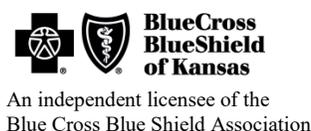


## Medical Policy



### Title: **Bio-Engineered Skin and Soft Tissue Substitutes**

*See Also:*

- *Amniotic Membrane and Amniotic Fluid medical policy*
- *Periodontal Soft Tissue Grafting dental policy*

#### **Professional**

Original Effective Date: February 13, 2007  
 Revision Date(s): May 21, 2008,  
 August 3, 2010; March 1, 2012;  
 January 15, 2013; December 12, 2013;  
 January 1, 2014; April 30, 2015;  
 May 1, 2016; March 20, 2017;  
 April 19, 2017; July 18, 2018  
 January 1, 2019  
 Current Effective Date: January 1, 2019

#### **Institutional**

Original Effective Date: December 15, 2008  
 Revision Date(s): September 2, 2010;  
 March 1, 2012; January 15, 2013;  
 December 12, 2013; January 1, 2014;  
 April 30, 2015; May 1, 2016;  
 March 20, 2017; April 19, 2017;  
 July 18, 2018; January 1, 2019  
 Current Effective Date: January 1, 2019

**State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).**

**The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.**

**The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.**

**If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.**

<b>Populations</b>	<b>Interventions</b>	<b>Comparators</b>	<b>Outcomes</b>
Individuals: <ul style="list-style-type: none"> <li>• Who are undergoing breast reconstruction</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Allogeneic acellular dermal matrix products</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Breast reconstruction without an acellular dermal matrix product</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Symptoms</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Quality of life</li> <li>• Treatment-related morbidity</li> </ul>

<b>Populations</b>	<b>Interventions</b>	<b>Comparators</b>	<b>Outcomes</b>
Individuals: • Who are undergoing tendon repair	Interventions of interest are: • Graftjacket	Comparators of interest are: • Surgical repair alone	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • Who are undergoing surgical repair of hernias or parastomal reinforcement	Interventions of interest are: • Acellular collagen-based scaffolds	Comparators of interest are: • Surgical repair alone • Standard surgical mesh	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With diabetic lower-extremity ulcers	Interventions of interest are: • Apligraf, Dermagraft, AlloPatch, or Integra	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life
Individuals: • With diabetic lower-extremity ulcers	Interventions of interest are: • Acellular dermal matrix products other than, Apligraf, Dermagraft, AlloPatch or Integra	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life
Individuals: • With lower-extremity ulcers due to venous insufficiency	Interventions of interest are: • Apligraf and Oasis Wound Matrix	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life
Individuals: • With lower-extremity ulcers due to venous insufficiency	Interventions of interest are: • Bioengineered skin substitutes other than Apligraf and Oasis Wound Matrix	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Disease-specific survival • Symptoms • Change in disease status • Morbid events • Quality of life
Individuals: • With dystrophic epidermolysis bullosa	Interventions of interest are: • Bioengineered skin substitutes (ie, OrCel)	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life
Individuals: • With deep dermal burns	Interventions of interest are: • Bioengineered skin substitutes (ie, Epicel, Integra Dermal Regeneration Template)	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Disease-specific survival • Symptoms • Morbid events • Functional outcomes • Quality of life • Treatment-related morbidity

## **DESCRIPTION**

Bioengineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman tissue (xenographic), synthetic materials, or a composite of these materials. Bioengineered skin and soft tissue substitutes are being

evaluated for a variety of conditions, including breast reconstruction and healing lower -xtremity ulcers and severe burns. Acellular dermal matrix (ADM) products are also being evaluated for soft tissue repair.

## **Objective**

The objective of this evidence review is to evaluate the evidence on the use of artificial skin and soft-tissue substitutes for reinforcement for surgical procedures, and healing of chronic wounds and burns.

## **Background**

### **Skin and Soft Tissue Substitutes**

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

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

### **Applications**

There are a large number of potential applications for artificial skin and soft tissue products. One large category is nonhealing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, nonhealing lower-extremity wounds represent an ongoing risk for infection, sepsis, limb amputation and death. Bioengineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

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

including rotator cuff repair, following oral and facial surgery, hernias, and other conditions.

## **Regulatory Status**

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

### **Acellular Dermal Matrix Products**

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

- AlloDerm® (LifeCell Corp.) is an ADM (allograft) tissue-replacement product created from native human skin and processed so that the basement membrane and cellular matrix remain intact. Originally, AlloDerm® required refrigeration and rehydration before use. It is currently available in a ready-to-use product stored at room temperature. An injectable micronized form of AlloDerm® (Cymetra) is also available.
- Cortiva® (previously marketed as AlloMax™ Surgical Graft and before that NeoForm™) is an acellular non-cross-linked human dermis allograft.
- AlloPatch® (Musculoskeletal Transplant Foundation) is an acellular human dermis allograft derived from the reticular layer of the dermis and marketed for wound care. This product is also marketed as FlexHD® for postmastectomy breast reconstruction.
- FlexHD® and the newer formulation FlexHD® Pliable™ (Musculoskeletal Transplant Foundation) are acellular hydrated reticular dermis allograft derived from donated human skin.
- DermACELL™ (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL® and PRESERVON®.
- DermaMatrix (Synthes) is a freeze-dried ADM derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation.
- DermaPure™ (Tissue Regenix Wound Care) is a single-layer decellularized human dermal allograft for the treatment of acute and chronic wounds.
- GraftJacket® Regenerative Tissue Matrix (also called GraftJacket Skin Substitute, KCI) is an acellular regenerative tissue matrix that has been processed from human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells, while preserving dermal structure. GraftJacket Xpress® is an injectable product.

FDA product code: FTM, OXF.

## **Xenogenic Products**

Cytal™ (previously called MatriStem®) Wound Matrix, Multilayer Wound Matrix, Pelvic Floor Matrix, MicroMatrix, and Burn Matrix (all manufactured by ACell) are composed of porcine-derived urinary bladder matrix.

Helicoll (Encol) is an acellular collagen matrix from bovine dermis. In 2004, it was cleared for marketing by FDA through the 510(k) process for topical wound management that includes partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (eg, abrasions, lacerations, second-degree burns, skin tears), and surgical wounds including donor sites/grafts.

Keramatrix® (Keraplast Research) is an open-cell foam comprised of freeze-dried keratin that is derived from acellular animal protein. In 2009, it was cleared for marketing by FDA through the 510(k) process under the name of Keratec. The wound dressings are indicated in the management of the following types of dry, light, and moderately exudating partial and full-thickness wounds: pressure (stage I-IV) and venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, donor sites, and grafts.

Kerecis™ Omega3 Wound (Kerecis) is an ADM derived from fish skin. It has a high content of omega 3 fatty acids and is intended for use in burn wounds, chronic wounds, and other applications.

Permacol™ (Covidien) is xenogenic and composed of cross-linked porcine dermal collagen. Cross-linking improves the tensile strength and long-term durability but decreases pliability.

PriMatrix™ (TEI Biosciences) is a xenogeneic ADM processed from fetal bovine dermis. It was cleared for marketing by FDA through the 510(k) process for partial- and full-thickness wounds; diabetic, pressure, and venous stasis ulcers; surgical wounds; and tunneling, draining, and traumatic wounds. FDA product code: KGN

SurgiMend® PRS (TEI Biosciences) is a xenogeneic ADM processed from fetal bovine dermis.

Strattice™ Reconstructive Tissue Matrix (LifeCell Corp) is a xenogenic non-cross-linked porcine-derived ADM. There are pliable and firm versions, which are stored at room temperature and come fully hydrated.

OASIS™ Wound Matrix (Cook Biotech) is a collagen scaffold (extracellular matrix) derived from porcine small intestinal submucosa. In 2000, it was cleared for marketing by FDA through the 510(k) process for the management of partial- and full-thickness wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds. FDA Product code: KGN.

### **Living Cell Therapy**

Apligraf® (Organogenesis) is a bilayered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. Apligraf® is supplied as needed, in 1 size, with a shelf-life of 10 days. In 1998, it was approved by FDA for use in conjunction with compression therapy for the treatment of noninfected, partial- and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower-extremity ulcers nonresponsive to standard wound therapy. FDA product code: FTM

Dermagraft® (Organogenesis) is composed of cryopreserved human-derived fibroblasts and collagen derived from newborn human foreskin and cultured on a bioabsorbable polyglactin mesh scaffold. Dermagraft has been approved by the FDA for repair of diabetic foot ulcers. FDA product code: PFC

TheraSkin® (Soluble Systems) is a cryopreserved split-thickness human skin allograft composed of living fibroblasts and keratinocytes and an extracellular matrix in epidermal and dermal layers. TheraSkin® is derived from human skin allograft supplied by tissue banks compliant with the AATB and FDA guidelines. It is considered a minimally processed human cell, tissue, and cellular- and tissue-based product by FDA.

Epicel® (Genzyme Biosurgery) is a cultured epithelial autograft composed of a patient's own keratinocytes cultured ex vivo and is FDA-approved under a humanitarian device exemption (HDE) for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. 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. FDA product code: OCE

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

### **Biosynthetic Products**

Biobrane®/Biobrane-L (Smith and Nephew) is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially imbedded into the film. The fabric creates a complex 3-dimensional structure of trifilament thread, which chemically binds collagen. Blood/sera clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs. FDA product code: FRO

Integra® Dermal Regeneration Template (also marketed as Omnigraft Dermal Regeneration Matrix, Integra LifeSciences) is a bovine, collagen/glycosaminoglycan

dermal replacement covered by a silicone temporary epidermal substitute. It was approved by FDA for use in postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable because of the physiologic condition of the patient and for certain diabetic foot ulcers. Integra™ Matrix Wound Dressing and Integra™ Meshed Bilayer Wound Matrix are substantially equivalent skin substitutes and were cleared for marketing by FDA through the 510(k) process for other indications. Integra® Bilayer Wound Matrix (Integra LifeSciences) is designed to be used in conjunction with negative pressure wound therapy. The meshed bilayer provides a flexible wound covering and allows drainage of wound exudate. FDA product code: MDD

TransCyte™ (Advanced Tissue Sciences) consists of human dermal fibroblasts grown on nylon mesh, combined with a synthetic epidermal layer and was approved by FDA in 1997. TransCyte is intended as a temporary covering over burns until autografting is possible. It can also be used as a temporary covering for some burn wounds that heal without autografting.

### **Synthetic Products**

Suprathel® (PolyMedics Innovations) is a synthetic copolymer membrane fabricated from a tripolymer of polylactide, trimethylene carbonate, and s-caprolactone. It is used to provide temporary coverage of superficial dermal burns and wounds. Suprathel® is covered with gauze and a dressing that is left in place until the wound has healed.

## **POLICY**

**Note: Use Q4100 for skin substitutes that do not have a unique code.**

- A. Breast reconstructive surgery:
- when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required,
  - when there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis, or
  - the inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed
- using the following allogeneic acellular dermal matrix products <sup>a</sup> may be considered **medically necessary**. (See Policy Guidelines)
1. AlloDerm (Q4116)
  2. AlloMax
  3. AlloMend
  4. Cortiva
  5. DermACELL (Q4122)
  6. DermaMatrix
  7. FlexHD (Q4128)
  8. FlexHD Pliable
  9. GraftJacket (Q4107)
- B. Treatment of chronic, noninfected, full-thickness diabetic lower-extremity ulcers using the following tissue-engineered skin substitutes may be considered **medically necessary**.
1. AlloPatch <sup>a</sup> (Q4128)
  2. Apligraf <sup>b</sup> (Q4101)
  3. Dermagraft <sup>b</sup> (Q4106)
  4. Integra Omnigraft Dermal Regeneration Matrix (also known as Omnigraft) (Q4105)
  5. Integra Flowable Wound Matrix (Q4114)
- C. Treatment of chronic, noninfected, partial- or full-thickness lower-extremity skin ulcers due to venous insufficiency, which have not adequately responded following a 1-month period of conventional ulcer therapy, using the following tissue-engineered skin substitutes may be considered **medically necessary**.
1. Apligraf <sup>b</sup> (Q4101)
  2. Oasis Wound Matrix <sup>c</sup> (Q4102)

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

1. OrCel

(for the treatment of mitten-hand deformity when standard wound therapy has failed and when provided in accordance with the humanitarian device exemption (HDE) specifications of the U.S. Food and Drug Administration [FDA])<sup>d</sup>

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

1. Epicel

(for the treatment of deep dermal or full-thickness burns comprising a total body surface area  $\geq 30\%$  when provided in accordance with the HDE specifications of the FDA)<sup>d</sup>

2. Integra Omnigraft Dermal Regeneration Matrix (also known as Omnigraft)<sup>b</sup> (Q4105)

<sup>a</sup> Banked human tissue

<sup>b</sup> FDA premarket approved

<sup>c</sup> FDA 510(k) cleared

<sup>d</sup> FDA-approved under an HDE

F. All other uses of the bioengineered skin and soft tissue substitutes listed above are considered **experimental / investigational**.

