inpatient or in the office setting. PuraPly and PuraPly AM are administered by applying the product to a wound using sutures or other fixation methods. PuraPly AM and PuraPly are supplied in a single-layer or double-layer fenestrated sheet of porcine intestinal collagen, approximately 0.05 to 0.07 mm in thickness. The products are available in a range of sizes from 2 cm x 4 cm to 6 cm x 9 cm.

PalinGen

According to the manufacturer Amino Technology LLC, PalinGen Membrane and PalinGen Hydromembrane are human allografts comprised of amniotic membrane, providing a wound covering and support for native tissues. These human allografts provide a biological and physical barrier to support and protect naturally occurring and
surgical wounds in vivo. The manufacturer states that PalinGen Membrane and PalinGen Hydromembrane are commonly used in the treatment of chronic wounds, and they are also indicated for the repair and reconstruction of a recipient’s cells or tissues, including venous leg ulcers, diabetic ulcers, pressure ulcers and in orthopedic, cardiac and ophthalmologic conditions. PalinGen Membrane and PalinGen Hydromembrane are supplied in ten different sizes, ranging from 1 sq.cm to 64 sq.cm.

PalinGen XPlus Membrane and PalinGen XPlus Hydromembrane are human allografts comprised of amniotic membrane. They provide a wound covering and support for native tissues. The manufacturer states that they are used to repair or replace soft tissue defects, soft trauma defects, tendinitis, tendinosis, chronic wound repair and localized inflammation. The patient population for the item are older Type I patients with diabetes for the treatment of chronic wounds. These products have also been used in the repair and reconstruction of a recipient’s cells or tissues including venous leg ulcers, diabetic ulcers, pressure ulcers, and in orthopedic, cardiac and ophthalmologic conditions. PalinGen XPlus Membrane and PalinGen XPlus Hydromembrane are supplied in ten different sizes, ranging from 1 sq.cm to 64 sq.cm.

PalinGen Flow and PalinGen SportFlow are human allografts comprised of amnion and amniotic fluid components, providing a liquid allograft to “aid in the healing” and repair of chronic wounds. PalinGen Flow and PalinGen SportFlow contain key growth factors, cytokines, amino acids, carbohydrates, hyaluronic acid, extracellular matrix proteins, and cellular components recognized as intrinsic to the complex wound healing process. According to the manufacturer, PalinGen Flow and PalinGen SportFlow are commonly used in the treatment of chronic wounds that are most prevalent in older populations, particularly in patients with Type I diabetes. PalinGen Flow and PalinGen SportFlow are amniotic membrane and fluid that are suspended in liquid. The product is applied directly on or in the wound with a 20-23 gauge needle. The prescribed dosage varies by the size of the wound. Typical doses range from 0.25 cc to 4.0 cc, depending on the size, depth and type of wound. PalinGen Flow and PalinGen SportFlow are similar, but separate products. They are supplied in liquid form in vials containing 0.25 cc, 0.5 cc, 1 cc, 2 cc, and 4 cc. These products are cryopreserved and should be stored frozen at a temperature of -80°C +/- 15°.

ProMatrX ACF

ProMatrX ACF is a human allograft comprised of amnion and amniotic fluid, providing a liquid allograft to “aid in the healing” and repair of chronic wounds. ProMatrX ACF contains key growth factors, cytokines, amino acids, carbohydrates, hyaluronic acid, extracellular matrix proteins, and cellular components recognized as intrinsic to the complex wound healing process. According to the manufacturer Amino Technology,
ProMatrX ACF is commonly used in the treatment of chronic wounds that are most prevalent in older populations, particularly in patients with Type I diabetes. ProMatrX ACF is amniotic membrane and fluid suspended in liquid. The product is applied directly on or in the wound with a 20-23 gauge needle. The prescribed dosage varies by the size of the wound. Typical doses range from 0.25 cc to 4.0 cc, depending on the size, depth and type of wound. ProMatrX ACF is supplied in liquid form in vials containing 0.25 cc, 0.5 cc, 1 cc, 2 cc, and 4 cc. These products are cryopreserved and should be stored frozen at a temperature at -80°C +/- 15°.

**Miroderm**

MIRODERM (Miromatrix Medical) is a non-crosslinked acellular wound matrix that is derived from porcine liver and is processed and stored in a phosphate buffered aqueous solution. The manufacturer states that it is clinically indicated for the management of wounds. MIRODERM is used on a chronic wound where it provides a scaffold to maintain and support a healing environment through constructive remodeling. It is used to cover the entire surface of the wound bed and extend slightly beyond all wound margins. MIRODERM is available in fenestrated and non-fenestrated form, in seven sizes ranging from 9 cm² to 120 cm².

**Stravix**

Stravix (Osiris Therapeutics Inc.) is a cryopreserved human placental tissue, composed of the Wharton’s jelly and umbilical amniotic membrane. Stravix is processed from human umbilical cord and contains: a collagen and hyaluronic acid-rich extracellular matrix; endogenous biofactors with anti-inflammatory, angiogenic, anti-scarring, and anti-microbial properties; and viable endogenous cells, including mesenchymal stem cells. The manufacturer states that Stravix is currently used in inpatient surgical applications only, including: as a wound cover in deep, acute wounds; surgical wound repair; and the majority of applications are surgical, below the knee, leg and foot tendon repairs, and neurovascular repair. Stravix is supplied as a cryopreserved placental tissue packaged in a wide-mouth jar. It is available in two sizes (3 x 6 cm, 2 x 4 cm). When stored frozen at -80°C, Stravix has a two year shelf-life.

**Miscellaneous Wound Care Products**

- The use of porcine-derived decellularized collagen products (e.g., Collamend, Cuffpatch™, Pelvicol®, Pelvisoft®, and Strattice™) has been proposed for use in various surgical procedures and in the treatment of dermal wounds. Currently, there is insufficient evidence to allow for proper evaluation regarding the effectiveness of this technology.
The use of porcine-derived polypropylene composite wound dressing (e.g., Avaulta Plus™) in the clinical setting has not been established. Until comparative studies of this product have been made available, a thorough evaluation of its safety and effectiveness cannot be completed.

Amnio Wound

Amnio Wound is a lyophilized human amniotic membrane allograft comprised of an epithelial layer and 2 fibrous connective tissue layers specifically processed to be used for the repair and replacement of lost or damaged dermal tissue (CMS, 2017). Amnio Wound is intended for use in the following conditions: neuropathic ulcers, venous stasis ulcers, post-traumatic wounds, pre-and post-surgical wounds and pressure ulcers, diabetic wounds, burn wounds, scar tissue, scarring, adhesion barrier. The graft is administered by placing the stromal side onto the external wound area followed by the clinician's standard closing procedures. It is stored at ambient temperature. There is a lack of evidence regarding the effectiveness of Amnio Wound allograft.

CellECT

Lee and Goodman (2009) described a novel treatment of secondary osteonecrosis (ON) of the femoral condyles that is relatively simple, has low morbidity, and does not preclude the patient from other more extensive treatments in the event of failure. A total of 3 patients with extensive secondary ON of the femoral condyles were treated with decompression and debridement of the area of ON and grafting with the Cellect DBM System (Depuy Spine, Inc., Raynham, MA), which provided a graft matrix enriched with a 3-fold to 4-fold increase in osteo-progenitor cells. At 2 years, all 3 patients had no complications and had excellent results with near-normal function and activity levels. The authors concluded that these preliminary results demonstrated that this technique is a viable option, at least in the short-term, especially in patients with extensive, multifocal lesions.

Englund et al (2010) summarized their efforts in deriving, characterizing and banking of 20 different human embryonic stem cell lines. These researchers derived a large number of human embryonic stem cell lines between 2001 and 2005. One of these cell lines was established under totally xeno-free culture conditions. In addition, several subclones have been established, including a karyotypical normal clone from a trisomic mother line. A master cell banking system has been utilized in concert with an extensive characterization program, ensuring a supply of high quality pluripotent stem cells for further research and development. In this report, these investigators also presented the first data on a proprietary novel antibody, hES-Cellect, that exhibits high specificity for undifferentiated hES cells. In addition to the traditional manual dissection approach of
propagating hES cells, the authors also reported on the successful approaches of feeder-free cultures as well as single cell cultures based on enzymatic digestion. All culture systems used as reported here have maintained the hES cells in a karyotypical normal and pluripotent state. These systems also have the advantage of being the principal springboards for further scale up of cultures for industrial or clinical applications that would require vastly more cells that can be produced by mechanical means.

Delibaltov et al (2016) introduced an interactive cell analysis application, called CellECT, for 3D+t microscopy datasets. The core segmentation tool is watershed-based and allowed the user to add, remove or modify existing segments by means of manipulating guidance markers. A confidence metric learns from the user interaction and highlights regions of uncertainty in the segmentation for the user's attention. User corrected segmentations are then propagated to neighboring time points. The analysis tool computes local and global statistics for various cell measurements over the time sequence. Detailed results on 2 large datasets containing membrane and nuclei data were presented: (i) a 3D+t confocal microscopy dataset of the ascidian Phallusia mammillata consisting of 18 time-points, and (ii) a 3D+t single plane illumination microscopy (SPIM) dataset consisting of 192 time-points. Additionally, CellECT was used to segment a large population of jigsaw-puzzle shaped epidermal cells from Arabidopsis thaliana leaves. The cell coordinates obtained using CellECT are compared to those of manually segmented cells. The authors concluded that CellECT provided tools for convenient segmentation and analysis of 3D+t membrane datasets by incorporating human interaction into automated algorithms. Users can modify segmentation results through the help of guidance markers, and an adaptive confidence metric highlights problematic regions. Segmentations can be propagated to multiple time-points, and once a segmentation is available for a time sequence cells can be analyzed to observe trends. The segmentation and analysis tools presented here generalize well to membrane or cell wall volumetric time series datasets.

**NeoPatch Chorioamniontic Membrane Allograft**

NeoPatch is a wound covering derived from terminally sterilized, dehydrated human placental membrane tissue comprised of both amnion and chorion. NeoPatch is an allograft intended for use as a wound covering, and applied externally to the wound. The constituent epithelium, basement membranes and collagen-rich extracellular matrix provide a protective covering to the wound. Individuals presenting with wounds including lower extremity ulceration caused by diabetes, chronic venous disease, and other chronic conditions, or who present with acute wounds may be appropriate for treatment with NeoPatch. NeoPatch is supplied in the following sizes: 14 mm round, 18 mm round, 24 mm round, 2 cm x 3 cm, 3 cm x 5 cm, 4 cm x 4 cm, 5 cm x 6 cm. There is a lack of evidence regarding the effectiveness of NeoPatch chorioamniontic membrane allograft.
FlowerDerm / FlowerFlo (FlowerAmnioFlo) / FlowerPatch (FlowerAMINOPatch)

FlowerDerm is a hydrated acellular (human) dermal allograft matrix used for the treatment of non-healing wounds and burn injuries. FlowerDerm contains extracellular matrix (ECM) that provides a scaffold for cellular ingrowth vascularization, tissue regeneration and formation of granulation tissue. The typical patient population includes individuals with chronic, non-infected, full thickness diabetic lower extremity ulcers, patients with chronic, non-infected, partial or full-thickness diabetic lower extremity skin ulcers due to venous insufficiency that have not adequately responded following conventional ulcer therapy and patients with 2nd and 3rd degree burns. FlowerDerm allografts are hydrated in saline and transported and stored at ambient temperature. FlowerDerm is supplied as a thin (0.5 mm) allograft, meshed and un-meshed, in a variety of sizes; as a medium (1 mm) allograft, meshed or unmeshed, in a variety of sizes; and as a thick (2 mm) unmeshed allograft in several sizes. FlowerDerm may be cut and shaped to the appropriate size. It is applied over the wound site following wound bed preparation. Absorbable/non-absorbable suture material and/or tissue adhesives may be used to apply the graft to the site, if necessary. There is a lack of evidence regarding the effectiveness of FlowerDerm.

FlowerFlo is a 100 % acellular liquid amniotic fluid allograft intended for the treatment of non-healing wounds and burn injuries. FlowerFlo delivers cytokines, proteins and growth factors to help generate soft tissue. The typical patient population includes individuals with chronic, non-infected, full thickness diabetic lower extremity ulcers, patients with chronic, non-infected, partial or full-thickness diabetic lower extremity skin ulcers due to venous insufficiency that have not adequately responded following conventional ulcer therapy and patients with 2nd and 3rd degree burns. FlowerFlo delivers cytokines, proteins and growth factors to help regenerate soft tissue. FlowerFlo is prescribed by a qualified health care profession for injection on or in the wound site, in a physician office, out-patient, or in-patient setting. The dosage is per cubic centimeter (cc), depending on the size of the wound, intended for external application. There is a lack of evidence regarding the effectiveness of FlowerFlo.

FlowerPatch is a dehydrated (human) amniotic membrane allograft used for the treatment of non-healing wounds and burn injuries. FlowerPatch delivers cytokines, proteins and growth factors help generate soft tissue. The product is directed to patients with chronic, non-infected, full thickness diabetic lower extremity ulcers due to venous insufficiency that have not adequately responded following conventional ulcer therapy and patients with 2nd and 3rd degree burns. FlowerPatch is transported and stored at ambient temperature. It is supplied in single-use packages in the following sizes: 2 cm X 2 cm, 2 cm X 4 cm, 4 cm X 6 cm, 4 cm X 8 cm. FlowerPatch is prescribed by a qualified health care professional for administration in a physician office, out-patient, or in-patient.
setting. FlowerPatch may be cut and shaped to the appropriate size. It is applied over
the wound site following wound preparation. Absorbable/non-absorbable suture material
and/or tissue adhesives may be used to apply the graft to the site, if necessary. There is
a lack of evidence regarding the effectiveness of FlowerPatch.

Revita

Revita (StimLabs, LLC.) is a human cellular and tissue based product -- donated allograft
placental tissue (CMS, 2017). It is comprised of dehydrated, sterile human amniotic
membrane and chorionic membrane obtained from donated human placental tissue.
Revita is comprised of all 3 layers of placental membrane (amnion, intermediate, and
chorion layers). Revita allograft is intended to be used as a wound covering, or barrier
membrane, over chronic and acute wounds, including dermal ulcers or defects. It is
supplied in 2 x 2 cm, 2 x 3 cm, 4 x 4 cm, 4 x 6 cm, and 6 x 8 cm sheets. There is a lack
of evidence regarding the effectiveness of Revita.

Bionect

Bionect (Innocutis Holdings, LLC., Charleston, SC) is a topical hyaluronic acid sodium
salt, 0.2%. According to the manufacturer, the sodium hyaluronate (Hyalastine®) is
derived from a natural fermentation process. Hyaluronic acid is a biological
polysaccharide (glycosaminoglycan) and is a major component of the extracellular matrix
of connective tissues. Bionect Cream was cleared for marketing under the 510(k)
process in February 1997. Bionect is now available in cream, gel, spray and foam
formulations for “the dressing and management of partial to full thickness dermal ulcers
(pressure sores, venous stasis ulcers, arterial ulcers, and diabetic ulcers), wounds
including cuts, abrasions, donor sites, and post-operative incisions, irritations of the skin,
and first and second degree burns. The dressing is intended to cover a wound or burn on
a patient’s skin, and protect against abrasion, friction, and desiccation.”

Shaharudin et al (2016) stated that hyaluronic acid (HA) and its derivatives are used for
chronic wounds, but evidence of their effectiveness remains unclear. The aim of this
study was to provide more updated evidence for the effectiveness of HA (or its
derivatives) compared with placebo or other agents for promoting healing in chronic
wounds. The Cochrane Central Register of Controlled Trials, MEDLINE via Ovid Online,
CINAHL and the EMBASE via EBSCO host databases were searched. Drug companies
and experts in wounds were also contacted. Randomised controlled trials of HA (or its
derivatives) compared with control were eligible for inclusion. The authors identified nine
randomised controlled trials involving 865 participants with chronic wounds were included
in the review. The reporting for mixed arterial and venous ulcers seems to be better
quality than that for venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs). Studies
provided little evidence regarding the claimed effects of HA or its derivatives on healing of chronic wounds. However, there is some evidence on their effectiveness for reducing pain intensity for mixed arterial and venous ulcers, which involved 255 patients (MD=-6.78 [95% CI: -11.10 to -2.46]). Evidence to guide decisions regarding the use of HA or its derivatives to promote wound healing is still limited. More good-quality randomised controlled trials are warranted.

