Skin Substitutes for Wound Care AHM

Clinical Indications

- Any **1 or more** of the following products for wound care are considered medically necessary if the individual criteria are met
  - **Apligraf (graftskin)** aculture-derived human skin equivalent (HSE) is considered medically necessary for **1 or more** of the following indications:
    - For use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three-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
    - 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 one-month duration using regular dressing changes and standard therapeutic compression
  - **Dermagraft,** a human fibroblast-derived dermal substitute, is considered medically necessary for any **1 or more** of the following [A] [B]
    - Treatment of full-thickness diabetic foot ulcers greater than six-week duration that extend through the dermis, but without tendon, muscle, joint capsule or bone exposure
    - Treatment of wounds related to dystrophic epidermolysis bullosa
  - **Systemic Hyperbaric Oxygen Therapy (HBOT**) **- Refer to the Hyperbaric Oxygen Therapy Guideline.**
  - **TransCyte,** made up of allogeneic human dermal fibroblasts, a biosynthetic dressing, is considered medically necessary for any **1 or more** of the following
    - 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
    - Treatment of mid-dermal to indeterminate depth burn wounds that typically require debridement and that may be expected to heal without autografting
  - **Orcel,** a bilayered cellular matrix, is considered medically necessary for any **1 or more** of the following
    - Healing donor site wounds in burn victims

    - Dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites.
  - **Biobrane biosynthetic dressing** is considered medically necessary for temporary covering of a superficial partial-thickness burn wound.
  - **Integra Dermal Regeneration Template**, **Integra Bilayer Matrix Wound Dressing, and Integra Meshed Bilayer Wound Matrix** (collagen-glycosaminoglycan copolymers) is considered 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.
  - **Alloderm,** acellular dermal tissue matrix, is considered medically necessary for breast reconstructive surgery
  - **Artiss fibrin sealant** is considered medically necessary for the treatment of individuals with severe burns
  - **Oasis Wound Matrix** is considered 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.
  - **Graftjacket Regenerative Tissue Matrix** is considered medically necessary 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 cultured epidermal autograft** is considered 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.
- Current role remains uncertain. Based on review of existing evidence, there are currently no clinical indications for this technology. See Inappropriate Uses for more detailed analysis of the evidence base. The following substitutes are considered investigational because there is inadequate evidence in the peer reviewed medical literature to support their clinical effectiveness Examples include
  - Allopatch for soft tissue augmentation and all other indications
  - Alloskin
  - Alloskin RT
  - AlloSource cryopreserved human cadaver skin
  - AmnioCare
  - AmnioExCel
  - AmnioFix
  - Amniomatrix

- AmnioMTM
- AmnioShield
- Amniotic fluid injection for corneal wound healing and for prevention of adhesions after orthopedic surgery
- Amniox (human embryonic membrane) for tarsel tunnel repair and all other indications
- 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
- Arthroflex (FlexGraft)
- Autologous blood-derived products (e.g., autologous platelet-rich plasma, autologous platelet gel, and autologous platelet-derived growth factors (e.g., Autologel, Procuren, and SafeBlood))
- Autologous fat for the treatment of scars
- Axogen 2 nerve wrap
- Avotermin for improvement of skin scarring
- BioDfactor/BioDfence human amniotic allograft
- Biostat Biologx fibrin sealant for wound healing and all other indications;
- Biotape reinforcement matrix for soft tissue augmentation and all other indications
- CellerateRX
- CollaFix
- Conexa reconstructive tissue matrix
- CorMatrix Patch for cardiac tissue repair and all other indications
- C-QUR biosynthetic mesh
- CRXa
- Cymetra injectable allograft for wound healing
- Dermacell
- DermaClose RC continuous external tissue expander for facilitation of wound closure and all other indications
- Dermagraft for chronic foot ulcer secondary to necrotizing fasciitis
- DermaMatrix for wound healing and other indications other than breast reconstruction
- DermaSpan
- 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
- DuraSeal
- Durepair Regeneration Matrix
- Endoform