G. All other skin and soft tissue substitutes not listed above are considered **experimental / investigational**, including, but not limited to:

<b>Experimental / Investigational</b>	
1.	ACell UBM Hydrated / Lyophilized Wound Dressing
2.	AlloSkin (Q4115)
3.	AlloSkin AC, per sq cm (Q4141)
4.	AlloSkin RT (Q4123)
5.	Amino wound (Q4181)
6.	Aongen Collagen Matrix
7.	Architect ECM, PX, FX (Q4147)
8.	ArthroFlex (Flex Graft) (Q4125)
9.	Atlas Wound Matrix
10.	Avagen Wound Dressing
11.	AxoGuard Nerve Protector (AxoGen)
12.	Biobrane / Biobrane-L
13.	Bio-ConneKt wound matrix, per sq cm (Q4161)
14.	CollaCare
15.	CollaCare Dental
16.	Collagen Wound Dressing (Oasis Research)
17.	CollaGUARD
18.	CollaMend
19.	CollaWound

<b>Experimental / Investigational</b>	
20.	Coll-e-derm, per square centimeter (Q4193)
21.	Collexa
22.	Collieva
23.	Conexa
24.	Coreleader Colla-Pad
25.	CorMatrix
26.	Cymetra (Micronized AlloDerm) (Q4112)
27.	Cytal (previously MatriStem) (Q4166)
28.	Dermadapt Wound Dressing
29.	Derma-gide, per square centimeter (Q4203)
30.	DermaPure (Q4152)
31.	DermaSpan (Q4126)
32.	DressSkin
33.	Durepair Regeneration Matrix
34.	Endoform Dermal Template
35.	ENDURAGen
36.	Excellagen (Q4149)
37.	ExpressGraft
38.	E-Z Derm (Q4136)
39.	FlexiGraft
40.	Floweramnioflo (Q4177)
41.	Floweramniopatch (Q4178)
42.	Flowerderm (Q4179)
43.	GammaGraft (Q4111)
44.	GraftJacket Xpress, injectable (Q4113)
45.	Helicoll (Q4164)
46.	hMatrix (Q4134)
47.	Hyalomatrix (Q4117)
48.	Hyalomatrix PA
49.	Integra Bilayer Wound Matrix (C9363, Q4104)
50.	Integra Matrix, per sq cm (Q4108)
51.	Keramatrix, per sq cm (Q4165)
52.	Kerecis (Q4158)
53.	Kerxxx (2.5g/cc), 1cc (Q4202)
54.	MariGen / Kerecis Omega3 (Q4158)
55.	MatriDerm
56.	MatriStem Micromatrix (Q4118)
57.	Matrix HD (Q4128)
58.	Mediskin (Q4135)
59.	MemoDerm (Q4126)
60.	Miroderm biologic wound matrix (Q4175)
61.	NeoForm
62.	Neopatch (Q4176)
63.	NuCel
64.	Oasis Burn Matrix (Q4103)
65.	Oasis Ultra (Q4124)
66.	Pelvicol / PelviSoft

<b>Experimental / Investigational</b>
67. Permacol (C9364)
68. PriMatrix (Q4110)
69. Primatrix Dermal Repair Scaffold
70. Puraply, per square centimeter (Q4195)
71. Puraply am, per square centimeter (Q4196)
72. Puraply xt, per square centimeter (Q4197)
73. Puros Dermis
74. RegenePro
75. Repliform
76. Repriza (Q4143)
77. Revita (Q4180)
78. Skin te, per square centimeter (Q4200)
79. StrataGraft
80. Strattice (xenograft) (Q4130)
81. Suprathel
82. SurgiMend (C9358, C9360)
83. Talymed (Q4127)
84. TenoGlide (C9356)
85. TenSix Acellular Dermal Matrix (Q4146)
86. TheraForm Standard/Sheet
87. TheraSkin (Q4121)
88. TissueMend
89. TransCyte (Q4182)
90. TruSkin (Q4167)
91. Veritas Collagen Matrix (C9354)
92. XCM Biologic Tissue Matrix (Q4142)
93. XenMatrix AB

**Note: Use Q4100 for skin substitutes that do not have a unique code.**

### **Policy Guidelines**

Clinical input has indicated that the various acellular dermal matrix (ADM) products used in breast reconstruction have similar efficacy. The products listed are those that have been identified for use in breast reconstruction. Additional ADM products may become available for this indication.

### **RATIONALE**

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through November 6, 2017.

The original review focused on the use of an allogeneic bioengineered skin substitutes in breast reconstructive surgery and was expanded in 2011 to address additional indications.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific

outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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

1. Incidence of complete wound closure.
2. Time to complete wound closure (reflecting accelerated wound closure).
3. Incidence of complete wound closure following surgical wound closure.
4. Pain control.

The following is a summary of key literature to date.

### **Breast Reconstruction**

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

A 2013 study used data from the American College of Surgeon's National Surgical Quality Improvement Program to compare ADM-assisted tissue expander breast reconstruction (n=1717) to submuscular tissue expander breast reconstruction (n=7442) after mastectomy.<sup>1</sup> Complication rates did not differ significantly between the ADM-assisted (5.5%) and the submuscular tissue expander groups (5.3%; p=0.68). Rates of reconstruction-related complications, major complications, and 30-day reoperation did not differ significantly between cohorts.

### **Systematic Reviews**

A 2016 meta-analysis by Lee and Mun included 23 studies (total N=6199 cases) on implant-based breast reconstruction that were published between February 2011 and December 2014.<sup>2</sup> The analysis included an RCT and 3 prospective comparative cohort studies; the remainder was retrospective comparative cohort studies. Use of ADM did not affect the total complication rate (see Table 1). ADM significantly increased the risk of major infection, seroma, and flap necrosis, but reduced risks of capsular contracture and implant malposition. Use of ADM allowed for significantly greater intraoperative expansion (mean difference [MD], 79.63; 95% confidence

interval [CI], 41.99 to 117.26;  $p < 0.001$ ) and percentage of intraoperative filling (MD=13.30; 95% CI, 9.95 to 16.65;  $p < 0.001$ ), and reduced the frequency of injections to complete expansion (MD = -1.56; 95% CI, -2.77 to -0.35;  $p = 0.01$ ).

**Table 1. Meta-Analysis of Breast Reconstruction Outcomes With and Without ADM**

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

Adapted from Lee and Mun (2016).<sup>2</sup>

ADM: acellular dermal matrix; *NS*: not significant.

## AlloDerm

### *Randomized Controlled Trials*

In 2012, McCarthy et al reported on a multicenter, blinded RCT of AlloDerm in 2-stage expander/implant reconstruction.<sup>3</sup> Seventy patients were randomized to AlloDerm ADM-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. The trial was adequately powered to detect clinically significant differences in immediate postoperative pain but underpowered to detect the secondary end point of pain during tissue expansion. There were no significant differences between the groups in the primary outcomes of immediate postoperative pain (54.6 AlloDerm vs 42.8 controls on a 100-point visual analog scale) or pain during the expansion phase (17.0 AlloDerm vs 4.6 controls), or in the secondary outcome of rate of tissue expansion (91 days AlloDerm vs 108 days controls) and patient-reported physical well-being. There was no significant difference in adverse events, although the total number of adverse events was small.

## Comparisons Between Products

### *AlloDerm vs AlloMax*

Hinchcliff et al (2017) conducted an RCT that compared AlloDerm with AlloMax (n=15 each) for implant-based breast reconstruction.<sup>4</sup> Complications were assessed 7, 14, and 30 days postoperatively and biopsies of the ADMs were taken during implant exchange. Vessel density in the AlloMax biopsies was higher than in the AlloDerm biopsies. Complications were reported in 26.1% of AlloMax cases and 8.0% of AlloDerm cases; these complication rates did not differ statistically with the 30 patients in this trial.

### *AlloDerm vs DermaMatrix*

Mendenhall et al (2017) conducted an RCT that compared AlloDerm with DermaMatrix in 111 patients (173 breasts).<sup>5</sup> There were no significant differences in overall rates of complications (AlloDerm, 15.4%; DermaMatrix, 18.3%;  $p = 0.8$ ) or implant loss (AlloDerm, 2.2%; DermaMatrix, 3.7%;  $p = 0.5$ ) between the 2 ADMs.

### *AlloDerm vs FlexHD*

A 2014 retrospective review by Liu et al compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts).<sup>6</sup> Eighty-one percent of the sample was immediate reconstruction: 165 used AlloDerm and 97 used FlexHD.

Mean follow-up was 6.4 months. Compared with breast reconstruction without the use of AlloDerm or FlexHD, ADM had a higher rate of delayed healing (20.2% vs 10.3%), although this finding might have been related to differences in fill volumes. In univariate analysis, there were no significant differences in complications (return to operating room, surgical site infection, seroma, hematoma, delayed healing, implant loss) between AlloDerm and FlexHD. In multivariate analysis, there were no significant differences between AlloDerm and FlexHD for the return to the operating room, surgical site infection, seroma, or delayed healing. Independent risk factors for implant loss included the use of FlexHD, single-stage reconstruction, and smoking.

***AlloDerm vs FlexHD Pliable and DermACELL***

Chang and Liu (2017) reported on a prospective comparison of FlexHD Pliable (32 breasts), AlloDerm (22 breasts), and DermACELL (20 breasts) in breast reconstruction.<sup>7</sup> The choice of ADM was based on different years when each ADM was available for use at the investigators' institution; patient demographics were comparable between groups. The pieces of ADM used were all the same size (8 × 16 cm) to eliminate an effect of size on outcomes. The time to drain removal was longer with AlloDerm (26 days) than with FlexHD (20 days) or DermACELL (15 days; p=0.001). Complications were low (4 in the Flex Pliable group, 2 in the AlloDerm group, 1 in the DermACELL group), with no significant differences between groups. At the time of exchange for a permanent implant or free flap reconstruction, all grafts had completely incorporated into the mastectomy skin flaps. No patients developed complications requiring removal of the ADM. Pittman et al (2017) reported a retrospective pilot study of the use of AlloDerm (50 breasts) and DermACELL (50 breasts).<sup>8</sup> The choice of ADM was based on products available during different years and patient demographics were similar between the 2 groups. Patients in the DermACELL group had a significantly lower incidence of "red breast syndrome" (0% vs 26%, p=0.001) and fewer days until drain removal (15.8 days vs 20.6 days, p=0.017). There were no significant differences in the rates of other complications.

**Strattice**

Dikmans et al (2017) reported on early safety outcomes from an open-label multicenter RCT that compared porcine ADM-assisted 1-stage expansion with 2-stage implant-based breast reconstruction (see Table 2).<sup>9</sup> One-stage breast reconstruction with porcine ADM was associated with a higher risk of surgical complications, reoperation, and with removal of implant, ADM, or both (see Table 3). The trial was stopped early due to safety concerns, but it cannot be determined from this study design whether the increase in complications was due to the use of the xenogenic ADM or to the comparison between 1-stage and 2-stage reconstruction.

**Table 2. Summary of Key RCT Characteristics**

Author	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Dikmans et al (2017) <sup>9</sup>	EU	8	2013-2015	Women intending to undergo skin-sparing mastectomy and immediate IBBR	59 patients (91 breasts) undergoing 1-stage IBBR with ADM	62 women (92 breasts) undergoing 2-stage IBBR

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

**Table 3. Summary of Key RCT Outcomes**

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

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

### Section Summary: Breast Reconstruction

Results of a systematic review found no difference in overall complication rates between ADM allograft and standard procedures for breast reconstruction. Although reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM, rates of capsular contracture and malposition of implants may be reduced. Thus, in cases where there is limited tissue coverage, the available studies may be considered sufficient to permit informed decision-making about risks and benefits of using allogeneic ADM for breast reconstruction.

### Tendon Repair

#### Graftjacket

In 2012, Barber et al reported an industry-sponsored multicenter RCT of augmentation with Graftjacket human ADM for arthroscopic repair of large (>3 cm) rotator cuff tears involving 2 tendons.<sup>10</sup> Twenty-two patients were randomized to Graftjacket augmentation and 20 patients to no augmentation. At a mean follow-up of 24 months (range, 12-38 months), the American Shoulder and Elbow Surgeons score improved from 48.5 to 98.9 in the Graftjacket group and from 46.0 to 94.8 in the control group (p=0.035). The Constant score improved from 41 to 91.9 in the Graftjacket group and from 45.8 to 85.3 in the control group (p=0.008). The University of California, Los Angeles score did not differ significantly between groups. Gadolinium-enhanced magnetic resonance imaging (MRI) scans showed intact cuffs in 85% of repairs in the Graftjacket group and 40% of repairs in the control group. However, no correlation was found between MRI findings and clinical outcomes. Rotator cuff retears occurred in 3 (14%) patients in the Graftjacket group and 9 (45%) patients in the control group.

#### Section Summary: Tendon Repair

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

### Surgical Repair of Hernias or Parastomal Reinforcement

A 2013 systematic review evaluated the clinical effectiveness of acellular collagen-based scaffolds for the repair of incisional hernias.<sup>11</sup> The bioprosthetic materials could be harvested from bovine pericardium, human cadaveric dermis, porcine small intestine mucosa, porcine dermal collagen, or bovine dermal collagen. Products included in the search were Surgisis, Tutomesh, Veritas, AlloDerm, FlexHD, AlloMax, CollaMend, Permacol, Strattice, FortaGen, ACell, DermaMatrix, XenMatrix, and SurgiMend. Sixty publications with 1212 repairs were identified and included in the review, although meta-analysis could not be performed. There were 4 level III studies (2

AlloDerm, 2 Permacol); the remainder was level IV or V. The largest number of publications were on AlloDerm (n=27) and Permacol (n=18). No publications on incisional hernia repair were identified for AlloMax, FortaGen, DermaMatrix, or ACell. The overall incidence of a surgical site occurrence (eg, postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, mechanical failure) was 82.6% for porcine small intestine mucosa, 50.7% for xenogenic dermis, 48.3% for human dermis, and 6.3% for xenogenic pericardium. No comparative data were identified that could establish superiority to permanent synthetic meshes.

### **AlloDerm as an Overlay**

In 2007, Espinosa-de-los-Monteros et al retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases.<sup>12</sup> They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

### **Comparisons Between Products**

#### ***AlloDerm vs Surgisis Gold***

Gupta et al (2006) compared the efficacy and complications associated with use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair.<sup>13</sup> The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine submucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7 to 10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in 8 (24%) hernia recurrences. Fifteen (45%) of the AlloDerm patients developed a diastasis or bulging at the repair site. Seroma formation was only a problem in 2 patients.