Brown et al (1999) stated hyaluronan has been introduced as a vehicle for topical application of drugs to the skin. We sought to determine whether hyaluronan acts solely as a hydrophilic reservoir on the surface of intact skin or might partly penetrate it. Drug-free hyaluronan gels were applied to the intact skin of hairless mice and human forearm in situ, with and without [3H] hyaluronan. [3H]hyaluronan was shown by autoradiography to disseminate through all layers of intact skin in mouse and human, reaching the dermis within 30 min of application in mice. Cellular uptake of [3H]hyaluronan was observed in the deeper layers of epidermis, dermis, and in lymphatic endothelium. Absorption through skin was confirmed in mice by chromatographic analysis of blood, urine, and extracts from skin and liver, which identified 3H as intact hyaluronan and its metabolites, free acetate and water. Hyaluronan absorption was similarly demonstrated without polyethylene glycol, which is usually included in the topical formulation. [3H]hyaluronan absorption was not restricted to its smaller polymers as demonstrated by the recovery of polymers of (360-400 kDa) from both blood and skin. This finding suggests that its passage through epidermis does not rely on passive diffusion but may be facilitated by active transport. This study establishes that hyaluronan is absorbed from the surface of the skin and passes rapidly through epidermis, which may allow associated drugs to be carried in relatively high concentration at least as far as the deeper layers of the dermis. This was a study in mice and human skin to establish that hyaluronic acid does permeate the normal epidermis to accumulate in the dermis. The primary limitation of this study was that it does not discuss clinical outcomes in a wound care setting.

Schlesinger et al (2014) stated that hyaluronic acid sodium salt gel 0.2% is a topical device effective in reducing skin inflammation. Facial seborrheic dermatitis, characterized by erythema and or flaking/scaling in areas of high sebaceous activity, affects up to five percent of the United States population. Despite ongoing study, the cause of the condition is yet unknown, but has been associated with yeast colonization and resultant immune derived inflammation. First-line management typically is with keratolytics, topical steroids, and topical antifungals as well as the targeted immunosuppressant agents pimecrolimus and tacrolimus. The objective of this study was to evaluate the efficacy and safety of a novel topical antiinflammatory containing low molecular weight hyaluronic acid. This was a prospective, observational, non-blinded safety and efficacy study in an outpatient setting. Individuals 18 to 75 years of age with facial seborrheic dermatitis were
included. Outcome measures included scale, erythema, pruritus, and the provider global assessment, all measured on a five-point scale. Subjects were assessed at baseline, Week 2, Week 4, and Week 8. Final data with 13 of 17 subjects are presented. Hyaluronic acid sodium salt gel 0.2% was shown through visual grading assessments to improve the provider global assessment by 65.48 percent from baseline to Week 4. Reductions in scale, erythema, and pruritus were 76.9, 64.3, and 50 percent, respectively, at Week 4. At Week 8, the provider global assessment was improved from baseline in 92.3 percent of subjects. Treatment with topical low molecular weight hyaluronic acid resulted in improvement in the measured endpoints. Final data reveal continued improvement from that seen in the interim data shown previously. Topical low molecular weight hyaluronic acid is another option that may be considered for the treatment of facial seborrheic dermatitis in the adult population. Compliance and tolerance were excellent. Limitations of this study include a small sample size, lack of blinding, a short follow-up period, and the studied indication was seborrheic dermatitis, not wound care.

Gariboldi et al (2008) stated that in sites of inflammation or tissue injury, hyaluronic acid (HA), ubiquitous in the extracellular matrix, is broken down into low m.w. HA (LMW-HA) fragments that have been reported to activate immunocompetent cells. The authors found that LMW-HA induces activation of keratinocytes, which respond by producing beta-defensin 2. This production is mediated by TLR2 and TLR4 activation and involves a c-Fos-mediated, protein kinase C-dependent signaling pathway. LMW-HA-induced activation of keratinocytes seems not to be accompanied by an inflammatory response, because no production of IL-8, TNF-alpha, IL-1beta, or IL-6 was observed. Ex vivo and in vivo treatments of murine skin with LMW-HA showed a release of mouse beta-defensin 2 in all layers of the epidermal compartment. Therefore, the breakdown of extracellular matrix components, for example after injury, stimulates keratinocytes to release beta-defensin 2, which protects cutaneous tissue at a time when it is particularly vulnerable to infection. In addition, the authors’ observation might be important to open new perspectives in the development of possible topical products containing LMW-HA to improve the release of beta-defensins by keratinocytes, thus ameliorating the self-defense of the skin for the protection of cutaneous tissue from infection by microorganisms. The authors concede their observations that LMW-HA may clarify a physiological mechanism that is probably present in the skin to avoid eventual bacterial infection is “only speculative at the moment”.

Weindl et al (2004) stated that glycosaminoglycan hyaluronic acid (HA), or hyaluronan, is a major component of the extracellular matrix of skin, joints, eye and many other tissues and organs. In spite of its simple structure, HA demonstrates remarkable rheological, viscoelastic and hygroscopic properties which are relevant for dermal tissue function.
Biological activities in skin, however, are also due to its interaction with various binding proteins (hyaladherins). Due to an influence on signaling pathways, HA is involved in the wound-healing process and scarless fetal healing. Increased HA concentrations have been associated with inflammatory skin diseases. In clinical trials, topical application of HA improved wound healing; in particular, acute radioepithelitis, venous leg ulcers or diabetic foot lesions responded to HA treatment. Moreover, as a topical drug delivery system for diclofenac, an HA gel has recently been approved for the treatment of actinic keratoses. Finally, chemical modifications led to new HA derivates and biomaterials, which may be introduced into therapy in the future. Therefore, ongoing research offers new horizons for the therapeutic use of this glycosaminoglycan which has been regarded as an inert structural component until recently.

Greco et al (1998) stated that human dermal fibroblasts suspended in a collagen matrix exhibit a 4-day delay in cell division, while the same cells in monolayer divided by day 1. The initial rates of 3H-thymidine incorporation by cells in monolayer or suspended in collagen were not significantly different. When suspended in collagen, there was a threefold increase in the proportion of cells in a tetraploidal (4N) DNA state compared to the same cells in monolayer. Flow cytometry analysis and 3H-thymidine incorporation studies identified the delay of cell division as a consequence of a block in the G2/M of the cell cycle and not an inhibition of DNA synthesis. The inclusion of 150 microg/ml of hyaluronic acid (HA) in the manufacture of fibroblast populated collagen lattices (FPCL) caused a stimulation of cell division, as determined by cell counting; increased the expression of tubulin, as determined by Western blot analysis; and reduced the proportion of cells in a 4N state, as determined by flow cytometry. HA added to the same cells growing in monolayer produced a minimal increase in the rate of cell division or DNA synthesis. HA supplementation of FPCLs stimulated cell division as well as tubulin concentrations, but it did not enhance lattice contraction. The introduction of tubulin isolated from pig brain or purchased tubulin into fibroblasts by electroporation prior to their transfer into collagen lattices promoted cell division in the first 24 hours and enhanced FPCL contraction. It is proposed that tubulin protein, the building blocks of microtubules, is limited in human fibroblasts residing within a collagen matrix. When human fibroblasts are suspended in collagen, one effect of added HA may be to stimulate the synthesis of tubulin which assists cells through the cell cycle. The primary limitation of this study was that it does not discuss clinical outcomes in a wound care setting.

Alloderm and Strattice for Surgical Repair of Complex Abdominal Wall Wounds

Booth et al (2013) stated that many surgeons believe that primary fascial closure with mesh reinforcement should be the goal of abdominal wall reconstruction (AWR), yet others have reported acceptable outcomes when mesh is used to bridge the fascial
edges. It has not been clearly shown how the outcomes for these techniques differ. These investigators hypothesized that bridged repairs result in higher hernia recurrence rates than mesh-reinforced repairs that achieve fascial coaptation. They retrospectively reviewed prospectively collected data from consecutive patients with 1 year or more of follow-up, who underwent mid-line AWR between 2000 and 2011 at a single center. These researchers compared surgical outcomes between patients with bridged and mesh-reinforced fascial repairs. The primary outcomes measure was hernia recurrence; multi-variate logistic regression analysis was used to identify factors predictive of or protective for complications. This study included 222 patients (195 mesh-reinforced and 27 bridged repairs) with a mean follow-up of 31.1 ± 14.2 months. The bridged repairs were associated with a significantly higher risk of hernia recurrence (56 % versus 8 %; hazard ratio [HR] 9.5; p < 0.001) and a higher overall complication rate (74 % versus 32 %; odds ratio [OR] 3.9; p < 0.001). The interval to recurrence was more than 9 times shorter in the bridged group (HR 9.5; p < 0.001). Multi-variate Cox proportional hazard regression analysis identified bridged repair and defect width greater than 15 cm to be independent predictors of hernia recurrence (HR 7.3; p < 0.001 and HR 2.5; p = 0.028, respectively). The authors concluded that mesh-reinforced AWRs with primary fascial coaptation resulted in fewer hernia recurrences and fewer overall complications than bridged repairs; and surgeons should make every effort to achieve primary fascial coaptation to reduce complications.

Sbitany et al (2015) stated that repair of grade 3 and grade 4 ventral hernias is a distinct challenge, given the potential for infection, and the co-morbid nature of the patient population. These investigators evaluated their institutional outcomes when performing single-stage repair of these hernias, with biologic mesh for abdominal wall reinforcement. A prospectively maintained database was reviewed for all patients undergoing repair of grade 3 (potentially contaminated) or grade 4 (infected) hernias, as classified by the Ventral Hernia Working Group. All those patients undergoing repair with component separation techniques and biologic mesh reinforcement were included. Patient demographics, co-morbidities, and post-operative complications were analyzed. Uni-variate analysis was performed to define factors predictive of hernia recurrence and wound complications. A total of 41 patients underwent single-stage repair of grade 3 and grade 4 hernias during a 4-year period. The overall post-operative wound infection rate was 15 %, and hernia recurrence rate was 12 %. Almost all recurrences were seen in grade 4 hernia repairs, and in those patients undergoing bridging repair of the hernia; 1 patient required removal of the biologic mesh. Those factors predicting hernia recurrence were smoking (p = 0.023), increasing body mass index (p = 0.012), increasing defect size (p = 0.010), and bridging repair (p = 0.042). No mesh was removed due to peri-operative infection. Mean follow-up time for this patient population was 25 months. The authors concluded that single-stage repair of grade 3 hernias performed with
component separation and biologic mesh reinforcement was effective and offered a low recurrence rate. Furthermore, the use of biologic mesh allows for avoidance of mesh explantation in instances of wound breakdown or infection. Bridging repairs were associated with a high recurrence rate, as is single-stage repair of grade 4 hernias.

Romain et al (2016) noted that different types of biologic mesh have been introduced as an alternative to synthetic mesh for use in repairing contaminated ventral hernias because of their biocompatible nature. These researchers compared the clinical outcomes of patients who underwent complex ventral hernia repairs with either non cross-linked or cross-linked porcine dermal meshes. This was retrospective analysis from a prospectively maintained database from January 2010 to May 2013. Patients undergoing open incisional hernia repair with a biologic mesh in the presence of a clean-contaminated, contaminated or dirty wound were reviewed. There were 39 patients who underwent single-staged abdominal wall reconstruction for a contaminated ventral hernia with a biologic mesh. In 15 cases, non-crosslinked mesh was used (Strattice, n = 8; Protexa, n = 1; XenMatrix, n = 6); a cross-linked mesh was used in the remaining 24 cases (Permacol n = 21; CollaMend n = 3). The median follow-up was 11.9 ± 10.6 months. The overall morbidity was 71.8 % (n = 28), with 15.4 % (n = 6) for grade I, 23.1 % (n = 9) for grade II, 23.1 % (n = 9) for grade III (n = 3 grade IIIA, n = 6 grade IIIB), 7.7 % (n = 3) for grade IV and 2.6 % (n = 1) for grade V. In the cross-linked group, there were 6 complications directly linked to the biologic mesh, compared with 3 in the non-cross-linked group. Overall wound morbidity was 41.0 % (n = 16). There were 13 hernia recurrences (33.3 %), and recurrence rate was not significantly different for both groups. The authors concluded that despite the high rate of wound morbidity associated with the single-staged reconstruction of contaminated fields, it could be safely performed with biologic mesh reinforcement. Recurrence rate was not significantly different between cross-linked and non-crosslinked porcine meshes.

Giordano et al (2017a) noted that previous studies suggested that bridged mesh repair for abdominal wall reconstruction may result in worse outcomes than mesh-reinforced, primary fascial closure, particularly when ADM was used. In a retrospective study, these researchers compared their outcomes of bridged versus reinforced repair using ADM in abdominal wall reconstruction procedures. This trial included 535 consecutive patients at the authors’ cancer center who underwent abdominal wall reconstruction either for an incisional hernia or for abdominal wall defects left after excision of malignancies involving the abdominal wall with underlay mesh. A total of 484 (90 %) patients underwent mesh-reinforced abdominal wall reconstruction and 51 (10 %) underwent bridged repair abdominal wall reconstruction; ADM was used, respectively, in 98 % of bridged and 96 % of reinforced repairs. These investigators compared outcomes between these 2 groups using propensity score analysis for risk-adjustment in multi-variate analysis and for 1-to-1
matching. Bridged repairs had a greater hernia recurrence rate (33.3 % versus 6.2 %, \( p < 0.001 \)), a greater overall complication rate (59 % versus 30 %, \( p = 0.001 \)), and worse freedom from hernia recurrence (log-rank \( p < 0.001 \)) than reinforced repairs. Bridged repairs also had a greater rate of wound dehiscence (26 % versus 14 %, \( p = 0.034 \)) and mesh exposure (10 % versus 1 %, \( p = 0.003 \)) than mesh-reinforced abdominal wall reconstruction. When the treatment method was adjusted for propensity score in the propensity-score-matched pairs (\( n = 100 \)), these researchers found that the rates of hernia recurrence (32 % versus 6 %, \( p = 0.002 \)), overall complications (32 % versus 6 %, \( p = 0.002 \)), and freedom from hernia recurrence (68 % versus 32 %, \( p = 0.001 \)) rates were worse after bridged repair. They did not observe differences in wound healing and mesh complications between the 2 groups. The authors concluded that in their population of primarily cancer patients at MD Anderson Cancer Center bridged repair for abdominal wall reconstruction was associated with worse outcomes than mesh-reinforced abdominal wall reconstruction; especially when employing ADM, reinforced repairs with biologic mesh should be used for abdominal wall reconstruction whenever possible.

Giordano et al (2017b) hypothesized that elderly patients (greater than or equal to 65 years) experience worse outcomes following AWR for hernia or oncologic resection. These researchers included all consecutive patients who underwent complex AWR using ADM between 2005 and 2015. Propensity score analysis was performed for risk adjustment in multi-variable analysis and for 1-to-1 matching. The primary outcome was hernia recurrence; the secondary outcomes included surgical site occurrence (SSO) and bulging. Mean follow-up for the 511 patients was 31.4 months; 184 (36 %) patients were elderly. The elderly and non-elderly groups had similar rates of hernia recurrence (7.6 % versus 10.1 %, respectively; \( p = 0.43 \)) and SSO (24.5 % versus 23.5 %, respectively; \( p = 0.82 \)). Bulging occurred significantly more often in elderly patients (6.5 % versus 2.8 %, respectively; \( p = 0.04 \)). After adjustment through the propensity score, which included 130 pairs, these results persisted. The authors concluded that contrary to their hypothesis, elderly patients did not have worse outcomes in AWR with ADM; and surgeons should not deny elderly patients AWR solely because of their age.