- ENDURAGen
- Epidex
- EpiFix amniotic membrane for indications other than ocular surface disorders
- EPIFLO transdermal continuous oxygen therapy for wound healing
- Equine-derived decellularized collagen products (e.g., OrthADAPT, Unite, and Unite Biomatrix)
- E-Z Derm for wound healing and all other indications
- Evicel fibrin sealant for repair of cerebrospinal fluid leakage and all other indications
- FlexHD acellular dermal matrix for wound healing; for FlexHD for breast reconstruction
- FloGraft
- Gammagraft skin substitute for wound healing and all other indications
- GORE BIO-A Fistula Plug
- Grafix Core and Grafix Prime
- Graftjacket express injectable allograft for wound healing and all other indications
- Hyalomatrix (hMatrix)
- HydroFix
- Inforce
- Integra Neural Wrap for peripheral nerve repair and all other indications
- 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
- LiquidGen
- Matriderm
- MatriStem wound micromatrix powder
- MediHoney
- Medeor
- Memoderm
- Menaflex Collagen Meniscus Implant
- Meso BioMatrix
- Neoform Dermis for wound healing; for NeoForm for breast reconstruction
- Neox 1K
- Neox 100
- Neuragen
- NeuraWrap
- Neuroflex

- NeuroMatrix collagen nerve cuff for peripheral nerve repair and all other indications
- NeuroMend collagen nerve wrap for peripheral nerve repair and all other indications
- NuCel liquid wound covering
- NuShield, NuShield Orthopaedics, and NuShield Spine
- Oasis burn matrix for wound healing and all other indications
- Oasis Tri-Layer Matrix
- OrthADAPT Bioimplant (type I collagen scaffold) for tendon repair and all other indications
- OsseoGuard
- Ovation
- PalinGen membrane for wound healing
- 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
- 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 acellular dermal tissue matrix for wound healing and all other indications
- Promogran
- Promogran
- PTFE felt
- Puracol
- Radiofrequency stimulation devices (e.g., Provant Wound Closure System, MicroVas Vascular Treatment System) for wound healing
- Seamguard
- Silver-coated wound dressings (e.g., Acticoat, Actisorb, and Silversorb) for wound healing and all other indications
- Solana allograft
- SportMatrix
- SportMesh
- Strattice tissue matrix for wound healing
- Suprathel

- 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 indications other than breast reconstruction; for SurgiMend for breast reconstruction
- Surgisis (including Surgisis AFP Anal Fistula Plug, Surgisis Gold Hernia Repair Grafts, and Surgisis Biodesign)
- Talymed
- TenoGlide tendon protector sheet (Tendon WrapTM 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
- 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
- Tornier BioFiber Absorbable Biological Scaffold, and Tornier Collagen Coated BioFiber Scaffold
- Vaso Shield
- Veritas collagen matrix for use as an implant in the surgical repair of soft tissue deficiencies and all other indications
- Vitagel surgical hemostat for wound healing and all other indications;
- X-Repair
- XCM Biologic
- Xelma
- XenMatri

Evidence Summary

Background

- **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) 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 fibrobasts are derived from neonatal forsekins. 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 teh 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.
- 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:**
- Another product approved by the FDA for repair of diabetic foot ulcers is Advanced BioHealing, Inc. (La Jolla, CA) Dermagraft, 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. Dermagraft has also been approved by the FDA for use in the treatment of wounds related to dystrophic epidermolysis bullosa.
- In May 2006, Advanced BioHealing purchased the global rights to Dermagraft from Smith & Nephew.
- **TransCyte**
- TransCyte (Advanced Tissue Sciences Inc. La Jolla, CA), a bioactive skin substitute, 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." TranCyte 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 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.
- **Autologous Blood Derived Products: Autologous Platelet-Rich Plasma, Autologous Platelet Gel, and Autologous Platelet-Derived Growth Factors (e.g., Procuren)**
- 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 a., 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 (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.

- PriMatrix Acellular Dermal Tissue Matrix
- PriMatrix acellular dermal tissue matrix, formerly known as DressSkin (TEI Biosciences Inc., Boston, MA) was cleared by the FDA via the 510(k) process. It is an acellular collagen dermal tissue matrix derived from fetal bovine skin. PriMatrix is indicated 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).
- 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 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 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 debridement. 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 Ultra Tri-Layer Wound Matrix**
- OASIS Ultra Tri-Layer Wound Matrix is an extracellular 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, second 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 remodeled 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 two 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.
- **Epicel**
- Epicel (Genzyme Biosurgery, Cambridge, MA) is a cultured epidermal autograft intended to treat deep dermal or full-thickness burns (Snyder, et al., 2012). 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 in 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".