#### ***AlloDerm vs FlexHD***

A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery.<sup>14</sup> From 2005 to 2007, AlloDerm was used to repair large (>200 cm<sup>2</sup>) symptomatic complicated ventral hernias that resulted from trauma or emergency surgery (n=55). From 2008 to 2010, FlexHD was used to repair large, complicated ventral hernias in patients meeting the same criteria (n=40). The 2 groups were comparable at baseline. At 1 year follow-up, all AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, true recurrence) requiring a second repair. Eleven (31%) patients in the FlexHD group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

#### ***FlexHD vs Strattice***

Roth et al (2017) reported on a prospective study assessing clinical and quality of life outcomes following complex hernia repair with a human (FlexHD) or porcine (Strattice) ADM.<sup>15</sup> The study was funded by the Musculoskeletal Transplant Foundation, which prepares and supplies FlexHD. Patients were enrolled if they had a hernia at least 6 cm in the transverse dimension, active or prior infection of the abdominal wall, and/or enterocutaneous fistula requiring mesh removal. Eighteen (51%) of the 35 patients had undergone a previous hernia repair. After abdominal wall repair with the ADM, 20 (57%) patients had a surgical site occurrence, and nearly one-third had

hospital readmission. The type of biologic material did not impact hernia outcomes. There was no comparison with synthetic mesh in this study, limiting interpretation.

### ***Strattice vs Synthetic Mesh***

In 2014, Bellows et al reported early results of an industry-sponsored multicenter RCT that compared Strattice (non-cross-linked porcine ADM, n=84) with a standard synthetic mesh (n=88) for the repair of inguinal hernias.<sup>16</sup> The trial was designed by the surgeons and was patient- and assessor-blinded to reduce risk of bias. Blinding continued through 2 years of follow-up. The primary outcome was resumption of activities of daily living at 1 year. Secondary outcomes included complications, recurrences, or chronic pain (ie, pain that did not disappear by 3 months postsurgery). At 3-month follow-up, there were no significant differences in either the occurrence or type of wound events (relative risk, 0.98; 95% CI, 0.52 to 1.86). Pain was reduced from 1 to 3 days postoperative in the group treated with Strattice, but at 3 month follow-up pain scores did not differ significantly between groups.

### ***Strattice vs No Reinforcement***

Also in 2014, the PRISM Study Group reported a multicenter, double-blinded, randomized trial of Strattice for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies.<sup>17</sup> Patients were randomized to standard stoma construction with no reinforcement (n=58) or stoma construction with Strattice as parastomal reinforcement (n=55). At 24-month follow-up (n=75), the incidence of parastomal hernias was similar for the 2 groups (13.2% of controls, 12.2% of study group).

## **Section Summary: Surgical Repair of Hernias or Parastomal Reinforcement**

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

## **Diabetic Lower-Extremity Ulcers**

### **Systematic Reviews**

A 2016 Cochrane review evaluated skin substitutes for the treatment of diabetic foot ulcers.<sup>18</sup> Seventeen trials (total N=1655 participants) were included in the meta-analysis. Most trials identified were industry-sponsored, and an asymmetric funnel plot indicated publication bias. Pooled results of published trials found that skin substitutes increased the likelihood of achieving complete ulcer closure compared with standard of care (SOC) alone (relative risk, 1.55; 95% CI, 1.30 to 1.85). Use of skin substitutes also led to a statistically significant reduction in amputations (relative risk, 0.43; 95% CI, 0.23 to 0.81), although the absolute risk difference was small. Analysis by individual products found a statistically significant benefit on ulcer closure for Apligraf, EpiFix, and Hyalograft-3D. The products that did not show a statistically significant benefit for ulcer closure were Dermagraft, Graftjacket, Kaloderm, and OrCel. Individual RCTs are described next.

Martinson and Martinson (2016) conducted an industry-sponsored analysis of Medicare claims data (13,193 treatment episodes) to compare efficacy and cost of skin substitutes for the management of diabetic foot ulcers.<sup>19</sup> Included in the analysis were treatment episodes with Apligraf (37%), Dermagraft (42%), Oasis (19%), and Cytal (MatriStem, 2%). The mean number of applications was 3.24 for Apligraf, 4.48 for Oasis, 5.53 for Cytal, and 5.96 for Dermagraft. All comparisons were statistically significant. Healing at 90 days was modestly but statistically higher

for Oasis (63%) and Cytal (62%) than for Apligraf (58%) or Dermagraft (58%). Amputation rates were similar after treatment with the 4 products, ranging from 1.3% for Oasis to 2.1% for Cytal.

Guo et al (2017) reported a systematic review of ADM for the treatment diabetic foot ulcer.<sup>20</sup> Most data were from an RCT of Integra Dermal Regeneration Template, which is a bilayer product with the outer layer composed of a thin silicone film and not a pure ADM.

### **Apligraf, Dermagraft, AlloPatch, Integra Dermal Regeneration Template, or Integra Flowable Wound Matrix**

#### ***Apligraf***

Veves et al (2001) reported on a randomized prospective trial on the effectiveness of Apligraf (previously called Graftskin), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers.<sup>21</sup> The trial involved 24 centers in the United States; 208 patients were randomized to ulcer treatment with Apligraf (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical débridement and adequate foot off-loading, was provided in both groups. Apligraf was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of 5 applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Apligraf-treated patients achieved complete wound healing compared with 36 (38%) in the control group ( $p=0.004$ ). The Kaplan-Meier method median time to complete closure was 65 days for Apligraf, significantly lower than the 90 days observed in the control group ( $p=0.003$ ). The rates of adverse reactions were similar between groups, except osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf group. Trialists concluded that application of Apligraf for a maximum of 4 weeks resulted in higher healing rates than state-of-the-art treatment and was not associated with any significant adverse events. This trial was reviewed in a 2001 TEC Assessment, which concluded that Apligraf, in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.<sup>22</sup>

Steinberg et al (2010) reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of noninfected diabetic foot ulcers.<sup>23</sup> Study design and patient population were similar to the 208-subject U.S. study (previously described), which led to Food and Drug Administration (FDA) approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with noninfected neuropathic diabetic foot ulcers present for at least 2 weeks were enrolled in prospective, multicenter, open-label RCTs that compared Apligraf use plus standard therapy (sharp débridement, standard wound care, off-loading) with standard therapy alone. Pooling of data was performed because of the similarity and consistency of the 2 studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration, which was significantly longer in the European study (21 months vs 10 months in the U.S. study). Reported adverse events by 12 weeks were comparable across treatment groups in the 2 studies. Efficacy measures demonstrated superiority of Apligraf treatment over control-treated groups in both studies. Combining the data from both studies, 55.2% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared with 34.3% (46/134) of control subjects ( $p<0.001$ ), and Apligraf subjects had a significantly shorter time to complete wound closure ( $p<0.001$ ). The authors concluded that both the EU and U.S. studies exhibited superior efficacy and comparable safety for subjects treated with Apligraf compared with control subjects and that the studies provided evidence of the benefit of Apligraf in treating diabetic foot ulcer.

In 2010, Kirsner et al analyzed 2517 patients with diabetic neuropathic foot ulcers treated between 2001 and 2004.<sup>24</sup> This retrospective analysis used a wound care database; the patients received advanced biologic therapy, specifically, Apligraf (446 patients), Regranex, or Procuren. The analysis found that advanced biologic therapy was used, on average, within 28 days from the first wound clinic visit and was associated with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biologic therapy were 31% more likely to heal than wounds first treated with topical recombinant growth factor ( $p < 0.001$ ) and 40% more likely to heal than those first treated with platelet releasate ( $p = 0.01$ ). Wound size, wound grade, duration of wound, and time to initiation of advanced biologic therapy affected the time to healing.

### ***Dermagraft***

A 2003 pivotal multicenter FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft (human-derived fibroblasts cultured on mesh) or control.<sup>25</sup> Over the 12-week study, patients received up to 8 applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91% compared with 78% for the control group. Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious adverse events were attributed to Dermagraft. Ulcer infections developed in 10.4% of the Dermagraft patients compared with 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group (19% vs 32.5%). A 2015 retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft (5.5% vs 12.6%,  $p = 0.031$ ).<sup>26</sup> Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

### ***AlloPatch***

AlloPatch Pliable human reticular acellular dermis was compared with SOC in a 2017 industry-sponsored multicenter trial by Zelen et al.<sup>27</sup> The trial was powered to detect a 45% difference between groups in percent healing at 6 weeks with 20 patients per group. Evaluation of the outcome measures was not blinded. At 6 weeks, 65% (13/20) of wounds treated using AlloPatch had healed compared with 5% (1/20) in the SOC-alone group ( $p < 0.001$ ). After adjusting for wound area at baseline, the hazard ratio for healing was 168 (95% CI, 10 to 2704;  $p < 0.001$ ), indicating a lack of precision in the estimate. Per protocol, 10 patients in the SOC group and 1 in the AlloPatch group exited the study at 6 weeks because their wounds failed to reduce in area by at least 50%. According to ITT analysis with last observation carried forward, the percentage of wounds healed at 12 weeks was 80% in the AlloPatch group compared with 20% in the SOC group. However, because there was a high (50%) withdrawal rate in the SOC group, this result has a high risk of bias.

### ***Integra Omnigraft Dermal Regeneration Template or Integra Flowable Wound Matrix***

Integra Dermal Regeneration Template is a biosynthetic skin substitute that is FDA-approved for life-threatening thermal injury. The FOUNDER (Foot Ulcer New Dermal Replacement) multicenter study (32 sites) assessed Integra Dermal Regeneration Template (marketed as Omnigraft) for chronic nonhealing diabetic foot ulcers under an FDA-regulated investigational device exemption.<sup>28</sup> A total of 307 patients with at least 1 chronic diabetic foot ulcer were randomized to treatment with the Integra Template or a control condition (sodium chloride gel 0.9%). Treatment was given for 16 weeks or until wound closure. There was a modest increase in wound closure with the Integra Template (51% vs 32%,  $p = 0.001$ ) and a shorter median time to

closure (43 days vs 78 days,  $p=0.001$ ). There was a strong correlation between investigator-assessed and computerized planimetry assessment of wound healing ( $r=0.97$ ). Kaplan-Meier analysis showed the greatest difference between groups in wound closure up to 10 weeks, with diminishing differences after 10 weeks. Trial strengths included adequate power to detect an increase in wound healing of 18%, which was considered to be clinically significant, secondary outcomes of wound closure and time to wound closure by computerized planimetry, and ITT analysis.

Integra Flowable Wound Matrix is composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. It is supplied as a granular product that is mixed with saline. Campitiello et al (2017) published an RCT that compared the flowable matrix with wet dressing in 46 patients who had Wagner grade 3 diabetic foot ulcers.<sup>29</sup> The ulcers had developed over 39 weeks. Complete healing at 6 weeks was achieved in significantly more patients in the Integra Flowable Wound Matrix group than in the control group, while the risk of rehospitalization and major amputation was reduced with Integra Flowable Wound Matrix (see Table 4).

**Table 4. Probability of Wound Healing With IFWM vs SOC**

Study	Complete Wound Healing	Rehospitalization	Major Amputation
Campitiello et al (2017) <sup>29</sup>			
IFWM, n (%)	20 (86.95)	2 (6.69)	1 (4.34)
SOC, n (%)	12 (52.17)	10 (43.47)	7 (30.43)
RR (95% CI)	1.67 (1.09 to 2.54)	0.10 (0.01 to 0.72)	0.16 (0.02 to 1.17)
p	0.010	0.001	0.028

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

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

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

**Bioengineered Skin Substitutes Other Than Apligraf, Dermagraft, AlloPatch, or Integra**

***Graftjacket Regenerative Tissue Matrix***

Brigido et al (2004) reported a small (N=40) randomized pilot study comparing Graftjacket with conventional treatment for chronic nonhealing diabetic foot ulcers.<sup>30</sup> Control patients received conventional therapy with débridement, wound gel with gauze dressing, and off-loading. Graftjacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the Graftjacket group. Preliminary one month results showed that, after a single treatment, ulcers treated with Graftjacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs 15%), width (50% vs 23%), area (73% vs 34%), and depth (89% vs 25%), respectively. With follow-up to four weeks, no data were reported on the proportion with complete closure or the mean time to heal. All grafts were incorporated into the host tissue.

Reyzelman et al (2009) reported an industry-sponsored multicenter randomized study that compared a single application of Graftjacket with SOC in 86 patients with diabetic foot ulcers.<sup>31</sup> Eight patients, six in the study group and two in the control group, did not complete the trial. At 12 weeks, complete healing was observed in 69.6% of the Graftjacket group and 46.2% of

controls. After adjusting for ulcer size at presentation, a statistically significant difference in nonhealing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks for the Graftjacket group vs 6.8 weeks for the control group. The authors did not report whether this difference was statistically significant. Median time to healing was 4.5 weeks for Graftjacket (range, 1-12 weeks) and 7.0 weeks for control (range, 2-12 weeks). Kaplan-Meier method survivorship analysis for time to complete healing at 12 weeks showed a significantly lower nonhealing rate for the study group (30.4%) than for the control group (53.9%). The authors commented that a single application of Graftjacket, as used in this study, was often sufficient for complete healing. Conclusions drawn from this study are limited by the small study population and differences in ulcer size at baseline. Questions also remain whether the difference in mean time to healing is statistically or clinically significant.

In 2015, Reyzelman and Bazarov<sup>32</sup> reported an industry-sponsored meta-analysis of Graftjacket for diabetic foot ulcers that included the 2 studies described above and a third RCT by Brigido (2006)<sup>33</sup> with 28 patients (total N=154 patients). The time to heal was estimated for the 2004 Brigido study, based on the average wound reduction per week. The estimated difference in time to heal was considerably larger for Brigido's 2004 study (-4.30 weeks) than for the other 2 studies that measured the difference in time to heal (-1.58 weeks and -1.10 weeks). Analysis of the proportion of wounds that healed included Brigido (2006) and Reyzelman et al (2009). The odds ratio in the smaller study by Brigido was considerably larger, with a lack of precision in the estimate (odds ratio, 15.0; 95% CI, 2.26 to 99.64), and the combined odds (3.75; 95% CI, 1.72 to 8.19) was not significant when analyzed using a random-effects model. Potential sources of bias, noted by Reyzelman and Bazarov, included publication and reporting biases, study selection biases, incomplete data selection, post hoc manipulation of data, and subjective choice of analytic methods. Overall, results of these studies do not provide convincing evidence that Graftjacket is more effective than SOC for healing diabetic foot ulcers.