Garvey et al (2017) stated that long-term outcomes data for hernia recurrence rates after AWR with ADM are lacking. These investigators evaluated the long-term durability of AWR using ADM. They studied patients who underwent AWR with ADM at a single center in 2005 to 2015 with a minimum follow-up of 36 months. Hernia recurrence was the primary end-point and SSO was a secondary end-point. The recurrence-free survival curves were estimated by Kaplan-Meier product limit method. Uni-variate and multi-variable Cox proportional hazards regression models and logistic regression models were used to evaluate the associations of risk factors at surgery with subsequent risks for
hernia recurrence and SSO, respectively. A total of 512 patients underwent AWR with ADM. After excluding those with follow-up less than 36 months, 191 patients were included, with a median follow-up of 52.9 months (range of 36 to 104 months); 26 of 191 patients had a hernia recurrence documented in the study. The cumulative recurrence rates were 11.5 % at 3 years and 14.6 % by 5 years. Factors significantly predictive of hernia recurrence developing included bridged repair, wound skin dehiscence, use of human cadaveric ADM, and coronary disease; component separation was protective. In a subset analysis excluding bridged repairs and human cadaveric ADM patients, cumulative hernia recurrence rates were 6.4 % by 3 years and 8.3 % by 5 years. The crude rate of SSO was 25.1 % (48 of 191). Factors significantly predictive of the incidence of SSO included at least 1 co-morbidity, BMI greater than or equal to 30 kg/m2, and defect width of greater than 15 cm. The authors concluded that the use of ADM for AWR was associated with 11.5 % and 14.6 % hernia recurrence rates at 3- and 5-years follow-up, respectively; a voiding bridged repairs and human cadaveric ADM could improve long-term AWR outcomes using ADM.

Mercli et al (2017) stated that the optimal strategy for AWR in the presence of a stomal-site hernia is unclear. These investigators hypothesized that the rate of ventral hernia recurrence in patients undergoing a combined ventral hernia repair and stomal-site herniorrhaphy would not differ clinically from the ventral hernia recurrence rate in patients undergoing an isolated ventral hernia repair. They also hypothesized that bridged ventral hernia repairs result in worse outcomes compared with reinforced repairs, regardless of stomal hernia. These researchers retrospectively reviewed prospectively collected data from consecutive AWR performed with ADM at a single center between 2000 and 2015. They compared patients who underwent a ventral hernia repair alone (AWR) and those who underwent both a ventral hernia repair and ostomy-associated herniorrhaphy (AWR+O). These investigators conducted a propensity score matched analysis to compare the outcomes between the 2 groups. Multi-variable Cox proportional hazards and logistic regression models were used to study associations between potential predictive or protective reconstructive strategies and surgical outcomes. The authors included 499 patients (median follow-up of 27.2 months; inter-quartile range [IQR] 12.4 to 46.6 months), 118 AWR+O and 381 AWR. After propensity score matching, 91 pairs were obtained. Ventral hernia recurrence was not statistically associated with ostomy-associated herniorrhaphy (adjusted HR 0.7; 95 % CI: 0.3 to 1.5; p = 0.34). However, the AWR+O group experienced a significantly higher percentage of SSO (34.1 %) than the AWR group (18.7 %; adjusted odds ratio [OR] 2.3; 95 % CI: 1.4 to 3.7; p < 0.001). In the AWR group, there were significantly fewer ventral hernia recurrences when the repair was reinforced compared with bridged (5.3 % versus 38.5 %; p < 0.001). The authors
concluded that there was no statistically significant difference in ventral hernia recurrence between the AWR and AWR+O groups' bridging was associated with an increased rate of hernia recurrence and should be avoided if possible.

**AmnioArmor**

AmnioArmor (Bone Bank Allografts, a subsidiary of Globus Medical, Inc.) is a dehydrated human amniotic membrane allograft derived from placental tissue submucosa. It is intended for topical application as a wound covering for acute and chronic wounds. It contains dual collagen layers and growth factors including epidermal growth factor, (EFG) basic fibroblast growth factor (BFGF), keratinocyte growth factor (KGF), vascular endothelial growth factor (VEGF), transforming growth factors (TGFs), nerve growth factor (NGF), and many chemokines/cytokines. There are no peer-reviewed published studies evaluating the safety and efficacy of AminoArmor. Once applied to the surgical site, AmnioArmor can be hydrated with sterile saline or other sterile solution, if needed. Suture material or tissue adhesives may be used to apply the graft to the surgical site. AmnioArmor is available in several sizes for optimal coverage and placement, including 1 cm x 1 cm, 2 cm x 2 cm, 2 cm x 3 cm, 4 cm x 4 cm, 4 cm x 6 cm, 4 cm x 8 cm, and 16 mm diameter.

**AmnyoFluid**

AmnyoFluid is a natural amniotic fluid product acquired through fluid donation at the time of a normal full-term cesarean section. All donors are screened and tested to meet FDA standards for tissue donations. The amniotic fluid is filtered and a cryo-preservative agent is added to stabilize fluid for safe storage and use.

Riboh et al (2016) stated that AM-derived products have been successfully used in ophthalmology, plastic surgery, and wound care, but little is known about their potential applications in orthopedic sports medicine. These researchers provided an updated review of the basic science and pre-clinical and clinical data supporting the use of AM-derived products and reviewed their current applications in sports medicine. A systematic search of the literature was conducted using the Medline, Embase, and Cochrane databases. The search term amniotic membrane was used alone and in conjunction with stem cell, orthopedic, tissue engineering, scaffold, and sports medicine. The search identified 6,870 articles, 80 of which, after screening of the titles and abstracts, were considered relevant to this study; 55 articles described the anatomy, basic science, and non-orthopedic applications of AM-derived products; 25 articles described pre-clinical and clinical trials of AM-derived products for orthopedic sports medicine. Because the level of evidence obtained from this search was not adequate for systematic review or meta-analysis, a current concepts review on the anatomy,
physiology, and clinical uses of AM-derived products was presented. The authors concluded that AM have many promising applications in sports medicine. They are a source of pluripotent cells, highly organized collagen, anti-fibrotic and anti-inflammatory cytokines, immuno-modulators, and matrix proteins. These properties may make it beneficial when applied as tissue engineering scaffolds, improving tissue organization in healing, and treatment of the arthritic joint. The current body of evidence in sports medicine is heavily biased on in-vitro and animal studies, with little to no human clinical data. Nonetheless, 14 companies or distributors offer commercial AM products. The preparation and formulation of these products alter their biological and mechanical properties, and a thorough understanding of these differences will help guide the use of AM-derived products in sports medicine research.

Muttini et al (2018) reported a study of amniotic epithelial cells, which form the innermost layer of the AM. These cells can be easily isolated and display peculiar and unique properties, such as plasticity and differentiation potential toward the 3 germinal layers, that may aid regeneration and/or repair of damaged or diseased tissues and organs. A robust literature based on in-vitro, experimental, and clinical studies in large animals demonstrated that these cells can enhance the regeneration of tendons, bone, and articular cartilage. The authors stated that on the basis of these considerations, allo-transplantation of human amniotic epithelial cells could be proposed for clinical trials in human orthopedic conditions.

Sultan et al (2018) evaluated the use of placental and amniotic tissue-based products as an adjuvant treatment to the operative management of orthopedic sports injuries. A comprehensive literature search was performed on PubMed, EBSCO Host, Embase, and SCOPUS. Studies published between January 1, 2000 and June 1, 2018 were reviewed. Inclusion criteria were that studies should have reported on: (i) operative uses of placental tissue matrix therapy in tendons and ligaments injuries; (ii) clinical outcomes; and (iii) human subjects. In addition, the following studies were excluded: (i) animal studies; (ii) basic science studies; (iii) non-English language studies; (iv) review studies; and (v) duplicate studies across databases. Additionally, to determine the various product compositions and indications for use, these investigators searched publicly available manufacturer’s website content, marketing literature, FDA registration documents, and Center for Medicare and Medicaid Services (CMS) submissions to assess the key differences for each of the products. Current evidence has led to investigation of various placental and AM products used as an adjuvant treatment to surgical reconstruction of various types of tendon injuries, with a demonstrated effectiveness found mostly in the short-term, with follow-up ranging between 5 weeks and 2 years. In addition, their safety and minimal complication profile have been demonstrated. Marked differences exist among the currently available products due to
variations in their formulations, tissue source, processing methodology, sterilization method, preservation and storage methods, indications for use, and FDA regulation. The authors concluded that operative uses of placental and AM-derived tissues appeared to be safe when utilized as an adjuvant or augmentation option along with surgical reconstruction. However, several factors may come into play when considering the diversity of commercially available products. These researchers stated that future clinical trials are needed to confirm the safety and demonstrate clearer indications and specific guidelines for use in each clinical scenario involving operative management of tendon injuries.

Duerr et al (2019) stated that in orthopedic sports medicine, amniotic-derived products have demonstrated promising pre-clinical and early clinical results for the treatment of tendon/ligament injuries, cartilage defects, and OA. The AM is a metabolically active tissue that has demonstrated anti-inflammatory, antimicrobial, anti-fibrotic, and epithelialization-promoting features that make it uniquely suited for several clinical applications. The authors stated that although the existing clinical literature is limited, there are several ongoing clinical trials aiming to elucidate the specific applications and benefits of these products.

Hannon et al (2019) noted that the use of intra-articular therapies as sources of growth factors, anti-inflammatory mediators, and medicinal signaling cells for osteo-arthritis (OA) is rapidly evolving. Amnion, chorion, amniotic fluid, and the umbilical cord are distinct placental tissues that have been investigated for use in OA. Amniotic membrane (AM) synthesizes a variety of growth factors, cytokines, and vasoactive peptides that modulate inflammation. In addition, they contain amniotic epithelial cells and amniotic mononuclear undifferentiated stromal cells, which have chondrogenic and osteogenic differentiation capacity. AMs are also rich sources of hyaluronic acid and proteoglycans, which could play a role in the potential therapeutic relief of OA. Currently, there are several commercially available formulations of AM that differ based on content as well as how they were preserved. Understanding the processing of amniotic tissue is important because of their distinct mechanical and biologic effects of preservation on AM grafts. To-date, there have been 2 pre-clinical and only 1 clinical study on the use of AM for OA, which showed promising results. The authors concluded that many high level of evidence clinical trials are currently underway investigating the use of AM of OA. They stated that future basic science and clinical research is needed to better understand the anti-inflammatory and chondro-regenerative properties of amniotic tissue and to determine clinically what amniotic tissue product is most effective for symptomatic OA.

Cellesta Amniotic Membrane

Cellesta Amniotic Membrane (Ventris Medical, LLC) is a minimally manipulated, single-layered, amniotic membrane allograft which is affixed to a poly mesh backing which can be sutured, glued, or laid over tissue. It is intended for homologous use only, and is available in various sizes in dry or hydrated forms. Cellesta Amniotic Membrane is primarily used as a biological covering or protective barrier in reconstructive procedures, such as for chronic wound healing. There are no peer-reviewed published studies evaluating the safety and efficacy of Cellesta.

Cellesta™ Flowable Amnion

Cellesta™ Flowable Amnion (Ventris Medical, LLC) is a minimally manipulated chorion-free, human amniotic membrane, suspended in a saline solution, intended for use as a regenerative wound filler for the treatment of acute, chronic and surgically-created wounds. It is available as a pre-filled syringe for direct application (not for injection) for homologous use only. It is specifically designed for treatment of deep dermal wounds, irregularly-shaped crevassing and tunneling wounds, augmentation of deficient/inadequate soft tissue, and other complex wound cases where a patch form of amniotic membrane may not provide complete wound coverage. There are no peer-reviewed published studies evaluating the safety and efficacy of Cellesta.

Coll-e-Derm

Coll-e-Derm (Parametrics Medical) is a dermal allograft derived from human dermal tissue. It is intended to support wound and burn healing for wounds that have not healed with conventional treatment. The product is applied by placing over a wound, which may be sutured when warranted. It is indicated for replacement of damaged homologous tissue, repair of soft tissue defects, breast reconstruction, abdominal wall repair, soft tissue augmentation, tendon augmentation, and tendon lengthening. There are no peer-reviewed published studies evaluating the safety and efficacy of Coll-e-Derm.

Derma-Gide

Derma-Gide (Geistlich Pharma North America, Princeton, NJ) was previously called Geistlich wound matrix. The manufacturer added additional smaller rectangular sizes and new round shapes and changed the name to Derma-Gide. Derma-Gide is intended to be used for the management of wounds including: partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic venous ulcers, surgical wounds and trauma skin wounds. Derma-Gide is a porcine, porous and resorbable 3D collagen matrix, that is derived from non-crosslinked, porcine (skin and connective)
tissue. The manufacturer states that the product consists of Types I and III collagen that have been specifically processed to support angiogenesis. Angiogenesis is vital to successful wound healing and in the formation of granulation tissue in the wound bed.

Genesis Amniotic Membrane

Genesis Amniotic Membrane (Genesis Biologics, Inc., Anaheim, CA) is a dehydrated, collagenous human tissue allograft used for the treatment of acute and chronic wounds, soft tissue injuries, and infection prevention. The placental product contains collagen, cytokines, and growth factors that aid in wound healing and reduced scarring. According to the manufacturer, the Genesis Amniotic Membrane is indicated for use for diabetic patients experiencing issues with wound healing. It is also indicated for patients who have undergone surgical reconstructions and other complex operative procedures. The product is applied in a manner that prevents displacement over the open wound. There is no need for any suturing or adhesions upon application.

Grafix Cryo-Preserved Placental Membrane

Lavery et al (2018) reported the results of the single-arm, open-label extension phase of the Grafix (cryo-preserved placental membrane; CPM; Osiris Therapeutics, Inc., Columbia, MD) multi-center, blinded, randomized, controlled clinical trial for chronic diabetic foot ulcers (DFUs). A total of 26 patients in the standard wound care (SWC) arm whose DFUs did not close in the blinded phase chose to receive weekly applications of the CPM in an open-label extension phase. In the extension phase, 17 (65.4 %) patients closed their wounds in a median of 34 days and 3 visits. There were fewer total adverse events (AEs) (24 CPM versus 52 SWC) and index wound-related infections (5 CPM versus 12 SWC) during the CPM application compared with the number of AEs for the same patients during the SWC treatment in the blinded phase of the trial. The authors concluded that these findings corroborated the benefits of this CPM combined with SWC over SWC alone for chronic DFUs previously reported for the blinded randomized phase of the trial, which directly related to lower health care costs.

The authors stated that although the use of a 3rd party for blinded assessment of wound closure reduced bias of the open-label phase of the trial, bias inherently could not be eliminated from these types of studies. This bias was due to knowledge of the treatment assignment that may influence the behavior of patients. The small sample size (n = 26) was an additional limitation of this study. Selection bias was always an issue in RCTs. There were strict inclusion and exclusion criteria that did not necessarily reflect the general population of patients with DFUs.
In a prospective, multi-center, single-blind study, Ananian et al (2018) analyzed clinical outcomes and product cost between a viable cryo-preserved placental membrane (vCPM) and a human fibroblast-derived dermal substitute (hFDS) for the treatment of chronic DFUs. The outcomes of 62 patients were analyzed: 31 patients in the vCPM treatment group and 31 patients in the hFDS treatment group. Utilizing a non-inferiority trial design and the established treatment regimen of 8 applications for hFDS, these researchers demonstrated that vCPM was not inferior to hFDS for the proportion of patients achieving complete wound closure (9.68, 90 % CI: 10.67 to 28.94%). However, preliminary findings showed that vCPM may have better outcomes for wounds of less than or equal to 5 cm²: 81.3 % (13/16) of wounds in the vCPM group versus 37.5 % (6/16) of wounds in the hFDS group reached complete closure at the end of treatment (p = 0.0118). A preliminary product cost analysis for wounds less than or equal to 5 cm² may showed significant savings for patients treated with vCPM. Average per-patient costs during the course of treatment were $3,846 and $7,968 (p < 0.0001) for vCPM and hFDS patients, respectively. The authors concluded that these findings may be used as guidance to wound care providers and payers.

The authors stated that the main drawbacks of this study included wound closure assessment after 8 weekly applications, which was not common in clinical studies for DFUs, and the lack of a follow-up period after the treatment phase of the trial. In addition, the imbalance of the number of plantar wounds and chronicity of DFUs between the 2 groups could have negatively impacted clinical outcomes recorded for the vCPM treatment group. Although the sample size was sufficient to meet the primary end-point, it was not large enough to make definitive conclusions about analyses performed for wounds less than or equal to 5 cm². These researchers stated that these are interesting data findings and future studies are needed to confirm these preliminary results. Furthermore, the single-blind design of the study, the lack of stratification by wound location and size for analyses, as well as the lack of specificity regarding wound location, were also recognized as limitations. These investigators stated that as placental membrane products become more widespread in the wound care space, future comparative analyses using other placental products will provide valuable data for health care providers and payers.