- **AlloDerm**
- AlloDerm (Life Cell Corp., The Woodlands, TX), an acellular dermal matrix processed from human allograft skin. 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 sikin 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 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-appoximation. 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; Breuing 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.
- 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 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 modified 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 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 (Vanstraelen, 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 neodermis 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."
- Integra Meshed Bilayer Wound Matrix is an advanced wound care device comprised of a porous matrix of cross-linked bovine tendon collagen and glyscosaminoglycan 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-MohaEYs 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 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.

- 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, quadriceps, 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
- 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, bronchila 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.
- **NeuroMatrixTM Collagen Nerve Cuff and NeuroMendTM 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 (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.
- **TenoGlideTM 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 (TEI Biosciences, Boston, MA) was cleared through the FDA 510(k) process in 2007. It is an acellular dermal tissue matrix derived from fetal 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 uncerlying 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, anc 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 foid 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 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 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.
- 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.

- **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. Gisselfalt 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.
- 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 may be used in diabetic foot ulcers, venous stasis ulcers, and pressure ulcers.
- 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 6.2cm2 (+/- 11.8) and 11.8cm2 (+/- 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.
- 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).
- **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) and a semipermeable silicone membrane (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." 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/grafts, 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/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, skin tears) and first and second degree bums." 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.
- 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 igroup 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 > or =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).

- **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.

- There is limited evidence from well-controlled studies of the use of EpiFix amniotic membrane allograft in the treatment of wounds, 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, clinical outcome studies of EpiFix are needed to determine its performance in wound care.
- **MatriStem Wound Care Matrix**
- 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 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 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 MicroMatrix is a porcine-derived, naturally occurring non cross-linked, completely resorbable, acellular extracellular matrix derived from specific layers of porcine urinary bladder.
- MatriStem MicroMatrix is made from the same material as the MartiStem Wound Sheet (see 10.062), 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 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 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 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 wound powder.
- MatriStem is a porcine-derived, naturally occurring lyophilized extracellular matrix that maintains and supports a healing environment for wound management. MatriStem 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 serveral types of collagen, adhesion proteins, glycoproteins, and other elements of an extracellular matrix which all act synergistically in supporting natural tissue healing. MatriStem triggers abundant new blood vessel formation and recruits numberous 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 wound sheets are supplies 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). 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.

- MatriStem 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 changes 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 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 Surgical Matrix products are supplied as follows: surgical Matrix RS as (box of 5) 1.5 cm discs, 1 ea. 2cm x 4 cm, 1 ea. 2cm x 4 cm, 1 ea. 5 cm x 5 cm, 1 ea. 7cm x 10cm, 1ea. 6cm x 15cm, 1ea. 10cm x 15 cm; Plastic Surgery Matrix as (box of 5) 1.5 cm discs, 1ea. 4cm x 12cm, 1ea. 6cm x 15cm, 1ea. 7cm x 10cm, 1ea. 10cm x 15cm; Plastic Surgery Matrix XS as 1ea. 4cm x 12cm, 1ea. 6cm x 15cm, 1ea. 7cm x 10cm and 1ea. 10cm x 15cm. 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.
- MatriStem Burn Matrix is a porcine-derived, naturally occurring dehydrated extracellular matrix that maintains and supports a healing environment for wound management. MatriStem 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. 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 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 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: 1) naturally occurring, non-cross-linked extracellular matrix; 2) completely resorbable; 3) acellular; 3) contains multiple naturally occurring growth factors; 4) bimodal surface characteristic; 5) may reduce scar tissue formation; 6) antimicrobial properties; 7) lyophilized; and 8) indicated in a complete range of wounds.