### ***DermACELL vs Graftjacket Regenerative Tissue Matrix or SOC***

DermACELL and Graftjacket are both composed of human ADM. In 2016, Walters et al reported on a multicenter randomized comparison of DermACELL, Graftjacket, or SOC (2:1:2 ratio) in 168 patients with diabetic foot ulcers.<sup>34</sup> The study was sponsored by LifeNet Health, a nonprofit organ procurement association and processor for DermACELL. At 16 weeks, the proportion of completely healed ulcers was 67.9% for DermACELL, 47.8% for Graftjacket, and 48.1% for SOC. The 20% difference in completely healed ulcers was statistically significant for DermACELL vs SOC ( $p=0.039$ ). The mean time to complete wound closure did not differ significantly for DermACELL (8.6 weeks), Graftjacket (8.6 weeks), and SOC (8.7 weeks).

A second report from this study was published in 2017.<sup>35</sup> This analysis compared DermACELL with SOC and did not include the Graftjacket arm. The authors reported that either 1 or 2 applications DermACELL led to a greater proportion of wounds healed compared with SOC in per protocol analysis (see Table 5), but there was no significant difference between DermACELL (1 or 2 applications) and SOC when analyzed by intention-to-treat. For the group of patients who received only a single application, the percentage of patients who achieved complete wound healing was significantly higher than SOC at 16 and 24 weeks, but not at 12 weeks. Although reported as ITT analysis, results were analyzed only for the group who received a single application of DermACELL. This would not typically be considered ITT unless the number of DermACELL applications was prespecified.

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

Study	Single Application			1 or 2 Applications		
	% With Wound Healing at 12 Wk	% With Wound Healing at 16 Wk	% With Wound Healing at 24 Wk	% With Wound Healing at 12 Wk	% With Wound Healing at 16 Wk	% With Wound Healing at 24 Wk
Cazzell et al (2017) <sup>35</sup>						
DermACELL, %	65.0%	82.5%	89.7%	NR	67.9%	83.7%
SOC, %	41.1%	48.1%	67.3%	NR	48.1%	67.3%
HR (95% CI)	1.97 (1.1 to 3.5)	2.40 (1.4 to 4.1)	2.11 (1.3 to 3.5)		1.72 (1.04 to 2.83)	1.55 (0.98 to 2.44)
p	0.012	<0.001	<0.001	NS	0.028	0.049

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

### ***TheraSkin vs Dermagraft***

Sanders et al (2014) reported on a small (N=23) industry-funded randomized comparison of TheraSkin (cryopreserved human skin allograft with living fibroblasts and keratinocytes) and Dermagraft for diabetic foot ulcers.<sup>36</sup> Wound size at baseline ranged from 0.5 to 18.02 cm<sup>2</sup>; the average wound size was about 5 cm<sup>2</sup> and was similar for the 2 groups (p=0.51). Grafts were applied according to manufacturers' instructions over the first 12 weeks of the study until healing, with an average of 4.4 TheraSkin grafts (every 2 weeks) compared with 8.9 Dermagraft applications (every week). At week 12, complete wound healing was observed in 63.6% of ulcers treated with TheraSkin and 33.3% of ulcers treated with Dermagraft (p<0.049). At 20 weeks, complete wound healing was observed in 90.9% of the TheraSkin-treated ulcers compared with 66.7% of the Dermagraft group (p=0.428).

### ***TheraSkin vs Apligraf***

DiDomenico et al (2011) compared TheraSkin with Apligraf for the treatment of diabetic foot ulcers in a small (N=29) RCT.<sup>37</sup> The risk of bias in this study is uncertain, because reporting did not include a description of power analysis, statistical analysis, method of randomization, or blinding. The percentage of wounds closed at 12 weeks was 41.3% in the Apligraf group and 66.7% in the TheraSkin group. Results at 20 weeks were not substantially changed from those at 12 weeks, with 47.1% of wounds closed in the Apligraf group and 66.7% closed in the TheraSkin group. The percentage healed in the Apligraf group was lower than expected based on prior studies. The average number of grafts applied was similar for both groups (1.53 for Apligraf, 1.38 for TheraSkin). The low number of dressing changes may have influenced results, with little change in the percentage of wounds closed between 12 and 20 weeks. An adequately powered trial with blinded evaluation of wound healing and a standard treatment regimen would permit greater certainty on the efficacy of this product.

### ***Cytal (MatriStem) vs Dermagraft***

Frykberg et al (2017) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cytal (a porcine urinary bladder-derived extracellular matrix) vs Dermagraft in 56 patients with diabetic foot ulcers.<sup>38</sup> The mean duration of ulcers before treatment was 263 days (range, 30-1095 days). The primary outcome was the percent wound closure with up to 8 weeks of treatment using blinded evaluation of photographs. Intention-to-treat (ITT) analysis found complete wound closure in 5 (18.5%) wounds treated with Cytal compared with 2 (6.9%) wounds treated with Dermagraft (p=NS). Quality of life, measured by the Diabetic Foot Ulcer

Scale, improved from 181.56 to 151.11 in the Cytal group and from 184.46 to 195.73 in the Dermagraft group ( $p=0.074$ ). It should be noted that this scale is a subjective measure and patients were not blinded to treatment. Power analysis indicated that 92 patients would be required; further recruitment is ongoing for completion of the study.

### ***PriMatrix***

Kavros et al (2014) reported a prospective multicenter study of PriMatrix (a xenograft fetal bovine dermal collagen matrix) for the treatment of chronic diabetic foot ulcers in 55 patients.<sup>39</sup> Average duration of ulcers before treatment was 286 days, and average wound area was 4.34 cm<sup>2</sup>. Of the 46 patients who completed the study, 76% healed by 12 weeks with an average of 2 applications of PriMatrix. For the ITT population, 64% of wounds healed by 12 weeks.

Karr (2011) published a retrospective comparison of PriMatrix and Apligraf in 40 diabetic foot ulcers.<sup>40</sup> The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. The criteria were: diabetic foot ulcers of 4 weeks in duration; ulcer of at least 1 cm<sup>2</sup> in diameter and to the depth of subcutaneous tissue; healthy tissue at the ulcer; adequate arterial perfusion to heal; and ability to off-load the diabetic ulcer. The time to complete healing for PriMatrix was 38 days with 1.5 applications compared with 87 days with 2 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to compare the efficacy of PriMatrix with current SOC or advanced wound therapies.

### ***Oasis Wound Matrix vs Regranex Gel***

Niezgoda et al (2005) compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix (a porcine acellular wound care product) to Regranex Gel.<sup>41</sup> This industry-sponsored, multicenter RCT was conducted at 9 outpatient wound care clinics and involved 73 patients with at least 1 diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix ( $n=37$ ) or Regranex Gel ( $n=36$ ) and a secondary dressing. Wounds were cleansed and débrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks, 18 (49%) Oasis-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients. Oasis treatment met the noninferiority margin but did not demonstrate that healing in the Oasis group was statistically superior ( $p=0.055$ ). Post hoc subgroup analysis showed no significant difference in incidence of healing in patients with type 1 diabetes (33% vs 25%) but showed a significant improvement in patients with type 2 diabetes (63% vs 29%). There was also an increased healing of plantar ulcers in the Oasis group (52% vs 14%). These post hoc findings are considered hypothesis-generating. Additional study with a larger number of subjects is needed to compare the effect of Oasis treatment to current SOC.

### **Section Summary: Bioengineered Skin Substitutes Other Than Apligraf, Dermagraft, AlloPatch, or Integra for Diabetic Lower-Extremity Ulcers**

Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients who only required a single application of the ADM. Studies are needed to further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of Graftjacket, TheraSkin, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies.

## Lower-Extremity Ulcers due to Venous Insufficiency

### Apligraf

Falanga et al (1998) reported on a multicenter randomized trial of Apligraf living cell therapy.<sup>42</sup> A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or to compression therapy and treatment with Apligraf. Apligraf was applied up to a maximum of 5 (mean, 3.3) times per patient during the initial 3 weeks. The primary end points were the percentage of patients with complete healing by 6 months after initiation of treatment and the time required for complete healing. At 6-month follow-up, the percentage of patients healed was higher with Apligraf (63% vs 49%), and the median time to complete wound closure was shorter (61 days vs 181 days). Treatment with Apligraf was superior to compression therapy in healing larger (>1000 mm<sup>2</sup>) and deeper ulcers and ulcers of more than 6 months in duration. There were no symptoms or signs of rejection, and the occurrence of adverse events was similar in both groups. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (Graftskin), in conjunction with good local wound care, met TEC criteria for the treatment of venous ulcers that fail to respond to conservative management.<sup>22</sup>

### Oasis Wound Matrix

Mostow et al (2005) reported on an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment using Oasis Wound Matrix (xenogenic collagen scaffold from porcine small intestinal mucosa) with SOC in 120 patients who had chronic ulcers due to venous insufficiency that had not adequately responding to conventional therapy.<sup>43</sup> Healing was assessed weekly for up to 12 weeks, with follow-up performed after 6 months to assess recurrence. After 12 weeks of treatment, there was a significant improvement in the percentage of wounds healed in the Oasis group (55% vs 34%). After adjusting for baseline ulcer size, patients in the Oasis group were 3 times more likely to heal than those in the group receiving SOC. Patients in the SOC group whose wounds did not heal by week 12 were allowed to cross over to Oasis treatment. None of the healed patients treated with Oasis wound matrix who was seen for the 6-month follow-up experienced ulcer recurrence.

A research group in Europe has described 2 comparative studies of the Oasis matrix for mixed arteriovenous ulcers. In a 2007 quasirandomized study, Romanelli et al compared the efficacy of 2 extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid).<sup>44</sup> Fifty-four patients with mixed arteriovenous leg ulcers were assigned to the 2 arms based on order of entry into the study; 50 patients completed the study. Patients were followed twice weekly, and dressings changed more than once a week, only when necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis-treated ulcers compared with 46.2% of Hyaloskin-treated ulcers. Oasis treatment significantly increased the time to dressing change (mean, 6.4 days vs 2.4 days), reduced pain on a 10-point scale (3.7 vs 6.2), and improved patient comfort (2.5 vs 6.7).

In a 2010 trial, Romanelli et al compared Oasis with a moist wound dressing (SOC) in 23 patients with mixed arteriovenous ulcers and 27 patients with venous ulcers.<sup>45</sup> The trial was described as randomized, but the method of randomization was not described. After the 8-week study period, patients were followed monthly for 6 months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis-treated ulcers at 8 weeks compared with 65% of the SOC group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks compared with 8.3 weeks for the SOC group. Treatment with Oasis also increased the time to dressing change (5.2 days vs 2.1 days) and the percentage of granulation tissue formed (65% vs 38%).

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

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

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

***Dermagraft***

Dermagraft living cell therapy has been approved by FDA for repair of diabetic foot ulcers. Use of Dermagraft for venous ulcers is an off-label indication. In 2013, Harding et al reported an open-label multicenter RCT that compared Dermagraft plus compression therapy (n=186) with compression therapy alone (n=180).<sup>46</sup> The trial had numerous inclusion and exclusion criteria that restricted the population to patients who had nonhealing ulcers with compression therapy but had the capacity to heal. ITT analysis revealed no significant difference between the 2 groups in the primary outcome measure, the proportion of patients with completely healed ulcers by 12 weeks (34% Dermagraft vs 31% control). Prespecified subgroup analysis revealed a significant improvement in the percentage of wounds healed for ulcers of 12 months or less in duration (52% vs 37%) and for ulcers of 10 cm or less in diameter (47% vs 39%). There were no significant differences in the secondary outcomes of time to healing, complete healing by week 24, and percent reduction in ulcer area.

***PriMatrix***

In 2011, Karr published a retrospective comparison of PriMatrix (xenogenic ADM) and Apligraf in 28 venous stasis ulcers.<sup>40</sup> The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Criteria were venous stasis ulcers of 4 weeks in duration, at least 1 cm<sup>2</sup> in diameter, and to a depth of subcutaneous tissue, with healthy tissue at the ulcer edge, adequate arterial perfusion to heal, and ability to tolerate compression therapy. The time to complete healing for PriMatrix was 32 days with 1.3 applications compared with 63 days with 1.7 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to assess the effect of PriMatrix treatment in compared with current SOC.

***Section Summary: Bioengineered Skin Substitutes Other Than Apligraf or Oasis Wound Matrix for Lower-Extremity Ulcers due to Venous Insufficiency***

In a moderately large RCT, Dermagraft was not shown to be more effective than controls in the primary or secondary end points for the entire population and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or wound diameter of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment compared with current SOC.

**Dystrophic Epidermolysis Bullosa**

OrCel was approved under an humanitarian device exemption (HDE) for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. HDE status has been withdrawn for Dermagraft for this indication.

Fivenson et al (2003) reported the off-label use of Apligraf in 5 patients with recessive dystrophic epidermolysis bullosa who underwent syndactyly release.<sup>47</sup>

### **Section Summary: Dystrophic Epidermolysis Bullosa**

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

### **Deep Dermal Burns**

#### **Epicel**

One case series from 2000 has described the treatment of 30 severely burned patients with Epicel.<sup>48</sup> The cultured epithelial autografts were applied to a mean of 37% of total body surface area (TBSA). Epicel achieved permanent coverage of a mean of 26% of TBSA, an area similar to that covered by conventional autografts (mean, 25%). Survival was 90% in these severely burned patients.

#### **Integra Dermal Regeneration Template**

A 2013 study compared Integra with split-thickness skin graft and with viscose cellulose sponge (Cellonex), using three 10×5 cm test sites on each of 10 burn patients.<sup>49</sup> The surrounding burn area was covered with meshed autograft. Biopsies were taken from each site on days 3, 7, 14, and 21, and at months 3 and 12. The tissue samples were stained and examined for markers of inflammation and proliferation. The Vancouver Scar Scale was used to assess scars. At 12-month follow-up, the 3 methods resulted in similar clinical appearance, along with similar histologic and immunohistochemical findings.