Raspovic et al (2018) evaluated the effectiveness of vCPM for DFU management using Net Health's WoundExpert electronic health records (EHR). The primary end-point was the proportion of DFUs that achieved complete closure. Other end-points included time and number of grafts to closure, probability of wound closure by week 12, and the number of wound-related infections and amputations. De-identified EHR data for 360 patients with 441 wounds treated with vCPM were extracted from the database. Average patient age was 63.7 years with a mean wound size of 5.1 cm² and an average wound
duration of 102 days prior to vCPM treatment. For evaluation of clinical outcomes, 350 DFUs larger than 0.25 cm² at baseline were analyzed. Closure at the end of treatment was achieved in 59.4 % of wounds with a median treatment duration of 42.0 days and 4 applications of vCPM. The probability of wound closure at week 12 was 71 %, and the number of amputations and wound-related infections was 13 (3.0 %) and 9 (2.0 %), respectively. Data also showed a correlation between wound size and closure rate as well as a correlation between greater 50 % wound area reduction by week 4 and wound closure by week 12. The authors concluded that the results of this study mirrored previous RCT efficacy data, supporting the benefits of vCPM for DFU management.

The authors stated that the most obvious drawback was the retrospective nature and absence of a control cohort in this trial, which relied on a large database. Also, the lack of a standardized treatment algorithm and treatment selection bias were known drawbacks of observational studies. The data obtained were only as good as the data recorded, thus potentially introducing measurement error. Measurement error occurred when any measurement about a subject was not accurate. The methods and tools used to measure wounds, define infection, or define “healing” may be systematically different among the centers that participated in the study. Selection bias was also a possibility since patients in this cohort were more likely to have insurance or the resources that could pay for this therapy or adjunctive therapies that made advanced wound care product more effective. Furthermore, these researchers stated that this study also outlined the importance of future studies to validate 50 % wound area reduction as a predictive surrogate marker of closure for vCPM and other advanced wound care modalities.

In a prospective, single-center, open-label, single-arm study, Farivar et al (2018) compared the efficacy of a human viable wound matrix (hVWM) of cryo-preserved placental tissue for the treatment of refractory chronic venous leg ulcers (VLUs) with standard therapy. This trial enrolled patients with Clinical, Etiology, Anatomy, and Pathophysiology clinical class C6 VLUs. The ulcers of all enrolled patients had failed to heal after a trial of standard therapy of at least 12 weeks, which included weekly multi-layer compression therapy along with local wound care. The same patients subsequently received application of hVWM (Grafix) every 1 to 2 weeks in addition to standard therapy. Healing with hVWM therapy was then compared with standard therapy, with each patient serving as his own control. There were 30 VLUs in 21 consecutive eligible patients who were enrolled in the study. All patients were men with an average age of 67 years (standard deviation [SD], ± 10.8 years), and the average area of venous ulcers before hVWM initiation was 12.2 cm² (SD, ± 14.6 cm²; range of 3.3 to 12.3 cm²). Duplex ultrasound (US) confirmed superficial or deep system venous reflux in all patients. Complete ulcer healing was achieved in 53 % (16/30) of VLUs refractory to standard
therapy after application of hVWM. There was a mean reduction in wound surface area by 79 % (SD, ± 27.3 %; p < 0.001 compared with standard therapy) after a mean treatment time of 10.9 weeks; 80 % of VLUs were reduced in size by half compared with 25 % with standard therapy (p < 0.001). The mean rate of reduction in ulcer area after hVWM applications was 1.69 % per day versus 0.73 % per day with standard therapy (p = 0.01). The authors concluded that cryo-preserved placental tissue (hVWM) improved healing processes to achieve complete wound closure in a significant proportion of chronic VLUs refractory to standard therapy; adjunctive therapy with hVWM provided superior healing rates in refractory VLUs.

This was a small (n = 21), single-center, open-label, single-arm study with relatively short follow-up (mean of 10.9 weeks). Moreover, the authors noted that relative wound surface area reduction per day was statistically significant, whereas absolute surface area reduction per day was not. This perhaps was indicative of the fact that hVWM therapy may be more beneficial in closure of smaller wounds compared with larger ones even though baseline wound size at initiation of each therapy did not differ significantly. However, it was difficult to examine this for certain because of the sample size studied; larger randomized trials are needed for further analysis. These researchers did not perform a comparative cost-benefit analysis in this small study; in the future, this information will facilitate decision-making on the overall benefit of this treatment modality. The study could not rule out that some ulcers may have healed with standard therapy. Importantly, though, the wound healing rate during standard therapy was significantly slower than during hVWM therapy, and wounds with greater than or equal to 50 % wound area reduction were significantly higher with hVWM treatment too. These 3 end-points together showed the same directionality and indicated an overall better and more rapid wound healing response to hVWM. These investigators stated that larger studies are needed to confirm these preliminary findings.

Keroxx Flowable Wound Matrix

Keroxx Flowable Wound Matrix (Molecular Biologicals, Inc., San Antonio, TX) is an injectable version of the single-use matrix sheet Keramatrix. Keroxx Flowable Wound Matrix is a wound matrix comprised of keratin enriched proteins containing the active ingredient Replicine Functional Keratins which are biologically active proteins extracted using proprietary processes where the inherent alpha-helical structure of the keratin molecule remains intact. These keratin proteins are extracted from sheep wool and are placed in an open celled injectable gel format. When Keroxx is injected, the Replicine Functional Keratins are absorbed into the developing tissues in the wound and provide a biocompatible matrix or scaffold for cellular proliferation, migration and capillary growth to aid in the growth of new tissue. The Replicine Functional Keratins have been shown to activate keratinocyte cells present in the wound and stimulate them to quickly enter a


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hyperproliferative phase essential for wound healing. Keroxx flowable is used to treat patients with chronic wounds such as pressure ulcers, diabetic ulcers, donor sites and grafts.

Matrion

Matrion (LifeNet Health, Virginia Beach, VA) is a regenerative human placental allograft procured and processed from donated human tissue. Matrion is a matrix scaffold derived from an intact decellularized placental membrane comprising both amniotic and chorionic layers. The resulting decellularized placental membrane is available in membrane, injectable, and sponge configurations for use in wound, tendon, and nerve applications. Decellularized placental membrane modulates inflammation in the surgical site, enhances healing, and acts as a barrier. Matrion is supplied as a decellularized placental allograft and is freeze-dried and stored at ambient room temperature.

Novachor

Novachor (Organogenesis, Inc., Canton, MA) is comprised of the chorion layer of the placental membranes. This membrane is known to contain 1) collagen types I, III, V, VI laminin, fibronectin and proteoglycans; 2) trophic proteins; 3) growth factors; 4) Tissue Inhibitors of Matrix Metallo-proteinases (TIMPs); and 5) pluri-potential cells. It is intended to be applied as a graft for acute and chronic wounds, including but not limited to, neuropathic ulcers, venous stasis ulcers, pressure ulcers, burns, post-traumatic wounds and post-surgical wounds. It is administered by applying the product to a wound using sutures or other fixation method. The product provides a physical covering which protects the wound and supports endogenous healing.

Restorigin Amnion Patch

Restorigin Amnion Patch (Parametrics Medical) is derived from the amnion layer of fetal membranes in the umbilical cord. It is intended to provide a protective barrier while providing a regenerative tissue matrix with anti-inflammatory, anti-scarring and anti-microbial properties to facilitate healing of chronic, non-healing wounds and burns. There are no peer-reviewed published studies evaluating the safety and efficacy of Restorigin.

Restorigin Amniotic Fluid Therapy (AFT)

Restorigin Amniotic Fluid Therapy (AFT) (Parametrics Medical) is an amniotic fluid product that is derived from donated human birth tissue and fluid. It is intended for the protection and treatment of non-healing wounds and burn injuries. Restorigin amniotic
fluid contains collagen substrates, growth factors, and cytokines (not an all-inclusive list). There are no peer-reviewed published studies evaluating the safety and efficacy of Restorigin.

**SkinTE**

SkinTE (PolarityTE, Inc., Salt Lake City, UT) is a fully autologous, homologous product for the repair, reconstruction, replacement, supplementation and regeneration of defects or functional losses of the skin of human patients. SkinTE is manufactured from a harvested sample of the patient’s full-thickness skin, composed of viable skin cells and an organized extracellular matrix, with no additional cell or tissue source from another human (allogeneic) or (xenogeneic). Following application to a wound bed, the product functions to regenerate full-thickness functional skin across the entire surface, including all layers (epidermis, dermis, hypodermis), and regenerate functional appendages native to skin. The product is intended to be used by physicians for homologous uses of the skin and integumentary system. The product is appropriate from treatment of acute burns requiring excision, grafting, and chronic wounds. Patients with functional loss of skin due to scarring may also be appropriate for treatment with SkinTE. The manufacturer states that SkinTE is patient and case specific, intended for autologous use, and single application only. The dosage of SkinTE corresponds to the surface area of the wound being treated in square centimeters.

**surgiGRAFT**

surgiGraft (Synergy Biologics) is a minimally manipulated human amnion-only regenerative extracellular tissue matrix derived from human placental tissue (amniotic tissue) which has been processed into an allograft. The allograft is intended for reconstruction, repair, or replacement of donor recipient tissue in the following conditions: neuropathic ulcers, venous stasis ulcers, post-traumatic wounds, pre- and post- surgical wounds and pressure ulcers, diabetic wounds, burn wounds, scar tissue, scarring, and adhesion barrier up to and including nerve bundle and peripheral wrap as a wound covering. surgiGraft serves to act as a tissue barrier/covering or to provide lubrication. It is offered in both dry and hydrated forms. surgiGraft is administered by placing the stromal side onto the external wound area followed by the clinician’s standard closing procedures. There are no peer-reviewed published studies evaluating the safety and efficacy of surgiGraft.

**Keracis Omega3 (formerly Marigen)**

Kerecis Omega3 is an extracellular matrix (ECM) xenograft made from fish (piscine) dermis designed for transplant into damaged tissue such as chronic wounds (CMS, 2017). Keresis Omega3 contains natural insoluble proteins such as collagen and proteoglycans, glycosaminoglycans, and fibronectin. Kerecis Omega3 Wound ECM also contains growth factors such as IGF-1 and TGFβ2. According to the manufacturer, Kerecis Omega3 acellular fish skins refocus the healing process of the tissue damage. The skin acts as a scaffold for revascularization and repopulation of the patient's cells, which are under attack from matrix metalloproteinases (MMPs) in the inflamed wound. It is used as a wound covering and wound matrix for full thickness wounds and burns as a covering for damaged membranes. Omega 3 is supplied in a sealed, sterilized package in the following sizes: 3 X 3.5cm (10 per package); 3 X 7 cm (10 per package); and 7 X 10cm (10 per package). The product is shipped freeze dried and must be rehydrated before it is applied.

**AxioBioMembrane**

According to the manufacturer, AxoBioMembrane (Axoloti Biologix, Inc.) is indicated for full and partial-thickness, chronic, acute, wounds and hard to heal wounds (CMS, 2019). After preparation of the wound site, the human amnion allograft is surgically applied to the wound surface by the physician, extended beyond the wound margin and secured in place using the clinician's choice of fixation. AxoBioMembrane is available in 3 sizes; 1cm x 2cm, 2cm x 3cm, and 4cm x 4cm.

**Axoloti Graft and Axoloti DualGraft**

According to the manufacturer Axoloti Biologix, Inc., Axoloti Graft and Axoloti DualGraft are "human amniotic allograft, decellularized, dehydrated placental membrane used as a wound barrier, nerve wrap, and serves as a selective membrane to allow for the repair or regeneration of damaged or diseased tissues" (CMS, 2019). Axoloti DualGraft is a thicker version of the allograft for wound areas that are more vulnerable to damage. The product is available in four sizes; 1 x 2cm, 2 x 3cm, 4 x 4cm, and 4 x 6cm.

**Axoloti Ambient and Axoloti Cryo**

According to the manufacturer, Axoloti Biologix, INc., Axoloti Ambient and Axoloti Cryo are intended for homologous use and to support the repair of soft tissue injury (CMS, 2019). The products are applied to the wound surface and/or injected into the wound margins. The products are available in 0.5 ml, 1 ml, and 2 ml dose sizes.

**SurgiCORD**

According to the manufacturer, Synergy Biologics, LLC., indication for use of SurgiCORD, a human umbilical tissue membrane allograft, is "intended neuropathic ulcers, venous stasis ulcers, post-traumatic and pressure ulcers" (CMS, 2019). "The minimally-processed allograft contains collagen types IV, V, and VII that will promote cellular differentiation and wound healing". SurgiCORD is applied topically to chronic, non-healing wounds. It is available in sizes: 1.5 x 1.5 cm, 3 x 2 cm, 3 x 4 cm and 3 x 6 cm.

**SurgiGRAFT-DUAL**

According to Synergy Biologics, LLC., SurgiGRAFT-DUAL is a bilayer human amniotic tissue allograft intended for use to repair or replace dermal tissue, including in the treatment of chronic, non-healing wounds including neuropathic ulcers, post-traumatic and pressure ulcers (CMS, 2019). The minimally-processed bilayer allograft contains collagen types IV, V, and VII that will promote cellular differentiation and wound healing. SurgiGRAFT-DUAL is applied topically to chronic, non-healing wounds. It is available in sizes 2 x 2 cm, 2 x 3 cm, 2 x 4 cm, 2 x 8 CM, 4 x 4 cm; and 12 mm, 15 mm and 18 mm diameter rounds.

**Novafix**

Novafix (DCI Donor Services, Inc.) is indicated for use in the management of wounds, including: partial and full thickness wounds, pressure sores/ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (e.g., donor sites, post-laser surgery, post-Mohs surgery, podiatric wounds and wound dehiscence), trauma wounds (abrasions, lacerations, partial thickness burns, skin tears), and draining wounds. Apply Novafix into the wound bed, and position as needed to completely contact the entire surface of the wound bed and extend slightly beyond wound margins. As medically necessary, Novafix can be secured to the wound site with the physician's preferred fixation method based on the type of wound, location of wound, patient's mobility and patient compliance. Novafix is supplied in sizes: 15mm disc, 2cm x 2cm, 4cm x 4cm, and 5cm x 5cm.

**SurGraft**

According to the manufacturer, Surgenex, LLC., SurGraft is a dehydrated human amniotic membrane allograft "intended for the treatment of non-healing wounds and burn injuries" (CMS, 2019). "SurGraft is directed for use in patients with acute or chronic wounds, including but not limited to, chronic, non-infected, diabetic foot ulcers, chronic, non-infected, partial or full-thickness diabetic foot skin ulcers (due to venous insufficiency), pressure ulcer, surgical wounds and burns which have not adequately
responded to conventional therapy." The manufacturer also stated that "SurGraft is minimally manipulated Human Cell Tissue Product (HCT/P) intended for homologous use." Surgraft is supplied in five sizes: 2 x 2 cm, 2 x 3, 2 x 4 cm and 4 x 8 cm.

AmnioWrap2

According to RegenTX Partners, LLC., AmnioWrap2 is an amniotic/chorionic tissue allograft intended for the treatment of wounds, including lower extremity ulceration caused by diabetes, chronic venous disease, and other chronic conditions (CMS, 2019). Acute wounds involving the dermal tissue layer may be appropriate for treatment with AmnioWrap2. AmnioWrap2 is provided dry in a double foil sterile pouch. It is available in various sizes, from 1 x 1 cm to 10 x 12 cm.

Membrane Graft and Membrane Wrap

Membrane Graft and Membrane Wrap (BioLab Sciences, Inc.) are human amniotic allograft membranes used to repair tissue deficits and to reduce healing time for chronic wounds and post-surgical wounds. "The patient population for use of the products includes children and adults suffering from non-healing acute and chronic wounds (diabetic, venous, mixed, venous-arterial, pressure ulcers), complex and/or open surgical wounds and burns." The product is available in six sizes: 1 x 1cm, 1 x 2cm, 2 x 3cm, 4 x 4cm, 4 x 6cm, and 4 x 8cm.