- MatriStem 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 PSMX changes the healing response, resulting in remodeled, functional, site specific tissue. MatriStem 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 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 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 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 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 Wound Matrix RS changes the healing response, resulting in remodeled, functional, site specific tissue. MatriStem 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 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 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 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 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 PSM changes the healing response, resulting in remodeled, functional, site specific tissue. MatriStem 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 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 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 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.
- **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**
- 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 vascularizaton 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 include 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).
- **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. However, there is a lack of evidence regarding the effectiveness of the Oasis tri-layer matrix.
- **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.
- Ferguson et al (2009) assessed scar improvement with avotermin (recombinant, active, human TGFbeta3). In 3 double-blind, placebo-controlled studies, intra-dermal avotermin (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 (avotermin and placebo or standard wound care) were randomly allocated to wound sites by a computer generated randomization scheme, and within-participant controls compared avotermin 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, avotermin 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, avotermin 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 (Euro 1,053 compared with Euro 1,825 for amniotic membrane grafts and Euro 5,767 for biocompatible skin grafts). At 6 months, however, amniotic membrane grafts would have cost Euro 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.

- **Grafix Core and Grafix Prime**
- 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.
- There is currently (last verified may 2012) an open-label clinical trial to examine the safety and effectiveness of Grafix for the treatment of chronic diabetic foot ulcers. http://clinicaltrials.gov/ct2/show/NCT01596920.
- **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.
- **Mediskin**
- 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 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 (allofibroblasts 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, multi-layer surgical wounds/openings and other damaged tissue. 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 & 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.
- **AllopatchHD**

- AlloPatchHD is a 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 vascularizaton 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 scaffold for tendon augmentation (Snyder, et al., 2012).
- **Arthroflex**
- According to the manufacturer, Arthroflex 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. 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 a 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 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 insufficient published evidence in the peer-reviewed medical literature on DermACELL (Chen, et al., 2012; Capito, et al., 2012).
- **Repriza**
- Repriza is an 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. 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 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**
- 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 indicated for local management of moderately to heavily exudating wounds. Unite Biomatrix was cleared by the FDA in 2011 based upon a 510(k) "For the management of moderately to severely exudating 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 Technlogies, Inc., Danvers, MA) is a sterile 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, ovine acellular, collagen, single-use wound dressing 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 & TGFB)."
- 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 ov 55 perccent collagen and 45 percent oxidized regenerated cellulose. Promogran Matrix wound ressing 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).

- **Grafix**
- 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.

- **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. Sixty-nine 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 percent. Nine cases required surgical revision, and there were four 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 Dental**
- 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). The Suprathel membrane is applied once to a clean debrided 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 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 debridement.
- 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."
- **Epidex**
- Epidex (Euroderm AG, Baden-Dattwil, 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. http://www.ogenix.com/. 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**
- 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.
- **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 can not be completed.

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Reviewed by a Board Certified Internist
Reviewed by David Evans, MD, Medical Director, Active Health Management- May 2016

Footnotes

[A] Dermagraft is contraindicated and has no proven value in infected ulcers and ulcers with sinus tracts. [A in Context Link 1]

[B] Note: Consistent with the FDA-approved labeling of Dermagraft, the product should be used in 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 [B in Context Link 1]

Codes

CPT® or HCPCS: 11042, 11043, 11044, 11045, 11046, 11047, 15002, 15003, 15004, 15005, 15050, 15100, 15101, 15110, 15111, 15115, 15116, 15120, 15121, 15130, 15131, 15135, 15136, 15150, 15151, 15152, 15155, 15156, 15157, 15200, 15220, 15221, 15240, 15241, 15261, 15340, 15341, 15777, 19357, 19361, 19364, 19366, 19367, 19368, 19369, 23420, 23470, 23472, 23473, 23474, 24344, 24345, 24346, 24360, 24361, 24362, 24363, 24365, 24366, 24370, 24371, 25320, 25337, 25390, 25391, 25392, 25393, 25441, 25442, 25446, 26135, 26140, 26390, 26490, 26492, 26494, 26496, 26500, 26502, 26530, 26531, 26535, 26536, 26541, 26542, 26545, 26548, 26551, 26553, 26554, 26555, 26556, 26587, 29806, 29807, 29819, 29820, 29822, 29823, 29824, 29825, 29826, 29827, 29828, 42410, 42415, 42420, 42425, 42426, 64910, 96372, 97597, 97598, 99183, C9250, G0440, G0441, q4101, Q4102, Q4104, Q4105, Q4106, Q4116, 15260, 26550, C1300, Q4101