Branski et al (2007) reported on a randomized trial that compared Integra with a standard autograft-allograft technique in 20 children with an average burn size of 73% TBSA (71% full-thickness burns).<sup>50</sup> Once vascularized (about 14-21 days), the Silastic epidermis was stripped and replaced with thin (0.05-0.13 mm) epidermal autograft. There were no significant differences between the Integra group and controls in burn size (70% vs 74% TBSA), mortality (40% vs 30%), and hospital length of stay (41 vs 39 days), all respectively. Long-term follow-up revealed a significant increase in bone mineral content and density (24 months) and improved scarring in terms of height, thickness, vascularity, and pigmentation (at 12 months and 18-24 months) in the Integra group. No differences were observed between groups in the time to first reconstructive procedure, cumulative reconstructive procedures required during 2 years, and cumulative operating room time required for these procedures. The authors concluded that Integra can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

Heimbach et al (2003) reported on a multicenter (13 U.S. burn care facilities) postapproval study involving 222 burn injury patients (36.5% TBSA; range, 1%-95%) who were treated with Integra Dermal Regeneration Template.<sup>51</sup> Within 2 to 3 weeks, the dermal layer regenerated, and a thin epidermal autograft was placed over the wound. The incidence of infection was 16.3%. Mean take rate (absence of graft failure) of Integra was 76.2%; the median take rate was 98%. The mean take rate of epidermal autograft placed over Integra was 87.7%; the median take rate was 95%.

#### **TransCyte**

TransCyte is no longer commercially available.

Earlier studies included a 2001 report by Lukish et al that found improved healing in 20 consecutive cases of pediatric burns greater than 7% TBSA that underwent wound closure using

TransCyte compared to the previous 20 consecutive burn cases greater than 7% TBSA that received standard therapy.<sup>52</sup> In 2006, Amani et al found significant improvement in healing in 110 consecutive patients who had deep partial-thickness burns treated with TransCyte as compared to results from the American Burn Association Patient Registry for similar burns.<sup>53</sup>

### **Section Summary: Deep Dermal Burns**

Epicel is FDA-approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a TBSA of 30% or more, with patient survival of 90%. Integra Dermal Regeneration Template has been compared with autograft in a within-subject study and with autograft-allograft in a small RCT with 10 patients per group. Outcomes are at least as good as with autograft or allograft, with a reduction in scarring and without risks associated with cadaver skin. This product has also been studied in a large series with over 222 burn patients, showing a take rate of 76% and with a take rate of epidermal autograft placed over Integra of 87.7%.

### **Other Indications**

#### **Punch Biopsy Wounds**

Baldursson et al (2015) reported a double-blinded RCT with 81 patients (162 punch biopsy wounds) that compared Kerecis Omega3 Wound (derived from fish skin) with Oasis SIS ECM (porcine small intestinal submucosa extracellular matrix).<sup>54</sup> The primary outcome (the percentage of wounds healed at 28 days) was similar for the fish skin ADM (95%) and the porcine SIS ECM (96.3%). The rate of healing was faster with Kerecis Omega3 ( $p=0.041$ ). At 21 days, 72.5% of the fish skin ADM group had healed compared with 56% of the porcine SIS ECM group. Interpretation of this study is limited because it did not include an accepted control condition for this indication.

#### **Split-Thickness Donor Sites**

There is limited evidence to support the efficacy of OrCel compared with SOC for the treatment of split-thickness donor sites in burn patients. In 2003, Still et al examined the safety and efficacy of bilayered OrCel to facilitate wound closure of split-thickness donor sites in 82 severely burned patients.<sup>55</sup> Each patient had 2 designated donor sites that were randomized to a single treatment of OrCel or standard dressing (Biobrane-L). The healing time for OrCel sites was significantly shorter than for sites treated with a standard dressing, enabling earlier recropping. OrCel sites also exhibited a nonsignificant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

#### **Miscellaneous**

In addition to indications previously reviewed, off-label uses of bioengineered skin substitutes have included pressure ulcers, inflammatory ulcers (eg, pyoderma gangrenosum, vasculitis), scleroderma digital ulcers, postkeloid removal wounds, genetic conditions, and variety of other conditions.<sup>56</sup> Products that have been FDA-approved or -cleared for one indication (eg, lower-extremity ulcers) have also been used off-label in place of other FDA-approved or -cleared products (eg, for burns).<sup>57</sup> No controlled trials were identified for these indications.

### **Summary of Evidence**

#### **Breast Reconstruction**

For individuals who are undergoing breast reconstruction who receive allogeneic ADM products, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. A systematic review found no difference in overall complication rates with ADM allograft compared with standard

procedures for breast reconstruction. Reconstructions with ADM have been reported to have higher seroma, infection, and necrosis rates than reconstructions without ADM. However, capsular contracture and malposition of implants may be reduced. Thus, in cases where there is limited tissue coverage, the available evidence may inform patient decision making about reconstruction options. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

### **Tendon Repair**

For individuals who are undergoing tendon repair who receive Graftjacket, the evidence includes an RCT. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. The RCT identified improved outcomes with the Graftjacket ADM allograft for rotator cuff repair. Although these results were positive, additional study with a larger number of patients is needed to evaluate the consistency of the effect. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Surgical Repair of Hernias or Parastomal Reinforcement**

For individuals who are undergoing surgical repair of hernias or parastomal reinforcement who receive acellular collagen-based scaffolds, the evidence includes RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Several comparative studies including RCTs have shown no difference in outcomes between tissue-engineered skin substitutes and either standard synthetic mesh or no reinforcement. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

### **Diabetic Lower-Extremity Ulcers**

For individuals who have diabetic lower-extremity ulcers who receive AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. RCTs have demonstrated the efficacy of AlloPatch (reticular ADM), Apligraf and Dermagraft (living cell therapy), and Integra (biosynthetic) over the standard of care. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have diabetic lower-extremity ulcers who receive ADM products other than AlloPatch, Apligraf, Dermagraft, or Integra, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Results from a multicenter RCT showed some benefit of DermACELL that was primarily for the subgroup of patients who only required a single application of the ADM. Studies are needed to further define the population who might benefit from this treatment. Additional study with a larger number of subjects is needed to evaluate the effect of Graftjacket, TheraSkin, DermACELL, Cytal, PriMatrix, and Oasis Wound Matrix, compared with current SOC or other advanced wound therapies. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Lower-Extremity Ulcers due to Venous Insufficiency**

For individuals who have lower-extremity ulcers due to venous insufficiency who receive Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. RCTs have demonstrated the efficacy of Apligraf living cell therapy and xenogenic Oasis Wound Matrix over

the standard of care. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have lower-extremity ulcers due to venous insufficiency who receive bioengineered skin substitutes other than Apligraf or Oasis Wound Matrix, the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. In a moderately large RCT, Dermagraft was not shown to be more effective than controls for the primary or secondary end points in the entire population and was only slightly more effective than controls (an 8%-15% increase in healing) in subgroups of patients with ulcer durations of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of the xenogenic PriMatrix skin substitute vs the current standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Dystrophic Epidermolysis Bullosa**

For individuals who have dystrophic epidermolysis bullosa who receive OrCel, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, morbid events, and quality of life. OrCel was approved under a humanitarian drug exemption for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. Outcomes have been reported in small series (eg, 5 patients). The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Deep Dermal Burns**

For individuals who have deep dermal burns who receive bioengineered skin substitutes (ie, Epicel, Integra Dermal Regeneration Template), the evidence includes RCTs. Relevant outcomes are disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, few skin substitutes have been approved, and the evidence is limited for each product. Epicel (living cell therapy) has received FDA approval under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. Comparative studies have demonstrated improved outcomes for biosynthetic skin substitute Integra Dermal Regeneration Template for the treatment of burns. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

### **Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

### **2016 Input**

In response to requests, input was received from 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2016. Input was requested on the equivalency of products within the categories of amniotic membrane, living cell therapies, and biosynthetic skin substitutes for the treatment of diabetic foot ulcers and nonocular burns (biosynthetic only). Input on the equivalency of products within these categories was mixed.

### **2014 Input**

In response to requests, input was received from 3 physician specialty societies and 4 academic medical centers while this policy was under review in 2014. In addition to questions on medical necessity for different indications, input was specifically requested on the equivalency of products within the different categories (eg, acellular dermal matrix [ADM], living cell therapy, xenogeneic collagen scaffold, amniotic membrane). Five reviewers addressed the use of ADM products for breast reconstruction and most considered the various ADM products (AlloDerm, AlloMax, DermaMatrix, FlexHD, Graftjacket) to have similar outcomes when used for breast reconstructive surgery, although differences in firmness and stretch of the products were noted. Six reviewers addressed questions on bioengineered skin and soft tissue substitutes for diabetic and venous lower-extremity ulcers. Responses were mixed, although most reviewers considered living cell therapies to be equivalent for these indications. Most reviewers did not consider xenogeneic ADM products (eg, PriMatrix) or amniotic membrane (eg, EpiFix) to be medically necessary for any indication.

### **2012 Input**

In response to requests, input was received from 3 physician specialty societies and 2 academic medical centers while this policy was under review in 2012. Most reviewers supported the indications and products described in this policy. Input was requested on the use of an interpositional spacer after parotidectomy. Support for this indication was mixed. Some reviewers suggested use of other products and/or additional indications; however, the input on these products/indications was not uniform. Reviewers provided references for the additional indications; these were subsequently reviewed.

### **2009 Input**

In response to requests, input was received from 1 physician specialty society (2 physicians) and 1 academic medical center while this policy was under review in 2009. All reviewers indicated that on use of AlloDerm in breast reconstruction surgery should be available for use during breast reconstructive surgery.

## **Practice Guidelines and Position Statements**

### **American Society of Plastic Surgeons and Wound Healing Society**

A literature review for the 2013 guidelines from the American Society of Plastic Surgeons (ASPS) found that use of ADM, although increasingly common in postmastectomy expander/implant breast reconstruction, can result in increased risk of complications in the presence of certain risk factors.<sup>58</sup> ASPS noted that cellular dermal matrix is currently used to increase soft tissue coverage, support the implant pocket, improve contour, and reduce pain with expansion. However, evidence to support these improved surgical outcomes are limited. Some evidence has suggested that use of ADM is associated with increased postoperative complications, specifically related to infection and seroma. Overall, ASPS found that evidence on ADM products in postmastectomy expander/implant breast reconstruction was varied and conflicting, and gave a grade C recommendation based on level III evidence that surgeons should evaluate each clinical case individually and objectively determine the use of ADM.

### **National Institute for Health and Care Excellence**

In 2016, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems.<sup>59</sup> The Institute recommended that clinicians “consider dermal or skin substitutes as an adjunct to standard care when treating

diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service.”

**Infectious Diseases Society of America**

The 2012 guidelines from the Infectious Diseases Society of America stated that, for selected diabetic foot wounds that are slow to heal, clinicians might consider using bioengineered skin equivalents (weak recommendation, moderate evidence), growth factors (weak, moderate), granulocyte colony-stimulating factors (weak, moderate), hyperbaric oxygen therapy (strong, moderate), or negative pressure wound therapy (weak, low).<sup>60</sup> It was emphasized that none of these measures had been shown to improve the resolution of infection and that they were expensive, not universally available, might require consultation with experts, and reports supporting their utility were mostly flawed.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 6.

**Table 6. Summary of Key Trials**

<b>NCT No.</b>	<b>Trial Name</b>	<b>Planned Enrollment</b>	<b>Completion Date</b>
<b>Ongoing</b>			
NCT01987700 <sup>a</sup>	Multi-Center Study To Examine The Use Of Flex HD® And Strattice In The Repair Of Large Abdominal Wall Hernias	120	Oct 2017 (ongoing)
NCT02587403 <sup>a</sup>	A Randomized, Prospective Study Comparing Fortiva™ Porcine Dermis vs. Strattice™ Reconstructive Tissue Matrix in Patients Undergoing Complex Open Primary Ventral Hernia Repair	120	Oct 2019
NCT02322554	The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers	50,000	Jan 2020
<b>Unpublished</b>			
NCT01970163 <sup>a</sup>	A Multicenter, Randomized, Controlled, Open Label Trial of DermACELL in Subjects With Chronic Wounds of the Lower Extremities	202	Apr 2016 (completed)

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## **CODING**

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

### CPT

#### Autografts and Tissue-cultured Autografts

- 15040 Harvest of skin for tissue cultured skin autograft, 100 sq cm or less
- 15050 Pinch graft, single or multiple, to cover small ulcer, tip of digit, or other minimal open area (except on face), up to defect size 2 cm diameter
- 15100 Split-thickness autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)
- 15101 Split-thickness autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15110 Epidermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
- 15111 Epidermal autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15115 Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
- 15116 Epidermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15120 Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children (except 15050)
- 15121 Split-thickness autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15130 Dermal autograft, trunk, arms, legs; first 100 sq cm or less, or 1% of body area of infants and children
- 15131 Dermal autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15135 Dermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 100 sq cm or less, or 1% of body area of infants and children
- 15136 Dermal autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15150 Tissue cultured skin autograft, trunk, arms, legs; first 25 sq cm or less

- 15151 Tissue cultured skin autograft, trunk, arms, legs; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
- 15152 Tissue cultured skin autograft, trunk, arms, legs; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15155 Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; first 25 sq cm or less
- 15156 Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; additional 1 sq cm to 75 sq cm (List separately in addition to code for primary procedure)
- 15157 Tissue cultured skin autograft, face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits; each additional 100 sq cm, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15200 Full thickness graft, free, including direct closure of donor site, trunk; 20 sq cm or less
- 15201 Full thickness graft, free, including direct closure of donor site, trunk; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
- 15220 Full thickness graft, free, including direct closure of donor site, scalp, arms, and/or legs; 20 sq cm or less
- 15221 Full thickness graft, free, including direct closure of donor site, scalp, arms, and/or legs; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
- 15240 Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; 20 sq cm or less
- 15241 Full thickness graft, free, including direct closure of donor site, forehead, cheeks, chin, mouth, neck, axillae, genitalia, hands, and/or feet; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)
- 15260 Full thickness graft, free, including direct closure of donor site, nose, ears, eyelids, and/or lips; 20 sq cm or less
- 15261 Full thickness graft, free, including direct closure of donor site, nose, ears, eyelids, and/or lips; each additional 20 sq cm, or part thereof (List separately in addition to code for primary procedure)