Fluid Flow and Fluid GF

Fluid Flow and Fluid GF (BioLab Sciences, Inc.) are human amniotic flowable allografts intended for homologous use and support the repair of soft tissue injury by providing natural growth factors and other extracellular components to the injured area to promote healing, reduce inflammation, and reduce healing time (CMS, 2019). "The patient population indicated for use of Fluid Flow and Fluid GF include acute and chronic wounds and soft tissue injury, muscle and meniscus tears, ligament and tendon sprains, degenerative tissue disorders and Inflammatory conditions (tendonitis and fasciitis)." The products are available in 0.5cc, 1cc and 2cc sizes.

MyOwnSkin

MyOwn Skin, from BioLab Sciences, Inc., is a fully autologous, homologous skin product that is manufactured from a harvested sample of the patients' partial-thickness skin, and is composed of viable skin cells and an organized extracellular matrix (CMS, 2019). MyOwn Skin is composed of a patient's own viable skin cells and contains extracellular matrix components to support cellular attachment and proliferation for tissue and skin
repair. It is used to repair tissue deficits and to reduce healing time for chronic wounds and post-surgical wounds, with minimal to no rejection. The product is available in a variety of sizes, ranging from 1 cm x 1 cm to 10 cm x 10 cm.

Cellesta Cord

According to the manufacturer, Ventris Medical, LLC., Cellesta Cord is an umbilical cord allograft product intended for use as a regenerative wound covering for the treatment of acute, chronic and surgically created wounds. Cellesta Cord can be sutured, or glued, or laid over the desired tissue. It is available in 8 sizes: 3 circular and 5 rectangular: 12 mm, 15 mm, 18 mm, 1.5 x 1.5 cm, 3 x 2 cm, 3 x 4 cm, 3 x 6 cm, and 3 x 8 cm.

Cellesta Duo

Cellesta Duo (Ventris Medical, LLC.), is a dual human amniotic membrane allograft. Cellesta Duo is intended for use as a regenerative wound covering for the treatment of acute, chronic and surgically created wounds (CMS, 2019). Cellesta Duo is available wet or dry in 5 different sizes: 2 x 2 cm, 2 x 4 cm, 2 x 6 cm, 3 x 3 cm, 4 x 4 cm, and 4 x 8 cm. Cellesta Duo is a dual allograft affixed to a layer of poly mesh. This can be sutured, or glued, or laid over the affected tissue.

AlloGen

According to Vivex Biomedical, Inc., "AlloGen is composed of 100% human liquid amnion" (CMS, 2019). It is "an amniotic fluid product derived from donated birth tissue... processed using aseptic techniques..." The allograft is exposed to electron beam radiation... to ensure terminal sterilization. "AlloGen is intended for treatment of non-healing wounds and burn injuries." The manufacturer claims that use of AlloGen liquid for the treatment of non-healing wounds and burn injuries is a homologous use in that "Just as amniotic fluid protects and nourishes the fetus during development, AllGen provides the same protection to injured or traumatized tissue." The dosage of AlloGen is per cubic centimeter (cc). It is intended for external application. It is supplied in single use vials ranging from 0.25 to 2.0 ml.

Ascent

Ascent (StimLabs, LLC.) is a dehydrated cell and protein concentrate (dCPC) injectable derived from human amniotic fluid. According to the manufacturer, Ascent combines a selected set of cells from amniotic fluid and their components, including TIMPs, growing factors, interleukins and hyaluronic acid. Through complex interactions, these components work together to provide protecting, cushioning, lubrication, and
inflammation reduction at the site of injury. Ascent is intended for the treatment of non-healing wounds and burn injuries. Ascent is offered in 7.5 mg, 15 mg, and 30 mg powdered weight. The suggested reconstitution volumes are 0.5 cc, 1 cc, and 2 cc respectively giving a 0.75%, 1.5% and 3% dose. Ascent is reconstituted using sterile saline based on recommended reconstitution amounts.

WoundFix and BioWound

According to the manufacturer, Human Regenerative Technologies, LLC., WoundFix Membrane and BioWound Membrane are single-layer wound coverings for common wounds. These are intended for use as a wound covering, surgical covering, wrap or barrier, application to partial-and full-thickness, acute and chronic wounds such as, traumatic and complex wounds, burns, surgical and Mohs surgery sites and diabetic, venous, arterial, pressure and other ulcers, including with exposed tendon, muscle, bone, or other vital structures. These products are supplied in single use packaging in sizes ranging from .786 to 486 sq. cm.

WoundFix Plus and BioWound Plus

According to the Human Regenerative Technologies, LLC., WoundFix Plus and BioWound Plus membranes are single layer wound coverings composed of human, chorion-based membranes (CMS, 2019). The products are intended for use as a wound covering, surgical covering, wrap or barrier, application to partial-and full-thickness, acute and chronic wounds such as traumatic and complex wounds, burns, surgical and Mohs surgery sites and diabetic, venous, arterial, pressure and other ulcers, including with exposed tendon, muscle, bone, or other vital structures. Typically, one application is applied per wound; however, the product may be reapplied if necessary. WoundFix Plus and BioWound Plus membrane are supplied in single use packaging in sizes ranging from .786 to 192 sq. cm.

WoundFix XPlus Membrane and BioWound XPlus

According to the manufacturer, Human Regenerative Technologies, LLC., WoundFix XPlus Membrane and BioWound XPlus Membrane are single layer human placental tissue-based membranes intended to be used as a wound covering, surgical covering, wrap or barrier, application to partial-and full-thickness, acute and chronic wounds such as, traumatic and complex wounds, burns, surgical and Mohs surgery sites and diabetic, venous, arterial, pressure and other ulcers, including with exposed tendon, muscle, bone, or other vital structures (CMS, 2019). WoundFix XPlus Membrane and BioWound XPlus Membrane are supplied in single-use packaging, in 6 sq. cm and 12 sq. cm. sizes.
**BellaCell HD**

According to HansBiomed Corp., BellaCell HD is a human acellular dehydrated dermis regenerative tissue matrix indicated "for use in skin reconstruction to repair skin loss from burn injuries, congenital diseases, abdominal wall repair, hiatal hernia repair, breast reconstruction, and ulcers or malformation" (CMS, 2019). BellCell HD is supplied as 1.0-1.39mm, 1.4-1.79mm, 1.8-2.29mm, 2.3-2.99mm and 3.0-3.49mm.

**SureDerm Acellular Dermal Matrix**

According to HansBiomed Corp., SureDerm is a human acellular dermal matrix indicated for use in "skin reconstruction to repair skin loss from burn injuries, car accidents, congenital diseases, periodontal diseases, urinary incontinence, and ulcers or malformations" (CMS, 2019). SureDerm is supplied as 0.25-0.59mm, 0.6-0.99mm, 1.0-1.39mm, 1.4-1.79mm and 1.8mm and over.

**ProgenaMatrix**

According to the manufacturer, Cell Constructs I, LLC., ProgenaMatrix is a graft matrix composed of human keratin proteins selectively extracted from human hair. ProgenaMatrix is indicated for dry and exuding partial and full thickness wounds such as pressure (stage I-IV) and venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, donor sites and grafts, first and second-degree burns, superficial injuries, cuts, abrasions and surgical wounds." ProgenaMatrix is applied directly to the wound bed after debridement of the wound site to remove necrotic debris, biofilm, and non-viable tissue. Each matrix provides the same amount of human keratin proteins per square centimeter of product. It is supplied in sizes: 2cm x 2cm, 4cm x 4cm, 6cm x 6cm 10cm x 10cm; and 12cm x 12cm.

**Kerasorb**

According to the manufacturer, Keraplst Research Limited, "Kerasorb Wound Matrix is clinically indicated for the patient population with the following types of chronic wounds: pressure ulcers (stages I-IV), venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, and donor sites and grafts." Kerasorb is supplied in single use pouches containing one 10 cm x 10 cm foam wound matrix. It is applied to the wound area using aseptic technique similar to Keramatrix and other cellular and /or tissue based products for the skin wounds.

**Renuva**

[Link to aetna.com]

08/27/2019
According to the Musculoskeletal Transplant Foundation, Renuva is an allograft adipose matrix derived from processed donated human adipose tissue (CMS, 2019). Renuva is intended for the replacement of damaged or inadequate integumental adipose tissue matrix such as facial deformities, craniofacial deformities, breast reconstructions, or for other homologous uses into areas of the body where native fat would exist. Renuva® Allograft Adipose Matrix may also be used for the reinforcement or supplemental support in underlying adipose tissue matrix as the result of damage or naturally occurring defects e.g., cleft lip, Parry-Romberg syndrome, and facial LDS. "The matrix is dehydrated and must be rehydrated prior to use. When ready to use, the allograft is injected into the site subcutaneously. The matrix is available in three sizes: 1.5cc, 3cc and 5cc tissue package.

**ACM Surgical Collagen and ACM Surgical Extra Advanced Collagen**

According to the manufacturer, Human Biosciences, Inc., ACM Surgical Collagen and ACM Surgical Extra Advanced Collagen are 100 percent native freeze-dried, type-1 bovine collagen matrix, provided in a collagen sheet configuration (CMS, 2019). The products are indicated for use as a scaffold in the "management of partial and full-thickness wounds [i.e. surgical wounds, donor sites, graft sites, second degree burns, traumatic wounds (pressure, venous, mixed vascular etiologies, diabetic ulcers)] to support healing." ACM Surgical Collagen and ACM Surgical Extra Advanced Collagen are administered by applying each individual matrix directly to the wound surface after preparation of the wound site to remove necrotic debris, biofilm, and non-viable tissue, using the clinician's choice of fixation. Each matrix provides the same amount of collagen per square centimeter of product. Usually one tissue is applied per application. Additional applications may be required, based on physician choice. These products are packaged in sterile, single-use pouches and available in sheet sizes: 2"x2", 4"x4", 4"x5", 7x7", 8"x12".

**ACM Surgical Extra Advanced Collagen Powder**

According to the manufacturer, Human Biosciences, ACM Surgical Extra Advanced Collagen Powder "is indicated for wound management of partial and full-thickness wounds such as second degree burns, ulcers (pressure, venous, mixed vascular etiologies, diabetic ulcers) and other wounds (e.g. surgical wounds, scrapes, traumatic wounds)" (CMS, 2019). The product is applied directly to the wound surface after preparation of the wound site to remove necrotic debris, biofilm, and non variable tissue. It is supplied as sterile, single-use 1gm pouch, 1gm vial, 5gm vial and 10gm bottle.
CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15271 - 15278</td>
<td>Application of skin substitute grafts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96574</td>
<td>Debridement of premalignant hyperkeratotic lesion(s) (ie, targeted curettage, abrasion) followed with photodynamic therapy by external application of light to destroy premalignant lesions of the skin and adjacent mucosa with application and illumination/activation of photosensitizing drug(s) provided by a physician or other qualified health care</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5271 - C5274</td>
<td>Application of low cost skin substitute graft to trunk, arms, legs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5275 - C5278</td>
<td>Application of low cost skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits</td>
</tr>
</tbody>
</table>

Medically necessary wound care treatments:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11042, 11045</td>
<td>Debridement; subcutaneous tissue</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11043, 11046</td>
<td>Debridement; muscle and/or fascia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11044, 11047</td>
<td>Debridement; bone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11047</td>
<td>bone, each additional 20 sq cm, or part thereof</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15002 - 15005</td>
<td>Surgical preparation or creation of recipient site</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15777</td>
<td>Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk) (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>97597</td>
<td>Debridement (eg, high pressure waterjet with/without suction, sharp selective debridement with scissors, scalpel and forceps), open wound, (eg, fibrin, devitalized epidermis and/or dermis, exudate, devris, biofilm), including topical application(s), wound assessment, use of a whirlpool, when performed and instructions (s) for ongoing care, per session, total wound(s) surface area; first 20 sq cm or less</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>97598</td>
<td>each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

Apligraf (graftskin):

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4101</td>
<td>Apligraf, per sq cm</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E08.621</td>
<td>Diabetes mellitus due to underlying condition with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]</td>
</tr>
<tr>
<td>E09.621</td>
<td>Drug or chemical induced diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]</td>
</tr>
<tr>
<td>E10.621</td>
<td>Type 1 diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]</td>
</tr>
<tr>
<td>E11.621</td>
<td>Type 2 diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]</td>
</tr>
<tr>
<td>E13.621</td>
<td>Other specified diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]</td>
</tr>
<tr>
<td>I83.001 - I83.029</td>
<td>Varicose veins of lower extremities with ulcer</td>
</tr>
<tr>
<td>I83.201 - I83.229</td>
<td>Varicose veins of lower extremities with ulcer and inflammation</td>
</tr>
<tr>
<td>I87.311 - I87.319</td>
<td>Chronic venous hypertension (idiopathic) with ulcer</td>
</tr>
<tr>
<td>I87.331 - I87.339</td>
<td>Chronic venous hypertension (idiopathic) with ulcer and inflammation</td>
</tr>
<tr>
<td>A49.01 - A49.8</td>
<td>Bacterial infection of unspecified site</td>
</tr>
<tr>
<td>B78.1</td>
<td>Cutaneous strongyloidiasis</td>
</tr>
<tr>
<td>B95.0 - B95.8, B96.0 - B96.89</td>
<td>Streptococcus, staphylococcus, enterococcus and other bacterial agents as the cause of diseases classified elsewhere</td>
</tr>
<tr>
<td>E83.2</td>
<td>Disorders of zinc metabolism</td>
</tr>
<tr>
<td>I96</td>
<td>Gangrene</td>
</tr>
<tr>
<td>L08.82 - L08.9</td>
<td>Other and unspecified local infections of skin and subcutaneous tissue</td>
</tr>
<tr>
<td>M72.6</td>
<td>Necrotizing fascitis</td>
</tr>
<tr>
<td>M86.00 - M86.86.9</td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>M87.00 - M87.9</td>
<td>Osteonecrosis</td>
</tr>
<tr>
<td>Numerous options</td>
<td>Open wounds [Codes not listed due to expanded specificity]</td>
</tr>
</tbody>
</table>

Dermagraft:

HCPCS codes covered if selection criteria are met:

| Q4106      | Dermagraft, per sq cm                                                            |

ICD-10 codes covered if selection criteria are met:

<p>| E08.621 | Diabetes mellitus due to underlying condition with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration] |</p>
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>E09.621</td>
<td>Drug or chemical induced diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]</td>
</tr>
<tr>
<td>E10.621</td>
<td>Type 1 diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]</td>
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<tr>
<td>E11.621</td>
<td>Type 2 diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]</td>
</tr>
<tr>
<td>E13.621</td>
<td>Other specified diabetes mellitus with foot ulcer [full-thickness neuropathic diabetic foot ulcers of greater than 3-weeks duration]</td>
</tr>
<tr>
<td>Q81.2</td>
<td>Epidermolysis bullosa dystrophica</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- A49.0 - A49.8: Bacterial infection of unspecified site
- B95.0 - B95.8, B96.0 - B96.89: Streptococcus, staphylococcus, enterococcus and other bacterial agents as the cause of diseases classified elsewhere
- I70.261 - I70.269: Atherosclerosis of the extremities with gangrene
- I83.201 - I83.229: Varicose veins of lower extremities with ulcer and inflammation
- I96: Gangrene
- L08.82 - L08.9: Other and unspecified local infection of skin and subcutaneous tissue
- M72.6: Necrotizing fascitis
- M86.00 - M86.9: Osteomyelitis
- M87.00 - M87.9: Osteonecrosis

Systemic Hyperbaric Oxygen Therapy (HBOT):

CPT codes covered if selection criteria are met:

- 99183: Physician or other qualified health care professional attendance and supervision of hyperbaric oxygen therapy, per session

HCPCS codes covered if selection criteria are met:

- G0277: Hyperbaric oxygen under pressure, full body chamber, per 30 minute interval

ICD-10 codes covered if selection criteria are met:

- E08.51 - E08.59, E09.51 - E09.59: Diabetes mellitus due to underlying condition with peripheral circulatory disorders
- E08.618 - E08.69, E09.618 - E09.69: Diabetes mellitus due to underlying conditions with other specified manifestations
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E11.618 - E11.69</td>
<td>Diabetes with other specified manifestations</td>
</tr>
<tr>
<td>E13.618 - E13.69</td>
<td></td>
</tr>
<tr>
<td>I83.201 - I83.229</td>
<td>Varicose veins of lower extremities with ulcer and inflammation</td>
</tr>
<tr>
<td>L08.82 - L08.9</td>
<td>Other and unspecified local infection of skin and subcutaneous tissue</td>
</tr>
<tr>
<td>T20.011+ -</td>
<td>Burns</td>
</tr>
<tr>
<td>T25.799+</td>
<td></td>
</tr>
<tr>
<td>Transcyte:</td>
<td></td>
</tr>
<tr>
<td>Q4182</td>
<td>Transcyte, per square centimeter</td>
</tr>
<tr>
<td>T20.011+ -</td>
<td>Burns</td>
</tr>
<tr>
<td>T25.799</td>
<td></td>
</tr>
<tr>
<td>Orcel:</td>
<td></td>
</tr>
<tr>
<td>Q4100</td>
<td>Skin substitute, not otherwise specified</td>
</tr>
<tr>
<td>Q81.2</td>
<td>Epidermolysis bullosa dystrophica</td>
</tr>
<tr>
<td>T20.011+ -</td>
<td>Burns</td>
</tr>
<tr>
<td>T25.799+</td>
<td></td>
</tr>
<tr>
<td>Biobrane biosynthetic dressing:</td>
<td></td>
</tr>
<tr>
<td>Q4104</td>
<td>Integra Bilayer Matrix Wound Dressing, per sq cm</td>
</tr>
<tr>
<td>Q4105</td>
<td>Integra Dermal Regeneration Template (DRT), per cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E08.621,</td>
<td>Diabetes mellitus with foot ulcer</td>
</tr>
<tr>
<td>E09.621,</td>
<td></td>
</tr>
<tr>
<td>E10.621,</td>
<td></td>
</tr>
<tr>
<td>E11.621, E13.621</td>
<td></td>
</tr>
<tr>
<td>T20.011+-</td>
<td>Burns</td>
</tr>
<tr>
<td>T25.799+</td>
<td></td>
</tr>
<tr>
<td>Alloderm:</td>
<td></td>
</tr>
<tr>
<td>Other CPT codes related to the CPB:</td>
<td></td>
</tr>
<tr>
<td>19357 - 19369</td>
<td>Breast reconstruction</td>
</tr>
<tr>
<td>23420</td>
<td>Reconstruction of complete shoulder (rotator cuff avulsion, chronic (includes acromioplasty)</td>
</tr>
<tr>
<td>23470 - 23472</td>
<td>Arthroplasty, glenohumeral joint</td>
</tr>
<tr>
<td>23473 - 23474</td>
<td>Revision of total shoulder arthroplasty, including allograft when performed</td>
</tr>
<tr>
<td>24344</td>
<td>Reconstruction lateral collateral ligament, elbow, with tendon graft (includes harvesting of graft)</td>
</tr>
<tr>
<td>24345</td>
<td>Repair medical collateral ligament, elbow, with local tissue</td>
</tr>
<tr>
<td>24346</td>
<td>Reconstruction medial collateral ligament, elbow, with tendon graft (includes harvesting of graft)</td>
</tr>
<tr>
<td>24360 - 24363</td>
<td>Arthroplasty, elbow</td>
</tr>
<tr>
<td>24365 - 24366</td>
<td>Arthroplasty, radial head</td>
</tr>
<tr>
<td>24370 - 24371</td>
<td>Revision of total elbow arthroplasty, including allograft when performed</td>
</tr>
<tr>
<td>25320</td>
<td>Capsulorrhaphy or reconstruction, wrist, open (eg, capsulodesis, ligament repair, tendon transfer or graft) (includes synovectomy, capsulotomy and open reduction) for carpal instability</td>
</tr>
<tr>
<td>25337</td>
<td>Reconstruction for stabilization of unstable distal ulna or distal radioulnar joint, secondary by soft tissue stabilization (eg, tendon transfer, tendon graft or weave, or tenodesis) with or without open reduction of distal</td>
</tr>
<tr>
<td>25390 - 25393</td>
<td>Osteoplasty, radius and/or ulna</td>
</tr>
<tr>
<td>25441 - 25442</td>
<td>Arthroplasty, with prosthetic replacement; distal radius and distal ulna</td>
</tr>
<tr>
<td>25446</td>
<td>Arthroplasty, with prosthetic replacement; distal radius and partial or entire carpus (total wrist)</td>
</tr>
<tr>
<td>26135</td>
<td>Synovectomy, metacarpophalangeal joint including intrinsic release and extensor hood reconstruction, each digit</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>26140</td>
<td>Synovectomy, proximal interphalangeal joint, including extensor reconstruction, each interphalangeal joint</td>
</tr>
<tr>
<td>26390</td>
<td>Excision flexor tendon, with implantation of synthetic rod for delayed tendon graft, hand or finger, each rod</td>
</tr>
<tr>
<td>26490 - 26496</td>
<td>Opponensplasty</td>
</tr>
<tr>
<td>26500 - 26502</td>
<td>Reconstruction of tendon pulley, each tendon</td>
</tr>
<tr>
<td>26530 - 26531</td>
<td>Arthroplasty, metacarpophalangeal joint</td>
</tr>
<tr>
<td>26535 - 26536</td>
<td>Arthroplasty interphalangeal joint</td>
</tr>
<tr>
<td>26541 - 26542</td>
<td>Reconstruction, collateral ligament, metacarpophalangeal joint, single</td>
</tr>
<tr>
<td>26545</td>
<td>Reconstruction, collateral ligament, interphalangeal joint, single, including graft, each joint</td>
</tr>
<tr>
<td>26548</td>
<td>Repair and reconstruction, finger, volar plate, interphalangeal joint</td>
</tr>
<tr>
<td>26550</td>
<td>Pollicization of a digit</td>
</tr>
<tr>
<td>26551 - 26554</td>
<td>Transfer, toe-to-hand with microvascular anastomosis</td>
</tr>
<tr>
<td>26555</td>
<td>Transfer, finger to another position without microvascular anastomosis</td>
</tr>
<tr>
<td>26556</td>
<td>Transfer, free toe joint, with microvascular anastomosis</td>
</tr>
<tr>
<td>26587</td>
<td>Reconstruction of polydactylyus digit, soft tissue and bone</td>
</tr>
<tr>
<td>42410 - 42426</td>
<td>Excision of parotid tumor or parotid gland</td>
</tr>
</tbody>
</table>

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4116</td>
<td>Alloderm, per square centimeter</td>
</tr>
<tr>
<td>Q4130</td>
<td>Strattice TM, per sq cm</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C50.011 - C50.929</td>
<td>Malignant neoplasm of breast</td>
</tr>
<tr>
<td>C79.81</td>
<td>Secondary malignant neoplasm of breast</td>
</tr>
<tr>
<td>D05.00 - D05.92</td>
<td>Carcinoma in situ of breast</td>
</tr>
<tr>
<td>Z15.01</td>
<td>Genetic susceptibility to malignant neoplasm of breast</td>
</tr>
<tr>
<td>Z15.02</td>
<td>Genetic susceptibility to malignant neoplasm of ovary</td>
</tr>
<tr>
<td>Z80.3</td>
<td>Family history of malignant neoplasm of breast</td>
</tr>
<tr>
<td>Z80.41</td>
<td>Family history of malignant neoplasm of ovary</td>
</tr>
<tr>
<td>Z85.3</td>
<td>Personal history of malignant neoplasm of breast</td>
</tr>
<tr>
<td>Z90.10 - Z90.13</td>
<td>Acquired absence of breast and nipple</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Z92.3</td>
<td>Personal history of irradiation</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes not covered for indications listed in the CPB (not all inclusive):</td>
</tr>
<tr>
<td>H65.00</td>
<td>Otitis media</td>
</tr>
<tr>
<td>H72.00</td>
<td>Perforation of tympanic membrane</td>
</tr>
<tr>
<td>K40.00</td>
<td>Hernia</td>
</tr>
<tr>
<td>L74.52</td>
<td>Secondary focal hyperhidrosis [Frey's syndrome]</td>
</tr>
<tr>
<td></td>
<td>Artiss:</td>
</tr>
<tr>
<td></td>
<td>HCPCS codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>C9250</td>
<td>Human plasma fibrin sealant, vapor-heated, solvent-detergent (Artiss), 2ml</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>T20.011</td>
<td>Burns</td>
</tr>
<tr>
<td>T25.799+</td>
<td>Burns</td>
</tr>
<tr>
<td></td>
<td>Oasis Wound Matrix:</td>
</tr>
<tr>
<td></td>
<td>HCPCS codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>Q4102</td>
<td>Oasis Wound Matrix, per sq cm</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes covered if selection criteria are met:</td>
</tr>
<tr>
<td>E08.621</td>
<td>Diabetes mellitus due to underlying condition with foot ulcer [difficult-to-heal</td>
</tr>
<tr>
<td></td>
<td>diabetic partial and full-thickness ulcers of the lower extremity that have failed</td>
</tr>
<tr>
<td></td>
<td>standard wound therapy of a least 4 weeks duration]</td>
</tr>
<tr>
<td>E09.621</td>
<td>Drug or chemical induced diabetes mellitus with foot ulcer [difficult-to-heal</td>
</tr>
<tr>
<td></td>
<td>diabetic partial and full-thickness ulcers of the lower extremity that have failed</td>
</tr>
<tr>
<td></td>
<td>standard wound therapy of a least 4 weeks duration]</td>
</tr>
<tr>
<td>E10.621</td>
<td>Type I diabetes mellitus with foot ulcer [difficult-to-heal diabetic partial and</td>
</tr>
<tr>
<td></td>
<td>full-thickness ulcers of the lower extremity that have failed standard wound</td>
</tr>
<tr>
<td></td>
<td>therapy of a least 4 weeks duration]</td>
</tr>
<tr>
<td>E11.621</td>
<td>Type II diabetes mellitus with foot ulcer [difficult-to-heal diabetic partial and</td>
</tr>
<tr>
<td></td>
<td>full-thickness ulcers of the lower extremity that have failed standard wound</td>
</tr>
<tr>
<td></td>
<td>therapy of a least 4 weeks duration]</td>
</tr>
<tr>
<td>E13.621</td>
<td>Other specified diabetes mellitus with foot ulcer [difficult-to-heal diabetic</td>
</tr>
<tr>
<td></td>
<td>partial and full-thickness ulcers of the lower extremity that have failed standard</td>
</tr>
<tr>
<td></td>
<td>wound therapy of a least 4 weeks duration]</td>
</tr>
<tr>
<td>I83.001-028</td>
<td>Varicose veins of lower extremities with ulcer [difficult-to-heal chronic venous</td>
</tr>
<tr>
<td></td>
<td>partial and full-thickness ulcers of the lower extremity that have failed standard</td>
</tr>
<tr>
<td></td>
<td>wound therapy of a least 4 weeks duration]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>I83.201 - I83.229</td>
<td>Varicose veins of lower extremities with ulcer and inflammation [difficult-to-heal chronic venous partial and full-thickness ulcers of the lower extremity that have failed standard wound therapy of a least 4 weeks duration]</td>
</tr>
<tr>
<td>I87.311 - I83.319</td>
<td>Chronic venous hypertension with ulcer [difficult-to-heal chronic venous partial and full-thickness ulcers of the lower extremity that have failed standard wound therapy of a least 4 weeks duration]</td>
</tr>
<tr>
<td>I87.331 - I87.339</td>
<td>Chronic venous hypertension with ulcer and inflammation [difficult-to-heal chronic venous partial and full-thickness ulcers of the lower extremity that have failed standard wound therapy of a least 4 weeks duration]</td>
</tr>
</tbody>
</table>

Graftjacket Regenerative Tissue Matrix:

HCPCS codes covered if selection criteria are met:

- **Q4107**

Graftjacket, per sq cm

ICD-10 codes covered if selection criteria are met:

- E08.621, E09.621, E10.621, E11.621, E13.621

Diabetes mellitus [covered for treatment of full-thickness diabetic foot ulcers greater than 3-week duration that extend through the dermis, but without tendon, muscle, joint capsule or bone exposure]

Epicel:

No specific code

CPT codes covered if selection criteria are met:

- **15150 - 15157**

Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits

ICD-10 codes covered if selection criteria are met:

- T20.30x+ - T20.39x+, T20.711+ - T20.79x+

Burn and corrosion of third degree of face, head, and neck [deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%]

- T21.30x+ - T21.39x+, T21.70x+ - T21.79x+

Burn and corrosion of third degree of trunk [deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%]

- T22.30x+ - T22.399+, T22.70x+ - T22.799+

Burn and corrosion of third degree of shoulder and upper limb [deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%]
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T23.301+ - T23.399+, T23.701+ - T23.799+</td>
<td>Burn and corrosion of third degree of wrist and hand [deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%]</td>
</tr>
<tr>
<td>T24.301+ - T24.399+, T24.701+ - T24.799+</td>
<td>Burn and corrosion of third degree of lower limb, except ankle and foot [deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%]</td>
</tr>
<tr>
<td>T25.311+ - T25.399+, T25.711+ - T25.799+</td>
<td>Burn and corrosion of third degree of ankle and foot [deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%]</td>
</tr>
<tr>
<td>T31.30 - T31.99, T32.30 - T32.99</td>
<td>Burn [any degree] 30 to 90 percent or more of body surface [deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%]</td>
</tr>
</tbody>
</table>

**Epifix and Grafix:**

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4132</td>
<td>Grafix core, per sq cm</td>
</tr>
<tr>
<td>Q4133</td>
<td>Grafix prime, per sq cm</td>
</tr>
<tr>
<td>Q4186</td>
<td>Epifix, per sq cm</td>
</tr>
<tr>
<td>Q4187</td>
<td>Epicord, per square centimeter</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E08.621, E09.621, E10.621, E11.621, E13.621</td>
<td>Diabetes mellitus with foot ulcer</td>
</tr>
<tr>
<td>I87.311 - I87.319</td>
<td>Chronic venous hypertension (idiopathic) with ulcer [chronic venous partial and full-thickness ulcers of the lower extremity]</td>
</tr>
<tr>
<td>L97.101 - L97.929</td>
<td>Non-pressure chronic ulcer of lower limb, not elsewhere classified [chronic venous partial and full-thickness ulcers of the lower extremity]</td>
</tr>
</tbody>
</table>

**DermACELL:**

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4122</td>
<td>Dermacell, per square centimeter</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E08.621</td>
<td>Diabetes mellitus due to underlying condition with foot ulcer [partial and full thickness neuropathic diabetic foot ulcers]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>E09.621</td>
<td>Drug or chemical induced diabetes mellitus with foot ulcer [partial and full and thickness neuropathic diabetic foot ulcers]</td>
</tr>
<tr>
<td>E10.621</td>
<td>Type 1 diabetes mellitus with foot ulcer [partial and full and thickness neuropathic diabetic foot ulcers]</td>
</tr>
<tr>
<td>E11.621</td>
<td>Type 2 diabetes mellitus with foot ulcer [partial and full and thickness neuropathic diabetic foot ulcers]</td>
</tr>
<tr>
<td>E13.621</td>
<td>Other specified diabetes mellitus with foot ulcer [partial and full and thickness neuropathic diabetic foot ulcers]</td>
</tr>
</tbody>
</table>