#### Skin Substitute Grafts

- 15271 Application of skin substitute graft to trunk, arms, legs total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
- 15272 Application of skin substitute graft to trunk, arms, legs total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
- 15273 Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
- 15274 Application of skin substitute graft to trunk, arms, legs, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)

- 15275 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
- 15276 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area up to 100 sq cm; each additional 25 sq cm wound surface area, or part thereof (List separately in addition to code for primary procedure)
- 15277 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; first 100 sq cm wound surface area, or 1% of body area of infants and children
- 15278 Application of skin substitute graft to face, scalp, eyelids, mouth, neck, ears, orbits, genitalia, hands, feet, and/or multiple digits, total wound surface area greater than or equal to 100 sq cm; each additional 100 sq cm wound surface area, or part thereof, or each additional 1% of body area of infants and children, or part thereof (List separately in addition to code for primary procedure)
- 15777 Implantation of biologic implant (eg, acellular dermal matrix) for soft tissue reinforcement (eg, breast, trunk) (List separately in addition to code for primary procedure)

#### HCPCS

- C9354 Acellular pericardial tissue matrix of nonhuman origin (Veritas), per sq cm
- C9356 Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (TenoGlide Tendon Protector Sheet), per sq cm
- C9358 Dermal substitute, native, nondenatured collagen, fetal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm
- C9360 Dermal substitute, native, nondenatured collagen, neonatal bovine origin (SurgiMend Collagen Matrix), per 0.5 sq cm
- C9363 Skin substitute (Integra Meshed Bilayer Wound Matrix), per square cm
- C9364 Porcine implant, Permacol, per sq cm
- Q4100 Skin substitute, not otherwise specified
- Q4101 Apligraf, per sq cm
- Q4102 Oasis wound matrix, per sq cm
- Q4103 Oasis burn matrix, per sq cm
- Q4104 Integra bilayer matrix wound dressing (BMWWD), per sq cm
- Q4105 Integra dermal regeneration template (DRT) or Integra Omnigraft dermal regeneration matrix, per sq cm
- Q4106 Dermagraft, per sq cm
- Q4107 GRAFTJACKET, per sq cm
- Q4108 Integra matrix, per sq cm
- Q4110 PriMatrix, per sq cm
- Q4111 GammaGraft, per sq cm
- Q4112 Cymetra, injectable, 1 cc
- Q4113 GRAFTJACKET XPRESS, injectable, 1cc
- Q4114 Integra flowable wound matrix, injectable, 1 cc
- Q4115 AlloSkin, per sq cm
- Q4116 AlloDerm, per sq cm
- Q4117 HYALOMATRIX, per sq cm
- Q4118 MatriStem micromatrix, 1 mg

Q4121	TheraSkin, per sq cm
Q4122	DermACELL, per sq cm
Q4123	AlloSkin RT, per sq cm
Q4124	OASIS ultra tri-layer wound matrix, per sq cm
Q4125	Arthroflex, per sq cm
Q4126	MemoDerm, DermaSpan, TranZgraft or InteguPly, per sq cm
Q4127	Talymed, per sq cm
Q4128	FlexHD, AllopatchHD, or Matrix HD, per sq cm
Q4130	Strattice TM, per sq cm
Q4134	hMatrix, per sq cm
Q4135	Mediskin, per sq cm
Q4136	E-Z Derm, per sq cm
Q4141	AlloSkin AC, per sq cm
Q4142	XCM biologic tissue matrix, per sq cm
Q4143	Repriza, per sq cm
Q4146	Tensix, per sq cm
Q4147	Architect, Architect PX, or Architect FX, extracellular matrix, per sq cm
Q4149	Excellagen, 0.1 cc
Q4152	Dermapure, per sq cm
Q4158	Marigen, per sq cm
Q4161	Bio-ConneKt wound matrix, per sq cm
Q4164	Helicoll, per sq cm
Q4165	Keramatrix, per sq cm
Q4166	Cytal, per sq cm
Q4167	Truskin, per sq cm
Q4175	Miroderm, per sq cm
Q4176	NeoPatch, per sq cm
Q4177	FlowerAmnioFlo, 0.1 cc
Q4178	FlowerAmnioPatch, per sq cm
Q4179	FlowerDerm, per sq cm
Q4180	Revita, per sq cm
Q4181	Amnio Wound, per sq cm
Q4182	TransCyte, per sq cm
Q4193	Coll-e-derm, per square centimeter
Q4195	Puraply, per square centimeter
Q4196	Puraply am, per square centimeter
Q4197	Puraply xt, per square centimeter
Q4200	Skin te, per square centimeter
Q4202	Kerxxx (2.5g/cc), 1cc
Q4203	Derma-gide, per square centimeter

- Application of skin replacements and skin substitutes is reported with CPT codes 15040-15278.
- Codes 15040-15261 are specific to autografts and tissue-cultured autografts.
- Codes 15271-15278 are specific to skin substitutes grafts.
- There is a specific add-on CPT code for the use of these materials as an implant: 15777.

- The HCPCS codes for these products used in outpatient and office settings are listed in the code table. There are also HCPCS modifiers to indicate whether the skin substitute is or is not used as a graft (ie, surface use vs use as an implant):
  - JC: Skin substitute used as a graft
  - JD: Skin substitute not used as a graft

### ICD-10 Diagnoses (Effective October 1, 2015)

C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
D05.01	Lobular carcinoma in situ of right breast
D05.02	Lobular carcinoma in situ of left breast
D05.11	Intraductal carcinoma in situ of right breast
D05.12	Intraductal carcinoma in situ of left breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
E10.40	Type 1 diabetes mellitus with diabetic neuropathy, unspecified
E10.41	Type 1 diabetes mellitus with diabetic mononeuropathy
E10.42	Type 1 diabetes mellitus with diabetic polyneuropathy
E10.43	Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E10.44	Type 1 diabetes mellitus with diabetic amyotrophy
E10.49	Type 1 diabetes mellitus with other diabetic neurological complication
E10.610	Type 1 diabetes mellitus with diabetic neuropathic arthropathy
E10.618	Type 1 diabetes mellitus with other diabetic arthropathy
E10.621	Type 1 diabetes mellitus with foot ulcer
E10.69	Type 1 diabetes mellitus with other specified complication
E11.40	Type 2 diabetes mellitus with diabetic neuropathy, unspecified
E11.41	Type 2 diabetes mellitus with diabetic mononeuropathy
E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
E11.43	Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.44	Type 2 diabetes mellitus with diabetic amyotrophy
E11.49	Type 2 diabetes mellitus with other diabetic neurological complication
E11.610	Type 2 diabetes mellitus with diabetic neuropathic arthropathy
E11.618	Type 2 diabetes mellitus with other diabetic arthropathy
E11.621	Type 2 diabetes mellitus with foot ulcer
E11.69	Type 2 diabetes mellitus with other specified complication
E13.40	Other specified diabetes mellitus with diabetic neuropathy, unspecified
E13.41	Other specified diabetes mellitus with diabetic mononeuropathy
E13.42	Other specified diabetes mellitus with diabetic polyneuropathy
E13.43	Other specified diabetes mellitus with diabetic autonomic (poly)neuropathy

- E13.44 Other specified diabetes mellitus with diabetic amyotrophy
- E13.49 Other specified diabetes mellitus with other diabetic neurological complication
- E13.610 Other specified diabetes mellitus with diabetic neuropathic arthropathy
- E13.618 Other specified diabetes mellitus with other diabetic arthropathy
- E13.621 Other specified diabetes mellitus with foot ulcer
- E13.69 Other specified diabetes mellitus with other specified complication
- I83.011 Varicose veins of right lower extremity with ulcer of thigh
- I83.012 Varicose veins of right lower extremity with ulcer of calf
- I83.013 Varicose veins of right lower extremity with ulcer of ankle
- I83.014 Varicose veins of right lower extremity with ulcer of heel and midfoot
- I83.015 Varicose veins of right lower extremity with ulcer other part of foot
- I83.018 Varicose veins of right lower extremity with ulcer other part of lower leg
- I83.021 Varicose veins of left lower extremity with ulcer of thigh
- I83.022 Varicose veins of left lower extremity with ulcer of calf
- I83.023 Varicose veins of left lower extremity with ulcer of ankle
- I83.024 Varicose veins of left lower extremity with ulcer of heel and midfoot
- I83.025 Varicose veins of left lower extremity with ulcer other part of foot
- I83.028 Varicose veins of left lower extremity with ulcer other part of lower leg
- I83.11 Varicose veins of right lower extremity with inflammation
- I83.12 Varicose veins of left lower extremity with inflammation
- I83.211 Varicose veins of right lower extremity with both ulcer of thigh and inflammation
- I83.212 Varicose veins of right lower extremity with both ulcer of calf and inflammation
- I83.213 Varicose veins of right lower extremity with both ulcer of ankle and inflammation
- I83.214 Varicose veins of right lower extremity with both ulcer of heel and midfoot and inflammation
- I83.215 Varicose veins of right lower extremity with both ulcer other part of foot and inflammation
- I83.218 Varicose veins of right lower extremity with both ulcer of other part of lower extremity and inflammation
- I83.221 Varicose veins of left lower extremity with both ulcer of thigh and inflammation
- I83.222 Varicose veins of left lower extremity with both ulcer of calf and inflammation
- I83.223 Varicose veins of left lower extremity with both ulcer of ankle and inflammation
- I83.224 Varicose veins of left lower extremity with both ulcer of heel and midfoot and inflammation
- I83.225 Varicose veins of left lower extremity with both ulcer other part of foot and inflammation
- I83.228 Varicose veins of left lower extremity with both ulcer of other part of lower extremity and inflammation
- I87.2 Venous insufficiency (chronic) (peripheral)
- L89.010 Pressure ulcer of right elbow, unstageable
- L89.012 Pressure ulcer of right elbow, stage 2
- L89.013 Pressure ulcer of right elbow, stage 3
- L89.014 Pressure ulcer of right elbow, stage 4
- L89.020 Pressure ulcer of left elbow, unstageable
- L89.022 Pressure ulcer of left elbow, stage 2
- L89.023 Pressure ulcer of left elbow, stage 3
- L89.024 Pressure ulcer of left elbow, stage 4
- L89.110 Pressure ulcer of right upper back, unstageable
- L89.112 Pressure ulcer of right upper back, stage 2
- L89.113 Pressure ulcer of right upper back, stage 3
- L89.114 Pressure ulcer of right upper back, stage 4
- L89.120 Pressure ulcer of left upper back, unstageable
- L89.122 Pressure ulcer of left upper back, stage 2
- L89.123 Pressure ulcer of left upper back, stage 3
- L89.124 Pressure ulcer of left upper back, stage 4
- L89.130 Pressure ulcer of right lower back, unstageable
- L89.132 Pressure ulcer of right lower back, stage 2
- L89.133 Pressure ulcer of right lower back, stage 3

L89.134	Pressure ulcer of right lower back, stage 4
L89.140	Pressure ulcer of left lower back, unstageable
L89.142	Pressure ulcer of left lower back, stage 2
L89.143	Pressure ulcer of left lower back, stage 3
L89.144	Pressure ulcer of left lower back, stage 4
L89.150	Pressure ulcer of sacral region, unstageable
L89.152	Pressure ulcer of sacral region, stage 2
L89.153	Pressure ulcer of sacral region, stage 3
L89.154	Pressure ulcer of sacral region, stage 4
L89.210	Pressure ulcer of right hip, unstageable
L89.212	Pressure ulcer of right hip, stage 2
L89.213	Pressure ulcer of right hip, stage 3
L89.214	Pressure ulcer of right hip, stage 4
L89.220	Pressure ulcer of left hip, unstageable
L89.222	Pressure ulcer of left hip, stage 2
L89.223	Pressure ulcer of left hip, stage 3
L89.224	Pressure ulcer of left hip, stage 4
L89.310	Pressure ulcer of right buttock, unstageable
L89.312	Pressure ulcer of right buttock, stage 2
L89.313	Pressure ulcer of right buttock, stage 3
L89.314	Pressure ulcer of right buttock, stage 4
L89.320	Pressure ulcer of left buttock, unstageable
L89.322	Pressure ulcer of left buttock, stage 2
L89.323	Pressure ulcer of left buttock, stage 3
L89.324	Pressure ulcer of left buttock, stage 4
L89.42	Pressure ulcer of contiguous site of back, buttock and hip, stage 2
L89.43	Pressure ulcer of contiguous site of back, buttock and hip, stage 3
L89.44	Pressure ulcer of contiguous site of back, buttock and hip, stage 4
L89.45	Pressure ulcer of contiguous site of back, buttock and hip, unstageable
L89.510	Pressure ulcer of right ankle, unstageable
L89.512	Pressure ulcer of right ankle, stage 2
L89.513	Pressure ulcer of right ankle, stage 3
L89.514	Pressure ulcer of right ankle, stage 4
L89.520	Pressure ulcer of left ankle, unstageable
L89.522	Pressure ulcer of left ankle, stage 2
L89.523	Pressure ulcer of left ankle, stage 3
L89.524	Pressure ulcer of left ankle, stage 4
L89.610	Pressure ulcer of right heel, unstageable
L89.612	Pressure ulcer of right heel, stage 2
L89.613	Pressure ulcer of right heel, stage 3
L89.614	Pressure ulcer of right heel, stage 4
L89.620	Pressure ulcer of left heel, unstageable
L89.622	Pressure ulcer of left heel, stage 2
L89.623	Pressure ulcer of left heel, stage 3
L89.624	Pressure ulcer of left heel, stage 4
L89.810	Pressure ulcer of head, unstageable
L89.812	Pressure ulcer of head, stage 2
L89.813	Pressure ulcer of head, stage 3
L89.814	Pressure ulcer of head, stage 4
L89.890	Pressure ulcer of other site, unstageable
L89.892	Pressure ulcer of other site, stage 2
L89.893	Pressure ulcer of other site, stage 3
L89.894	Pressure ulcer of other site, stage 4
L97.112	Non-pressure chronic ulcer of right thigh with fat layer exposed

L97.122	Non-pressure chronic ulcer of left thigh with fat layer exposed
L97.212	Non-pressure chronic ulcer of right calf with fat layer exposed
L97.222	Non-pressure chronic ulcer of left calf with fat layer exposed
L97.312	Non-pressure chronic ulcer of right ankle with fat layer exposed
L97.322	Non-pressure chronic ulcer of left ankle with fat layer exposed
L97.412	Non-pressure chronic ulcer of right heel and midfoot with fat layer exposed
L97.422	Non-pressure chronic ulcer of left heel and midfoot with fat layer exposed
L97.512	Non-pressure chronic ulcer of other part of right foot with fat layer exposed
L97.522	Non-pressure chronic ulcer of other part of left foot with fat layer exposed
L97.812	Non-pressure chronic ulcer of other part of right lower leg with fat layer exposed
L97.822	Non-pressure chronic ulcer of other part of left lower leg with fat layer exposed
L97.912	Non-pressure chronic ulcer of unspecified part of right lower leg with fat layer exposed
L97.922	Non-pressure chronic ulcer of unspecified part of left lower leg with fat layer exposed
L98.412	Non-pressure chronic ulcer of buttock with fat layer exposed
L98.422	Non-pressure chronic ulcer of back with fat layer exposed
L98.492	Non-pressure chronic ulcer of skin of other sites with fat layer exposed
Q81.2	Epidermolysis bullosa dystrophica
T20.211A	Burn of second degree of right ear [any part, except ear drum], initial encounter
T20.211D	Burn of second degree of right ear [any part, except ear drum], subsequent encounter
T20.211S	Burn of second degree of right ear [any part, except ear drum], sequela
T20.212A	Burn of second degree of left ear [any part, except ear drum], initial encounter
T20.212D	Burn of second degree of left ear [any part, except ear drum], subsequent encounter
T20.212S	Burn of second degree of left ear [any part, except ear drum], sequela
T20.22xA	Burn of second degree of lip(s), initial encounter
T20.22xD	Burn of second degree of lip(s), subsequent encounter
T20.22xS	Burn of second degree of lip(s), sequela
T20.23xA	Burn of second degree of chin, initial encounter
T20.23xD	Burn of second degree of chin, subsequent encounter
T20.23xS	Burn of second degree of chin, sequela
T20.24xA	Burn of second degree of nose (septum), initial encounter
T20.24xD	Burn of second degree of nose (septum), subsequent encounter
T20.24xS	Burn of second degree of nose (septum), sequela
T20.25xA	Burn of second degree of scalp [any part], initial encounter
T20.25xD	Burn of second degree of scalp [any part], subsequent encounter
T20.25xS	Burn of second degree of scalp [any part], sequela
T20.26xA	Burn of second degree of forehead and cheek, initial encounter
T20.26xD	Burn of second degree of forehead and cheek, subsequent encounter
T20.26xS	Burn of second degree of forehead and cheek, sequela
T20.27xA	Burn of second degree of neck, initial encounter
T20.27xD	Burn of second degree of neck, subsequent encounter
T20.27xS	Burn of second degree of neck, sequela
T20.29xA	Burn of second degree of multiple sites of head, face, and neck, initial encounter
T20.29xD	Burn of second degree of multiple sites of head, face, and neck, subsequent encounter
T20.29xS	Burn of second degree of multiple sites of head, face, and neck, sequela
T20.311A	Burn of third degree of right ear [any part, except ear drum], initial encounter
T20.311D	Burn of third degree of right ear [any part, except ear drum], subsequent encounter
T20.311S	Burn of third degree of right ear [any part, except ear drum], sequela
T20.312A	Burn of third degree of left ear [any part, except ear drum], initial encounter
T20.312D	Burn of third degree of left ear [any part, except ear drum], subsequent encounter
T20.312S	Burn of third degree of left ear [any part, except ear drum], sequela
T20.32xA	Burn of third degree of lip(s), initial encounter
T20.32xD	Burn of third degree of lip(s), subsequent encounter
T20.32xS	Burn of third degree of lip(s), sequela
T20.33xA	Burn of third degree of chin, initial encounter

T20.33xD	Burn of third degree of chin, subsequent encounter
T20.33xS	Burn of third degree of chin, sequela
T20.34xA	Burn of third degree of nose (septum), initial encounter
T20.34xD	Burn of third degree of nose (septum), subsequent encounter
T20.34xS	Burn of third degree of nose (septum), sequela
T20.35xA	Burn of third degree of scalp [any part], initial encounter
T20.35xD	Burn of third degree of scalp [any part], subsequent encounter
T20.35xS	Burn of third degree of scalp [any part], sequela
T20.36xA	Burn of third degree of forehead and cheek, initial encounter
T20.36xD	Burn of third degree of forehead and cheek, subsequent encounter
T20.36xS	Burn of third degree of forehead and cheek, sequela
T20.37xA	Burn of third degree of neck, initial encounter
T20.37xD	Burn of third degree of neck, subsequent encounter
T20.37xS	Burn of third degree of neck, sequela
T20.39xA	Burn of third degree of multiple sites of head, face, and neck, initial encounter
T20.39xD	Burn of third degree of multiple sites of head, face, and neck, subsequent encounter
T20.39xS	Burn of third degree of multiple sites of head, face, and neck, sequela
T20.611A	Corrosion of second degree of right ear [any part, except ear drum], initial encounter
T20.611D	Corrosion of second degree of right ear [any part, except ear drum], subsequent encounter
T20.611S	Corrosion of second degree of right ear [any part, except ear drum], sequela
T20.612A	Corrosion of second degree of left ear [any part, except ear drum], initial encounter
T20.612D	Corrosion of second degree of left ear [any part, except ear drum], subsequent encounter
T20.612S	Corrosion of second degree of left ear [any part, except ear drum], sequela
T20.62xA	Corrosion of second degree of lip(s), initial encounter
T20.62xD	Corrosion of second degree of lip(s), subsequent encounter
T20.62xS	Corrosion of second degree of lip(s), sequela
T20.63xA	Corrosion of second degree of chin, initial encounter
T20.63xD	Corrosion of second degree of chin, subsequent encounter
T20.63xS	Corrosion of second degree of chin, sequela
T20.64xA	Corrosion of second degree of nose (septum), initial encounter
T20.64xD	Corrosion of second degree of nose (septum), subsequent encounter
T20.64xS	Corrosion of second degree of nose (septum), sequela
T20.65xA	Corrosion of second degree of scalp [any part], initial encounter
T20.65xD	Corrosion of second degree of scalp [any part], subsequent encounter
T20.65xS	Corrosion of second degree of scalp [any part], sequela
T20.66xA	Corrosion of second degree of forehead and cheek, initial encounter
T20.66xD	Corrosion of second degree of forehead and cheek, subsequent encounter
T20.66xS	Corrosion of second degree of forehead and cheek, sequela
T20.67xA	Corrosion of second degree of neck, initial encounter
T20.67xD	Corrosion of second degree of neck, subsequent encounter
T20.67xS	Corrosion of second degree of neck, sequela
T20.69xA	Corrosion of second degree of multiple sites of head, face, and neck, initial encounter
T20.69xD	Corrosion of second degree of multiple sites of head, face, and neck, subsequent encounter
T20.69xS	Corrosion of second degree of multiple sites of head, face, and neck, sequela
T20.711A	Corrosion of third degree of right ear [any part, except ear drum], initial encounter
T20.711D	Corrosion of third degree of right ear [any part, except ear drum], subsequent encounter
T20.711S	Corrosion of third degree of right ear [any part, except ear drum], sequela
T20.712A	Corrosion of third degree of left ear [any part, except ear drum], initial encounter
T20.712D	Corrosion of third degree of left ear [any part, except ear drum], subsequent encounter
T20.712S	Corrosion of third degree of left ear [any part, except ear drum], sequela
T20.72xA	Corrosion of third degree of lip(s), initial encounter
T20.72xD	Corrosion of third degree of lip(s), subsequent encounter
T20.72xS	Corrosion of third degree of lip(s), sequela
T20.73xA	Corrosion of third degree of chin, initial encounter

T20.73xD	Corrosion of third degree of chin, subsequent encounter
T20.73xS	Corrosion of third degree of chin, sequela
T20.74xA	Corrosion of third degree of nose (septum), initial encounter
T20.74xD	Corrosion of third degree of nose (septum), subsequent encounter
T20.74xS	Corrosion of third degree of nose (septum), sequela
T20.75xA	Corrosion of third degree of scalp [any part], initial encounter
T20.75xD	Corrosion of third degree of scalp [any part], subsequent encounter
T20.75xS	Corrosion of third degree of scalp [any part], sequela
T20.76xA	Corrosion of third degree of forehead and cheek, initial encounter
T20.76xD	Corrosion of third degree of forehead and cheek, subsequent encounter
T20.76xS	Corrosion of third degree of forehead and cheek, sequela
T20.77xA	Corrosion of third degree of neck, initial encounter
T20.77xD	Corrosion of third degree of neck, subsequent encounter
T20.77xS	Corrosion of third degree of neck, sequela
T20.79xA	Corrosion of third degree of multiple sites of head, face, and neck, initial encounter
T20.79xD	Corrosion of third degree of multiple sites of head, face, and neck, subsequent encounter
T20.79xS	Corrosion of third degree of multiple sites of head, face, and neck, sequela
T21.21xA	Burn of second degree of chest wall, initial encounter
T21.21xD	Burn of second degree of chest wall, subsequent encounter
T21.21xS	Burn of second degree of chest wall, sequela
T21.22xA	Burn of second degree of abdominal wall, initial encounter
T21.22xD	Burn of second degree of abdominal wall, subsequent encounter
T21.22xS	Burn of second degree of abdominal wall, sequela
T21.23xA	Burn of second degree of upper back, initial encounter
T21.23xD	Burn of second degree of upper back, subsequent encounter
T21.23xS	Burn of second degree of upper back, sequela
T21.24xA	Burn of second degree of lower back, initial encounter
T21.24xD	Burn of second degree of lower back, subsequent encounter
T21.24xS	Burn of second degree of lower back, sequela
T21.25xA	Burn of second degree of buttock, initial encounter
T21.25xD	Burn of second degree of buttock, subsequent encounter
T21.25xS	Burn of second degree of buttock, sequela
T21.26xA	Burn of second degree of male genital region, initial encounter
T21.26xD	Burn of second degree of male genital region, subsequent encounter
T21.26xS	Burn of second degree of male genital region, sequela
T21.27xA	Burn of second degree of female genital region, initial encounter
T21.27xD	Burn of second degree of female genital region, subsequent encounter
T21.27xS	Burn of second degree of female genital region, sequela
T21.29xA	Burn of second degree of other site of trunk, initial encounter
T21.29xD	Burn of second degree of other site of trunk, subsequent encounter
T21.29xS	Burn of second degree of other site of trunk, sequela
T21.31xA	Burn of third degree of chest wall, initial encounter
T21.31xD	Burn of third degree of chest wall, subsequent encounter
T21.31xS	Burn of third degree of chest wall, sequela
T21.32xA	Burn of third degree of abdominal wall, initial encounter
T21.32xD	Burn of third degree of abdominal wall, subsequent encounter
T21.32xS	Burn of third degree of abdominal wall, sequela
T21.33xA	Burn of third degree of upper back, initial encounter
T21.33xD	Burn of third degree of upper back, subsequent encounter
T21.33xS	Burn of third degree of upper back, sequela
T21.34xA	Burn of third degree of lower back, initial encounter
T21.34xD	Burn of third degree of lower back, subsequent encounter
T21.34xS	Burn of third degree of lower back, sequela
T21.35xA	Burn of third degree of buttock, initial encounter

T21.35xD	Burn of third degree of buttock, subsequent encounter
T21.35xS	Burn of third degree of buttock, sequela
T21.36xA	Burn of third degree of male genital region, initial encounter
T21.36xD	Burn of third degree of male genital region, subsequent encounter
T21.36xS	Burn of third degree of male genital region, sequela
T21.37xA	Burn of third degree of female genital region, initial encounter
T21.37xD	Burn of third degree of female genital region, subsequent encounter
T21.37xS	Burn of third degree of female genital region, sequela
T21.39xA	Burn of third degree of other site of trunk, initial encounter
T21.39xD	Burn of third degree of other site of trunk, subsequent encounter
T21.39xS	Burn of third degree of other site of trunk, sequela
T21.61xA	Corrosion of second degree of chest wall, initial encounter
T21.61xD	Corrosion of second degree of chest wall, subsequent encounter
T21.61xS	Corrosion of second degree of chest wall, sequela
T21.62xA	Corrosion of second degree of abdominal wall, initial encounter
T21.62xD	Corrosion of second degree of abdominal wall, subsequent encounter
T21.62xS	Corrosion of second degree of abdominal wall, sequela
T21.63xA	Corrosion of second degree of upper back, initial encounter
T21.63xD	Corrosion of second degree of upper back, subsequent encounter
T21.63xS	Corrosion of second degree of upper back, sequela
T21.64xA	Corrosion of second degree of lower back, initial encounter
T21.64xD	Corrosion of second degree of lower back, subsequent encounter
T21.64xS	Corrosion of second degree of lower back, sequela
T21.65xA	Corrosion of second degree of buttock, initial encounter
T21.65xD	Corrosion of second degree of buttock, subsequent encounter
T21.65xS	Corrosion of second degree of buttock, sequela
T21.66xA	Corrosion of second degree of male genital region, initial encounter
T21.66xD	Corrosion of second degree of male genital region, subsequent encounter
T21.66xS	Corrosion of second degree of male genital region, sequela
T21.67xA	Corrosion of second degree of female genital region, initial encounter
T21.67xD	Corrosion of second degree of female genital region, subsequent encounter
T21.67xS	Corrosion of second degree of female genital region, sequela
T21.69xA	Corrosion of second degree of other site of trunk, initial encounter
T21.69xD	Corrosion of second degree of other site of trunk, subsequent encounter
T21.69xS	Corrosion of second degree of other site of trunk, sequela
T21.71xA	Corrosion of third degree of chest wall, initial encounter
T21.71xD	Corrosion of third degree of chest wall, subsequent encounter
T21.71xS	Corrosion of third degree of chest wall, sequela
T21.72xA	Corrosion of third degree of abdominal wall, initial encounter
T21.72xD	Corrosion of third degree of abdominal wall, subsequent encounter
T21.72xS	Corrosion of third degree of abdominal wall, sequela
T21.73xA	Corrosion of third degree of upper back, initial encounter
T21.73xD	Corrosion of third degree of upper back, subsequent encounter
T21.73xS	Corrosion of third degree of upper back, sequela
T21.74xA	Corrosion of third degree of lower back, initial encounter
T21.74xD	Corrosion of third degree of lower back, subsequent encounter
T21.74xS	Corrosion of third degree of lower back, sequela
T21.75xA	Corrosion of third degree of buttock, initial encounter
T21.75xD	Corrosion of third degree of buttock, subsequent encounter
T21.75xS	Corrosion of third degree of buttock, sequela
T21.76xA	Corrosion of third degree of male genital region, initial encounter
T21.76xD	Corrosion of third degree of male genital region, subsequent encounter
T21.76xS	Corrosion of third degree of male genital region, sequela
T21.77xA	Corrosion of third degree of female genital region, initial encounter