Experimental and investigational wound care treatments - No specific code:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherus Dural Sealant,</td>
<td>AlloMax, Allopatch, AlloSource cryopreserved human cadaver skin,</td>
</tr>
<tr>
<td>AmnioCare, AmnioExCel,</td>
<td>AmnioHeal amniotic membrane, Cook Medical anal fistula plug,</td>
</tr>
<tr>
<td>AmnioMTM, AmnioShield,</td>
<td>AmnioStrip, Amniox (human embryonic membrane), BioDFactor,</td>
</tr>
<tr>
<td>BioDRestore Elemental</td>
<td>Tissue Matrix, Bionect, Biostat Biologx Fibrin Sealant, PTFE felt, Biotape</td>
</tr>
<tr>
<td>Reinforcement Matrix,</td>
<td>CellECT (human amnion and amniotic fluid allograft), CellerateRX, Clarix</td>
</tr>
<tr>
<td>Clarix 100, Clarix Cord</td>
<td>1K, CollaFix, CollaMend, Connexa reconstruction tissue matrix, CorMatrix</td>
</tr>
<tr>
<td>Patch, Cortiva Allograft</td>
<td>Dermis, C-Qur biosynthetic mesh, CRXa, Cuffpatch, dehydrated human amniotic</td>
</tr>
<tr>
<td>Matrix, HydroFix,</td>
<td>membrane allograft (e.g., AmnioPro, BioFix and FlowerPatch), Dermamatrix,</td>
</tr>
<tr>
<td>HydroFix, Inforce,</td>
<td>DuraGen Plus Dural Regeneration Matrix, DuraMatrix, DuraSeal, Durepair Regeneration</td>
</tr>
<tr>
<td>LiquidGen, Matriderm,</td>
<td>Matrix, ENDURAgeN, Epicord, EPIFLO transdermal continuous oxygen therapy,</td>
</tr>
<tr>
<td>MatriStem Burn Matrix,</td>
<td>Mediskin, MariStem Micro Matrix, MediHoney, Medeor, Neox 1K, MesobioMatrix,</td>
</tr>
<tr>
<td>Matrix PSM , Mediskin,</td>
<td>MariStem Micro Matrix, MediHoney, Medeor, Neox 1K, MesobioMatrix, Neuroflex,</td>
</tr>
<tr>
<td>MariStem Micro Matrix,</td>
<td>Neoform Dermis, NuCel liquid wound covering, NuShield Orthopaedics, NuShield</td>
</tr>
<tr>
<td>MediHoney, Medeor,</td>
<td>Spine, OrthADAPT Bioimplant (type I collagen scaffold), OrthoFlo, OsseoGuard,</td>
</tr>
<tr>
<td>Neox 1K, MesobioMatrix,</td>
<td>Ovation, PalinGen membrane for wound healing, Pelvico, Pelvisoft, Peri-Guard</td>
</tr>
<tr>
<td>Neoform Dermis,</td>
<td>Repair Patch, Peri-Strips Dry, Peri-Strips Dry with Veritas Collagen Matrix,</td>
</tr>
<tr>
<td>NuCel liquid wound</td>
<td>covering, NuShield Orthopaedics, NuShield Spine, OrthADAPT Bioimplant (type I</td>
</tr>
<tr>
<td>covering, NuShield</td>
<td>collagen scaffold), OrthoFlo, OsseoGuard, Ovation, PalinGen membrane for wound</td>
</tr>
<tr>
<td>OrthoFlo, OsseoGuard,</td>
<td>healing, Pelvico, Pelvisoft, Peri-Guard Repair Patch, Peri-Strips Dry, Peri-</td>
</tr>
<tr>
<td>Ovation, PalinGen</td>
<td>Strips Dry with Veritas Collagen Matrix, placental tissue matrix allograft.</td>
</tr>
<tr>
<td>membrane for wound</td>
<td>Porcine-derived polypropylene composite wound dressing (eg, Avaulta Plus™),</td>
</tr>
<tr>
<td>healing, Pelvico,</td>
<td>Promogran, Puracol, Puros Dermis, Repliform, Seamguard, Solana allograft,</td>
</tr>
<tr>
<td>Pelvico, Peri-Guard</td>
<td>Sonafine wound dressing, SportMatrix, SportMesh, Sterishield II Dual Layer Amnion</td>
</tr>
<tr>
<td>Repair Patch, Peri-</td>
<td>Patch, Stravix, Viaflow Placental Tissue Matrix, Supraphel, Surgisis (including</td>
</tr>
<tr>
<td>Strips Dry, Peri-Strips</td>
<td>Surgisis AFP Anal Fistula Plug, Surgisis Gold Hernia Repair Grafts, and Surgisis</td>
</tr>
<tr>
<td>Dry with Veritas Collagen</td>
<td>Biodesign), TenSix (acellular dermal matrix), TissueMend, Tornier BioFiber</td>
</tr>
<tr>
<td>Matrix, placental tissue</td>
<td>Absorbable Biological Scaffold, Tornier Collagen Coated BioFiber Scaffold,</td>
</tr>
<tr>
<td>matrix allograft.</td>
<td>Unite Biomatix, Vaso Shield, Viaflow C Flowable Placental Tissue Matrix,</td>
</tr>
<tr>
<td>Porcine-Dermis,</td>
<td>Vitagel Surgical Heomstat, XCM Biologic, Xelma, X-Repair, XenMatrix, XWrap Dry</td>
</tr>
<tr>
<td>Gore Bio-A Fistula Plug,</td>
<td>or Hydrol Plus, ACM Surgical Collagen, ACM Surgical Extra Advanced Collagen, ACM</td>
</tr>
<tr>
<td>Graffjet regenerative</td>
<td>Surgical Extra Advanced Collagen, ACM Surgical Extra Advanced Collagen Powder,</td>
</tr>
<tr>
<td>tissue matrix for rotator</td>
<td>Allogen, AlloGen Liquid, AlloPatch Pliable, AlphaGems, Altiplast, Altiply,</td>
</tr>
<tr>
<td>cuff repair, HydroFix,</td>
<td>Ambio Choice, AmnioArmor, AmnioBand Allograft Placental Matrix, AmnioCord,</td>
</tr>
<tr>
<td>Inforce, LiquidGen,</td>
<td>AmnioFill, Amnion Bio, Aminios, AmnioWrap2, AmnioyFluid, Aquacel Ag, Artacent</td>
</tr>
<tr>
<td>Matriderm, MatriStem</td>
<td>Cord, Arthrex Amnion Matrix, Arthrex Amnion Viscous, Ascens, Axobiomembrane,</td>
</tr>
<tr>
<td>Burn Matrix, Matrix PSM</td>
<td>Axolotl Ambient, Axolotl Cryo, Axolotl DualGraft, Axolotl Graft, BellaCell HD,</td>
</tr>
<tr>
<td>, Mediskin, MariStem</td>
<td>BioFix Flow Placental Tissue Matrix Allograft, BioSkin Flow, BioWound Membrane,</td>
</tr>
<tr>
<td>MicroMatrix, MyOwn Skin,</td>
<td>BioWound Plus Membrane, BioWound XPlus Membrane, Cellesta Cord, Cellesta Duo,</td>
</tr>
<tr>
<td>Novachor, Novafix, Ologen</td>
<td>Cellesta Flowable Amnion, Colla-Pad, CollaSorb, CollaWound, Coll-e-Derm, Collax</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>A6196 - A6199</td>
<td>Alginate or other fiber gelling dressing, wound cover, sterile</td>
</tr>
<tr>
<td>A6206 - A6208</td>
<td>Contact layer, sterile, each dressing</td>
</tr>
<tr>
<td>A6209 - A6211</td>
<td>Foam dressing, wound cover, sterile, each dressing</td>
</tr>
<tr>
<td>C1781</td>
<td>Mesh (implantable)</td>
</tr>
<tr>
<td>C9352</td>
<td>Microporous collagen implantable tube (NeuraGen Nerve Guide), per cm length</td>
</tr>
<tr>
<td>C9353</td>
<td>Microporous collagen implantable slit tube (NeuraWrap Nerve Protector), per cm length</td>
</tr>
<tr>
<td>C9354</td>
<td>Acellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm</td>
</tr>
<tr>
<td>G0428</td>
<td>Collagen meniscus implant procedure for filling meniscal defects (e.g., CMI, collagen scaffold, Menaflex)</td>
</tr>
<tr>
<td>Q4100</td>
<td>Skin substitute, not otherwise specified</td>
</tr>
<tr>
<td>Q4110</td>
<td>PriMatrix, per sq cm</td>
</tr>
<tr>
<td>Q4111</td>
<td>GammaGraft, per sq cm</td>
</tr>
<tr>
<td>Q4113</td>
<td>GRAFTJACKET XPRESS, injectable, 1cc</td>
</tr>
<tr>
<td>Q4115</td>
<td>AlloSkin, per square centimeter</td>
</tr>
<tr>
<td>Q4117</td>
<td>HYALOMATRIX, per sq cm</td>
</tr>
<tr>
<td>Q4119</td>
<td>MatriStem wound matrix, per sq cm</td>
</tr>
<tr>
<td>Q4121</td>
<td>TheraSkin, per sq cm</td>
</tr>
<tr>
<td>Q4122</td>
<td>DermACELL, per sq cm</td>
</tr>
<tr>
<td>Q4123</td>
<td>AlloSkin RT, per square centimeter</td>
</tr>
<tr>
<td>Q4124</td>
<td>OASIS ultra tri-layer wound matrix, per sq cm</td>
</tr>
<tr>
<td>Q4125</td>
<td>Arthroflex, per sq cm</td>
</tr>
<tr>
<td>Q4126</td>
<td>MemoDerm, DermaSpan, TranZgraft or InteguPly, per square centimeter</td>
</tr>
<tr>
<td>Q4127</td>
<td>Talymed, per sq cm</td>
</tr>
<tr>
<td>Q4128</td>
<td>Flex hd, allopacht hd, or matrix hd, per square centimeter</td>
</tr>
<tr>
<td>Q4129</td>
<td>Unite biomatrix, per sq cm</td>
</tr>
<tr>
<td>Q4134</td>
<td>hMatrix, per sq cm</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Q4135</td>
<td>Mediskin, per sq cm</td>
</tr>
<tr>
<td>Q4136</td>
<td>E-Z Derm, per sq cm</td>
</tr>
<tr>
<td>Q4137</td>
<td>Amnioexcel or biodexcel, per sq cm</td>
</tr>
<tr>
<td>Q4138</td>
<td>Biodfence dryflex, per sq cm</td>
</tr>
<tr>
<td>Q4139</td>
<td>Amniomatrix or biodmatrix, injectable, 1 cc</td>
</tr>
<tr>
<td>Q4140</td>
<td>Biodfence, per sq cm</td>
</tr>
<tr>
<td>Q4141</td>
<td>AlloSkin AC, per square centimeter</td>
</tr>
<tr>
<td>Q4142</td>
<td>XCM biologic tissue matrix, per sq cm</td>
</tr>
<tr>
<td>Q4143</td>
<td>Repriza, per sq cm</td>
</tr>
<tr>
<td>Q4145</td>
<td>Epifix, injectable, 1 mg</td>
</tr>
<tr>
<td>Q4147</td>
<td>Architect, architect PX, or architect FX, extracellular matrix, per sq cm</td>
</tr>
<tr>
<td>Q4149</td>
<td>Excellagen, 0.1 cc</td>
</tr>
<tr>
<td>Q4150</td>
<td>Allowrap DS or dry, per sq cm</td>
</tr>
<tr>
<td>Q4151</td>
<td>Amnioband or guardian, per sq cm</td>
</tr>
<tr>
<td>Q4152</td>
<td>Dermapure, per sq cm</td>
</tr>
<tr>
<td>Q4153</td>
<td>Dermavest and Plurivest, per sq cm</td>
</tr>
<tr>
<td>Q4154</td>
<td>Biovance, per sq cm</td>
</tr>
<tr>
<td>Q4155</td>
<td>Neoxflo or clarixflo 1 mg</td>
</tr>
<tr>
<td>Q4156</td>
<td>Neox 100, per sq cm</td>
</tr>
<tr>
<td>Q4157</td>
<td>Revitalon, per sq cm</td>
</tr>
<tr>
<td>Q4158</td>
<td>Marigen, per sq cm</td>
</tr>
<tr>
<td>Q4159</td>
<td>Affinity, per sq cm</td>
</tr>
<tr>
<td>Q4160</td>
<td>Nushield, per square centimeter</td>
</tr>
<tr>
<td>Q4161</td>
<td>Bio-connekt wound matrix, per per sq cm</td>
</tr>
<tr>
<td>Q4162</td>
<td>Woundex flow, bioskin flow, 0.5 cc</td>
</tr>
<tr>
<td>Q4165</td>
<td>Keramatrix, per sq cm</td>
</tr>
<tr>
<td>Q4166</td>
<td>Cytal, per square centimeter{Cytal Burn Matrix, Cytal Wound Matrix}</td>
</tr>
<tr>
<td>Q4167</td>
<td>Truskin, per square centimeter</td>
</tr>
<tr>
<td>Q4168</td>
<td>Amnioband, 1 mg</td>
</tr>
<tr>
<td>Q4169</td>
<td>Artacent wound, per square centimeter</td>
</tr>
<tr>
<td>Q4170</td>
<td>Cygnus, per square centimeter</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Q4171</td>
<td>Interfyl, 1 mg</td>
</tr>
<tr>
<td>Q4173</td>
<td>Palingen or palingen xplus, per square centimeter</td>
</tr>
<tr>
<td>Q4174</td>
<td>Palingen or promatrix, 0.36 mg per 0.25 cc</td>
</tr>
<tr>
<td>Q4175</td>
<td>Miroderm, per square centimeter</td>
</tr>
<tr>
<td>Q4176</td>
<td>Neopatch, per square centimeter</td>
</tr>
<tr>
<td>Q4177</td>
<td>Floweramnioflo, 0.1 cc</td>
</tr>
<tr>
<td>Q4178</td>
<td>Floweramniopatch, per square centimeter</td>
</tr>
<tr>
<td>Q4179</td>
<td>Flowerderm, per square centimeter</td>
</tr>
<tr>
<td>Q4180</td>
<td>Revita, per square centimeter</td>
</tr>
<tr>
<td>Q4181</td>
<td>Amnio wound, per square centimeter</td>
</tr>
<tr>
<td>Q4189 - Q4190</td>
<td>Artacent ac</td>
</tr>
<tr>
<td>Q4195 - Q4197</td>
<td>Puraply</td>
</tr>
<tr>
<td>Q4204</td>
<td>Xwrap, per square centimeter</td>
</tr>
</tbody>
</table>

Artelon (poly[urethane urea] elastomer):
No specific code

HCPCS codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L8658</td>
<td>Interphalangeal joint spacer, silicone or equal, each</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB (not all inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M18.0 - M18.12</td>
<td>Bilateral and unilateral primary osteoarthritis of first carpometacarpal [trapezio-metacarpal joint osteoarthritis]</td>
</tr>
<tr>
<td>M18.2 - M18.52</td>
<td>Bilateral and unilateral post-traumatic osteoarthritis and other bilateral and unilateral secondary osteoarthritis of first carpometacarpal [trapezio-metacarpal joint osteoarthritis]</td>
</tr>
<tr>
<td>M19.041 - M19.049</td>
<td>Primary osteoarthritis [trapezio-metacarpal joint osteoarthritis]</td>
</tr>
<tr>
<td>M19.141 - M19.149</td>
<td>Post-traumatic osteoarthritis, hand [trapezio-metacarpal joint osteoarthritis]</td>
</tr>
<tr>
<td>M23.50 - M23.52</td>
<td>Chronic instability of knee</td>
</tr>
<tr>
<td>M66.211 - M66.219, M66.811 - M66.819</td>
<td>Spontaneous rupture of extensor tendons, upper arm and shoulder</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>M75.100 - M75.122</td>
<td>Complete rupture of rotator cuff</td>
</tr>
<tr>
<td>M75.50 - M75.52</td>
<td>Bursitis of shoulder</td>
</tr>
<tr>
<td>S43.421+ - S43.429+</td>
<td>Sprain and strain of rotator cuff (capsule)</td>
</tr>
<tr>
<td>S83.501+ - S83.529+</td>
<td>Sprain of cruciate ligament of knee</td>
</tr>
<tr>
<td></td>
<td>Amniotic Fluid Injection (e.g., AmniFix™):</td>
</tr>
<tr>
<td></td>
<td>No specific code</td>
</tr>
</tbody>
</table>
|               | CPT codes not covered for indications listed in the CPB:
| 20100 - 29999  | Musculoskeletal system [not covered for prevention of adhesions after orthopedic surgery] |
|               | ICD-10 codes not covered for indications listing in the CPB (not all inclusive):
| H18.821 - H18.829 | Corneal disorder due to contact lens [corneal wound] |
| S05.00x+ - S05.02x+ | Injury of conjunctiva and corneal abrasion without foreign body [corneal wound] |
| S05.8X1+ = S05.92x+ | Other injuries of eye and orbit [corneal wound]       |
|               | Arthres GraftRope:                                     |
|               | No specific code                                       |
|               | Other CPT codes related to the CPB:                   |
| 29806 - 29828 | Arthroscopy, shoulder, surgical                       |
|               | ICD-10 codes not covered for indications listed in the CPB (not all inclusive):
<p>| S41.001+ - S41.009+ | Unspecified open wounds of shoulder [open dislocation] |
| S43.101+ - S43.159+ | Subluxation and dislocation of acromioclavicular (joint) |
|               | Autologous Fat:                                        |
|               | CPT not covered for indications listed in the CPB:     |</p>
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11950 - 11954</td>
<td>Subcutaneous injection of filling material (e.g., collagen)</td>
</tr>
<tr>
<td>15770</td>
<td>Graft; derma-fat-fascia</td>
</tr>
<tr>
<td>15877</td>
<td>Suction assisted lipectomy; trunk</td>
</tr>
<tr>
<td>20926</td>
<td>Tissue grafts, other (e.g., paratenon, fat, dermis)</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listing in the CPB (not all inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L90.5</td>
<td>Scar conditions and fibrosis of skin</td>
</tr>
<tr>
<td>L91.0</td>
<td>Keloid scar</td>
</tr>
</tbody>
</table>

Autologous platelet-rich plasma, autologous platelet gel, and autologous platelet-derived growth factors (e.g., Autogel, Procuren, and Safeblood):

CPT not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0232T</td>
<td>Injection(s), platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed</td>
</tr>
<tr>
<td>0481T</td>
<td>Injection(s), autologous white blood cell concentrate (autologous protein solution), any site, including image guidance, harvesting and preparation, when performed</td>
</tr>
</tbody>
</table>

HCPCS codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S9055</td>
<td>Procure or other growth factor preparation to promote wound healing</td>
</tr>
</tbody>
</table>

Other HCPCS codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P9020</td>
<td>Platelet rich plasma, each unit</td>
</tr>
<tr>
<td>P9022</td>
<td>Red blood cells, washed, each unit</td>
</tr>
</tbody>
</table>

Axogen Nerve Wrap:

No specific code

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>64912</td>
<td>Nerve repair; with nerve allograft, each nerve, first strand (cable)</td>
</tr>
<tr>
<td>64913</td>
<td>Nerve repair; with nerve allograft, each additional strand (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

Avotemrin:

No specific code

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listing in the CPB (not all inclusive):

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L90.5</td>
<td>Scar conditions and fibrosis of skin</td>
</tr>
</tbody>
</table>

Cymetra Injectable Allograft:

HCPCS codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4112</td>
<td>Cymetra, injectable, 1 cc [for vocal cord paralysis - see CPB 253]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td><strong>DermaClose RC Continuous External Tissue Expander:</strong></td>
</tr>
<tr>
<td></td>
<td>No specific code</td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>11960</td>
<td>Insertion of tissue expander(s) for other than breast, including subsequent</td>
</tr>
<tr>
<td></td>
<td>expansion</td>
</tr>
<tr>
<td></td>
<td><strong>Evical Fibrin Sealant:</strong></td>
</tr>
<tr>
<td></td>
<td>No specific code</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>G96.0</td>
<td>Cerebrospinal fluid leak</td>
</tr>
<tr>
<td></td>
<td><strong>Integra Neural Wrap, NeuroMatrix Collagen Nerve Cuff, and NeuroMend Collagen Nerve Wrap:</strong></td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>64912</td>
<td>Nerve repair; with nerve allograft, each nerve, first strand (cable)</td>
</tr>
<tr>
<td>64913</td>
<td>Nerve repair; with nerve allograft, each additional strand (List separately in</td>
</tr>
<tr>
<td></td>
<td>addition to code for primary procedure)</td>
</tr>
<tr>
<td></td>
<td>HCPCS codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>C9355</td>
<td>Collagen nerve cuff (neuromatrix), per 0.5 centimeter length</td>
</tr>
<tr>
<td>C9361</td>
<td>Collagen matrix nerve wrap (neuromend collagen nerve wrap), per 0.5</td>
</tr>
<tr>
<td></td>
<td>centimeter length</td>
</tr>
<tr>
<td></td>
<td><strong>Integra Matrix Wound Dressing and Flowable Wound Matrix:</strong></td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB (not all-inclusive):</td>
</tr>
<tr>
<td>10040</td>
<td>Surgery, integumentary system</td>
</tr>
<tr>
<td></td>
<td>HCPCS codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>Q4108</td>
<td>Integra Matrix, per sq cm</td>
</tr>
<tr>
<td>Q4114</td>
<td>Integra Flowable Wound Matrix, injectable, 1 cc</td>
</tr>
<tr>
<td></td>
<td><strong>Oasis Burn Matrix:</strong></td>
</tr>
<tr>
<td></td>
<td>HCPCS codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>Q4103</td>
<td>Oasis Burn Matrix, per sq cm</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes not covered for indications listed in the CPB (not all inclusive):</td>
</tr>
<tr>
<td>T20.011+</td>
<td>Burns</td>
</tr>
<tr>
<td>T25.799+</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Parietex® Composite (PCO) Mesh:</strong></td>
</tr>
<tr>
<td></td>
<td>HCPCs codes not covered for the indications listed in the CPB:</td>
</tr>
<tr>
<td>C1781</td>
<td>Mesh (implantable)</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes not covered for indications listing in the CPB (not all inclusive):</td>
</tr>
<tr>
<td>N81.0 - N81.9</td>
<td>Female genital prolapse</td>
</tr>
<tr>
<td></td>
<td><strong>Permacol Biologic Implant:</strong></td>
</tr>
</tbody>
</table>


08/27/2019
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td></td>
<td>Too many to list.</td>
</tr>
<tr>
<td></td>
<td>HCPCS codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>C9364</td>
<td>Porcine implant, Permacol, per square centimeter</td>
</tr>
<tr>
<td></td>
<td>ICD-10 codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>K56.1</td>
<td>Intussusception [rectum]</td>
</tr>
<tr>
<td>K62.3</td>
<td>Rectal prolapse</td>
</tr>
<tr>
<td>N81.6</td>
<td>Rectocele</td>
</tr>
<tr>
<td></td>
<td>Radiofrequency stimulation:</td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>97032</td>
<td>Application of a modality to one or more areas; electrical stimulation, (manual), each 15 minutes</td>
</tr>
<tr>
<td></td>
<td>HCPCS codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>G0281</td>
<td>Electrical stimulation, (unattended), to one or more areas, for chronic Stage III and Stage IV pressure ulcers, arterial ulcers, diabetic ulcers, and venous stasis ulcers not demonstrating measurable signs of healing after 30 days of conventional care, as part of a therapy plan of care [if billed for Provant or MicroVas]</td>
</tr>
<tr>
<td>G0282</td>
<td>Electrical stimulation, (unattended), to one or more areas, for wound care other than described in G0281 [if billed for Provant or MicroVas]</td>
</tr>
<tr>
<td></td>
<td>SurgiMend:</td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td></td>
<td>Too many to list.</td>
</tr>
<tr>
<td></td>
<td>HCPCS codes not covered for indications listed in the CPB:</td>
</tr>
<tr>
<td>C9358</td>
<td>Dermal substitute, native, non-denatured collagen (SurgiMend Collagen Matrix), per 0.5 square centimeters</td>
</tr>
<tr>
<td>C9360</td>
<td>Dermal substitute, native, non-denatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 square centimeters</td>
</tr>
<tr>
<td></td>
<td>TenoGlide Tendon Protector Sheet:</td>
</tr>
<tr>
<td></td>
<td>CPT codes not covered for indications listed in the CPB (not all-inclusive):</td>
</tr>
<tr>
<td>20924</td>
<td>Tendon graft</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>23405 - 23406, 24300 - 24342, 25260 - 25316, 26350 - 26502, 26510, 27097 - 27098, 27380 - 27660 - 28262</td>
<td>Repair, revision, and/or reconstruction, tendon</td>
</tr>
<tr>
<td>25109, 26170, 26180</td>
<td>Excision of tendon</td>
</tr>
<tr>
<td>24357 - 24359, 26060, 27000 - 27006, 27306 - 27307, 27605 - 27606, 28010 - 28011</td>
<td>Tenotomy</td>
</tr>
</tbody>
</table>

HCPCS codes not covered for indications listed in the CPB:

| C9356 | Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (Tenoglide Tendon Protector Sheet), per square centimeter |

ICD-10 codes not covered for indications listed in the CPB (not all inclusive):

| Numerous options | Injury to nerves and spinal cord [Codes not listed due to expanded specificity] |

The above policy is based on the following references:

**General References**

2. School of Health and Related Research (ScHARR), University of Sheffield. Clinical Guidelines for Type 2 Diabetes: Prevention and Management of Foot Problems [Internet]. Sheffield, UK: University of Sheffield; 2003.


21. Canadian Agency for Drugs and Technologies in Health. Non-adherent versus traditional dressings for wound care: Comparative effectiveness, safety, and guidelines. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); 2011.


**Autologous Platelet-Derived Growth Factors (e.g., Procuren)**

https://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?

27. Centers for Medicare & Medicaid Services (CMS). National coverage
determination (NCD) for blood derived products for chronic non-healing
wounds (270.3). Baltimore, MD: CMS; August 2, 2012.

28. Wasiak J, Cleland H, Campbell F. Dressings for superficial and partial thickness

Publishing Group; September 2007.


plasma for treating chronic wounds. Cochrane Database Syst Rev. 2012;
(10):CD006899.

Apligraf

1. Eaglstein WH, Iriondo M, Laszlo K. A composite skin substitute (graftskin) for

of clinical rejection with an allogeneic cultured human skin equivalent. Human

3. Eaglstein WH, Falanga V. Tissue engineering and the development of Apligraf, a

4. Fahey C. Experience with a new human skin equivalent for healing venous leg


fibroblasts within in vitro reconstructed skin for grafting in humans. Plast

8. Sorensen JC. Living skin equivalents and their application in wound healing. Clin


10. Eaglstein WH, Falanga V. Tissue engineering and the development of Apligraf, a


Silver-Coated Wound Dressings (e.g., Acticoat, Actisorb)


15. Canadian Agency for Drugs and Technologies in Health (CADTH). Silver dressings for the treatment of patients with infected wounds: A review of clinical and cost-effectiveness. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); 2010.

Dermagraft


**TransCyte**


5. Amani H, Dougherty WR, Blome-Eberwein S. Use of Transcyte(R) and dermabrasion to treat burns reduces length of stay in burns of all size and etiology. Burns. 2006;32(7):828-832.

Orcel


MicroVas Vascular Treatment System


Provant Wound Closure System


Graftjacket Regenerative Tissue Matrix and Graftjacket Xpress


Platelet-Rich Plasma


Platelet Gel


PriMatrix Acellular Dermal Tissue Matrix


Oasis Wound Dressing and Oasis Burn Matrix


**Epicel Cultured Epidermal Autograft**


**Biobrane Biosynthetic Dressing**


**Alloderm**


Cymetra


Gore Bio-A Fistula Plug


E-Z Derm


Integra (Collagen-Glycosaminoglycan Copolymer)


**TissueMend**


**Veritas Collagen Matrix**


**NeuroMatrix Collagen Nerve Cuff and NeuroMend Collagen Nerve Wrap**


**TenoGlide**


**SurgiMend**


Gammagraft


Artiss


Permacol Biologic Implant


34. Bano F, Barrington JW, Dyer R. Comparison between porcine dermal implant (Permacol) and silicone injection (Macroplastique) for urodynamic stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 2005;16(2):147-150; discussion 150.

Artelon


**TheraSkin**


7. Lin Q, Rosines E, Taylor BM, Clagett J. TheraSkin analysis, stage 1 findings: Identification of key growth factors, cytokines and collagen in TheraSkin. Study conducted at Albany Medical Center and the University of Maryland, Institute of Human Virology through funding from Skin and Wound Allograft Institute, A Subsidiary of Lifenet Health. Scientific Data Series SDS 20-00. Newport News, VA: Soluble Systems; revised April 22, 2011.


FlexHD


**Hyalomatrix (hMatrix)**


22. Voigt J, Driver VR. Hyaluronic acid derivatives and their healing effect on burns, epithelial surgical wounds, and chronic wounds: A systematic review and meta-


**EpiFix**


EpiCord


AmnioExcel


Amniotic Fluid Injection


BioDfactor Human Amnion Allograft

DermaClose


Talymed


Fibrin Sealant for Breast Reconstruction


Pariete Composite (PCO) Mesh

Pelvicol


**Pelvisoft**


3. Long EL, Rebibo JD, Caremel R, Grise P. Efficacy of Pelvisoft® Biomesh for
(6):828-834.

Avaulta

1. Dass AK, Lo TS, Khanuengkitkong S, Tan YL. A delayed type of ureteric injury
developed after transobturator mesh procedure for massive prolapse. Female
3. Auzin M, Teune TM, Hogewoning CJ. Bladder polyps following Avaulta anterior
4. Bondili A, Duguara C, Cooper J. Medium-term effects of a monofilament
polypropylene mesh for pelvic organ prolapse and sexual function symptoms. J
5. Vollebregt A, Fischer K, Gietelink D, van der Vaart CH. Primary surgical repair of
anterior vaginal prolapse: A randomised trial comparing anatomical and
functional outcome between anterior colporrhaphy and trocar-guided
transobturator anterior mesh. BJOG. 2011;118(12):1518-1527.
delivery system for the correction of pelvic organ prolapse: Subjective and
objective findings at least 1 year after surgery. Am J Obstet Gynecol. 2010;203

CollaMend

Collamend® in trauma: Report of a case and review of the literature. World J
4. Harth KC, Rosen MJ. Major complications associated with xenograft biologic
mesh implantation in abdominal wall reconstruction. Surg Innov. 2009;16
Strattice


Vitagel


08/27/2019

Evicel


Endoform

**Enduragen**


**Epidex**


**Neoform**


MatriStem


Medihoney


Duragen


**Allomax**


**AlloPatch**


**AmnioBand and Guardian**


Alloskin


Axogen


Amniox


Artelon


GraftRope


Avotemin


CellerateRx


Xelma


Suprathel


EPIFLO Transdermal Continuous Oxygen Therapy [TCOT] for Wound Healing


Arthroflex


Conexa


Cormatrix


**DermACELL**


Dermamatrix


Duraseal


**Durepair**


**Orthadapt**


**Grafix**


Matriderm


**Medeor**


**Neox Flo**


**Neuragen**


**Neurawrap**


**Osseoguard**


Parietex for genitourinary prolapse


Peri-Guard


Peri-Strips and Peri-Strips Dry


**Cuffpatch**


**Promogan**


**PTFE Felt**


**Puracol**


**Seamguard**


19. Hawkins WG. To mesh or not to mesh, that is the question: Comment on "Use of Seamguard to prevent pancreatic leak following distal pancreatectomy". Arch Surg. 2009;144(10):899.


Sportmesh


Surgisis


**X- Repair**


**XCM Biologic Tissue Matrix**


**Xenmatrix**


**Unite**

2. Mulder G, Lee DK. Case presentation: Xenograft resistance to protease

3. Fleischli JG, Laughlin TJ, Fleischli JW. Equine pericardium collagen wound

Biovance


Repriza

1. Solomon MP, Komlo C, Defrain M. Allograft materials in phalloplasty: A

Dehydrated Human Amniotic Membrane Allograft (e.g., BioFix, FlowerPatch)

dehydrated human amnion/chorion membrane attenuates osteoarthritis

2016;104(7):1495-1503.

Placental Tissue Matrix Allograft (e.g., Viaflow and Viaflow C Flowable Placental
Tissue Matrices)

1. Lullove E. A Flowable Placental tissue matrix allograft in lower extremity injuries:
A pilot study. Cureus. 2015;7(6):e275. Available at:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4494536/.

chorion matrix as a favorable source of small-diameter vascular grafts. Acta

Cook Medical Anal Fistula Plug


CellECT


Bionect


7. Prescribing information for Bionect (hyaluronic acid sodium salt, 0.2%). Charleston, SC: Innocutis Holdings, LLC; June 2014.

WoundEx Flow


Alloderm and Strattice for Surgical Repair of Complex Abdominal Wall Wounds


Grafrix Cryo-Preserved Placental Membrane


Amniotic-Derived Products


Amendment to
Aetna Clinical Policy Bulletin Number: 0244 Wound Care

There are no amendments for Medicaid.