T21.77xD	Corrosion of third degree of female genital region, subsequent encounter
T21.77xS	Corrosion of third degree of female genital region, sequela
T21.79xA	Corrosion of third degree of other site of trunk, initial encounter
T21.79xD	Corrosion of third degree of other site of trunk, subsequent encounter
T21.79xS	Corrosion of third degree of other site of trunk, sequela
T22.211A	Burn of second degree of right forearm, initial encounter
T22.211D	Burn of second degree of right forearm, subsequent encounter
T22.211S	Burn of second degree of right forearm, sequela
T22.212A	Burn of second degree of left forearm, initial encounter
T22.212D	Burn of second degree of left forearm, subsequent encounter
T22.212S	Burn of second degree of left forearm, sequela
T22.221A	Burn of second degree of right elbow, initial encounter
T22.221D	Burn of second degree of right elbow, subsequent encounter
T22.221S	Burn of second degree of right elbow, sequela
T22.222A	Burn of second degree of left elbow, initial encounter
T22.222D	Burn of second degree of left elbow, subsequent encounter
T22.222S	Burn of second degree of left elbow, sequela
T22.231A	Burn of second degree of right upper arm, initial encounter
T22.231D	Burn of second degree of right upper arm, subsequent encounter
T22.231S	Burn of second degree of right upper arm, sequela
T22.232A	Burn of second degree of left upper arm, initial encounter
T22.232D	Burn of second degree of left upper arm, subsequent encounter
T22.232S	Burn of second degree of left upper arm, sequela
T22.241A	Burn of second degree of right axilla, initial encounter
T22.241D	Burn of second degree of right axilla, subsequent encounter
T22.241S	Burn of second degree of right axilla, sequela
T22.242A	Burn of second degree of left axilla, initial encounter
T22.242D	Burn of second degree of left axilla, subsequent encounter
T22.242S	Burn of second degree of left axilla, sequela
T22.251A	Burn of second degree of right shoulder, initial encounter
T22.251D	Burn of second degree of right shoulder, subsequent encounter
T22.251S	Burn of second degree of right shoulder, sequela
T22.252A	Burn of second degree of left shoulder, initial encounter
T22.252D	Burn of second degree of left shoulder, subsequent encounter
T22.252S	Burn of second degree of left shoulder, sequela
T22.261A	Burn of second degree of right scapular region, initial encounter
T22.261D	Burn of second degree of right scapular region, subsequent encounter
T22.261S	Burn of second degree of right scapular region, sequela
T22.262A	Burn of second degree of left scapular region, initial encounter
T22.262D	Burn of second degree of left scapular region, subsequent encounter
T22.262S	Burn of second degree of left scapular region, sequela
T22.291A	Burn of second degree of multiple sites of right shoulder and upper limb, except wrist and hand, initial encounter
T22.291D	Burn of second degree of multiple sites of right shoulder and upper limb, except wrist and hand, subsequent encounter
T22.291S	Burn of second degree of multiple sites of right shoulder and upper limb, except wrist and hand, sequela
T22.292A	Burn of second degree of multiple sites of left shoulder and upper limb, except wrist and hand, initial encounter
T22.292D	Burn of second degree of multiple sites of left shoulder and upper limb, except wrist and hand, subsequent encounter
T22.292S	Burn of second degree of multiple sites of left shoulder and upper limb, except wrist and hand, sequela
T22.311A	Burn of third degree of right forearm, initial encounter

T22.311D	Burn of third degree of right forearm, subsequent encounter
T22.311S	Burn of third degree of right forearm, sequela
T22.312A	Burn of third degree of left forearm, initial encounter
T22.312D	Burn of third degree of left forearm, subsequent encounter
T22.312S	Burn of third degree of left forearm, sequela
T22.321A	Burn of third degree of right elbow, initial encounter
T22.321D	Burn of third degree of right elbow, subsequent encounter
T22.321S	Burn of third degree of right elbow, sequela
T22.322A	Burn of third degree of left elbow, initial encounter
T22.322D	Burn of third degree of left elbow, subsequent encounter
T22.322S	Burn of third degree of left elbow, sequela
T22.331A	Burn of third degree of right upper arm, initial encounter
T22.331D	Burn of third degree of right upper arm, subsequent encounter
T22.331S	Burn of third degree of right upper arm, sequela
T22.332A	Burn of third degree of left upper arm, initial encounter
T22.332D	Burn of third degree of left upper arm, subsequent encounter
T22.332S	Burn of third degree of left upper arm, sequela
T22.341A	Burn of third degree of right axilla, initial encounter
T22.341D	Burn of third degree of right axilla, subsequent encounter
T22.341S	Burn of third degree of right axilla, sequela
T22.342A	Burn of third degree of left axilla, initial encounter
T22.342D	Burn of third degree of left axilla, subsequent encounter
T22.342S	Burn of third degree of left axilla, sequela
T22.351A	Burn of third degree of right shoulder, initial encounter
T22.351D	Burn of third degree of right shoulder, subsequent encounter
T22.351S	Burn of third degree of right shoulder, sequela
T22.352A	Burn of third degree of left shoulder, initial encounter
T22.352D	Burn of third degree of left shoulder, subsequent encounter
T22.352S	Burn of third degree of left shoulder, sequela
T22.361A	Burn of third degree of right scapular region, initial encounter
T22.361D	Burn of third degree of right scapular region, subsequent encounter
T22.361S	Burn of third degree of right scapular region, sequela
T22.362A	Burn of third degree of left scapular region, initial encounter
T22.362D	Burn of third degree of left scapular region, subsequent encounter
T22.362S	Burn of third degree of left scapular region, sequela
T22.391A	Burn of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, initial encounter
T22.391D	Burn of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, subsequent encounter
T22.391S	Burn of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, sequela
T22.392A	Burn of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, initial encounter
T22.392D	Burn of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, subsequent encounter
T22.392S	Burn of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, sequela
T22.611A	Corrosion of second degree of right forearm, initial encounter
T22.611D	Corrosion of second degree of right forearm, subsequent encounter
T22.611S	Corrosion of second degree of right forearm, sequela
T22.612A	Corrosion of second degree of left forearm, initial encounter
T22.612D	Corrosion of second degree of left forearm, subsequent encounter
T22.612S	Corrosion of second degree of left forearm, sequela
T22.621A	Corrosion of second degree of right elbow, initial encounter

T22.621D	Corrosion of second degree of right elbow, subsequent encounter
T22.621S	Corrosion of second degree of right elbow, sequela
T22.622A	Corrosion of second degree of left elbow, initial encounter
T22.622D	Corrosion of second degree of left elbow, subsequent encounter
T22.622S	Corrosion of second degree of left elbow, sequela
T22.631A	Corrosion of second degree of right upper arm, initial encounter
T22.631D	Corrosion of second degree of right upper arm, subsequent encounter
T22.631S	Corrosion of second degree of right upper arm, sequela
T22.632A	Corrosion of second degree of left upper arm, initial encounter
T22.632D	Corrosion of second degree of left upper arm, subsequent encounter
T22.632S	Corrosion of second degree of left upper arm, sequela
T22.641A	Corrosion of second degree of right axilla, initial encounter
T22.641D	Corrosion of second degree of right axilla, subsequent encounter
T22.641S	Corrosion of second degree of right axilla, sequela
T22.642A	Corrosion of second degree of left axilla, initial encounter
T22.642D	Corrosion of second degree of left axilla, subsequent encounter
T22.642S	Corrosion of second degree of left axilla, sequela
T22.651A	Corrosion of second degree of right shoulder, initial encounter
T22.651D	Corrosion of second degree of right shoulder, subsequent encounter
T22.651S	Corrosion of second degree of right shoulder, sequela
T22.652A	Corrosion of second degree of left shoulder, initial encounter
T22.652D	Corrosion of second degree of left shoulder, subsequent encounter
T22.652S	Corrosion of second degree of left shoulder, sequela
T22.661A	Corrosion of second degree of right scapular region, initial encounter
T22.661D	Corrosion of second degree of right scapular region, subsequent encounter
T22.661S	Corrosion of second degree of right scapular region, sequela
T22.662A	Corrosion of second degree of left scapular region, initial encounter
T22.662D	Corrosion of second degree of left scapular region, subsequent encounter
T22.662S	Corrosion of second degree of left scapular region, sequela
T22.691A	Corrosion of second degree of multiple sites of right shoulder and upper limb, except wrist and hand, initial encounter
T22.691D	Corrosion of second degree of multiple sites of right shoulder and upper limb, except wrist and hand, subsequent encounter
T22.691S	Corrosion of second degree of multiple sites of right shoulder and upper limb, except wrist and hand, sequela
T22.692A	Corrosion of second degree of multiple sites of left shoulder and upper limb, except wrist and hand, initial encounter
T22.692D	Corrosion of second degree of multiple sites of left shoulder and upper limb, except wrist and hand, subsequent encounter
T22.692S	Corrosion of second degree of multiple sites of left shoulder and upper limb, except wrist and hand, sequela
T22.711A	Corrosion of third degree of right forearm, initial encounter
T22.711D	Corrosion of third degree of right forearm, subsequent encounter
T22.711S	Corrosion of third degree of right forearm, sequela
T22.712A	Corrosion of third degree of left forearm, initial encounter
T22.712D	Corrosion of third degree of left forearm, subsequent encounter
T22.712S	Corrosion of third degree of left forearm, sequela
T22.721A	Corrosion of third degree of right elbow, initial encounter
T22.721D	Corrosion of third degree of right elbow, subsequent encounter
T22.721S	Corrosion of third degree of right elbow, sequela
T22.722A	Corrosion of third degree of left elbow, initial encounter
T22.722D	Corrosion of third degree of left elbow, subsequent encounter
T22.722S	Corrosion of third degree of left elbow, sequela
T22.731A	Corrosion of third degree of right upper arm, initial encounter

T22.731D	Corrosion of third degree of right upper arm, subsequent encounter
T22.731S	Corrosion of third degree of right upper arm, sequela
T22.732A	Corrosion of third degree of left upper arm, initial encounter
T22.732D	Corrosion of third degree of left upper arm, subsequent encounter
T22.732S	Corrosion of third degree of left upper arm, sequela
T22.741A	Corrosion of third degree of right axilla, initial encounter
T22.741D	Corrosion of third degree of right axilla, subsequent encounter
T22.741S	Corrosion of third degree of right axilla, sequela
T22.742A	Corrosion of third degree of left axilla, initial encounter
T22.742D	Corrosion of third degree of left axilla, subsequent encounter
T22.742S	Corrosion of third degree of left axilla, sequela
T22.751A	Corrosion of third degree of right shoulder, initial encounter
T22.751D	Corrosion of third degree of right shoulder, subsequent encounter
T22.751S	Corrosion of third degree of right shoulder, sequela
T22.752A	Corrosion of third degree of left shoulder, initial encounter
T22.752D	Corrosion of third degree of left shoulder, subsequent encounter
T22.752S	Corrosion of third degree of left shoulder, sequela
T22.761A	Corrosion of third degree of right scapular region, initial encounter
T22.761D	Corrosion of third degree of right scapular region, subsequent encounter
T22.761S	Corrosion of third degree of right scapular region, sequela
T22.762A	Corrosion of third degree of left scapular region, initial encounter
T22.762D	Corrosion of third degree of left scapular region, subsequent encounter
T22.762S	Corrosion of third degree of left scapular region, sequela
T22.791A	Corrosion of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, initial encounter
T22.791D	Corrosion of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, subsequent encounter
T22.791S	Corrosion of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, sequela
T22.792A	Corrosion of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, initial encounter
T22.792D	Corrosion of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, subsequent encounter
T22.792S	Corrosion of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, sequela
T23.211A	Burn of second degree of right thumb (nail), initial encounter
T23.211D	Burn of second degree of right thumb (nail), subsequent encounter
T23.211S	Burn of second degree of right thumb (nail), sequela
T23.212A	Burn of second degree of left thumb (nail), initial encounter
T23.212D	Burn of second degree of left thumb (nail), subsequent encounter
T23.212S	Burn of second degree of left thumb (nail), sequela
T23.221A	Burn of second degree of single right finger (nail) except thumb, initial encounter
T23.221D	Burn of second degree of single right finger (nail) except thumb, subsequent encounter
T23.221S	Burn of second degree of single right finger (nail) except thumb, sequela
T23.222A	Burn of second degree of single left finger (nail) except thumb, initial encounter
T23.222D	Burn of second degree of single left finger (nail) except thumb, subsequent encounter
T23.222S	Burn of second degree of single left finger (nail) except thumb, sequela
T23.231A	Burn of second degree of multiple right fingers (nail), not including thumb, initial encounter
T23.231D	Burn of second degree of multiple right fingers (nail), not including thumb, subsequent encounter
T23.231S	Burn of second degree of multiple right fingers (nail), not including thumb, sequela
T23.232A	Burn of second degree of multiple left fingers (nail), not including thumb, initial encounter
T23.232D	Burn of second degree of multiple left fingers (nail), not including thumb, subsequent encounter

T23.232S	Burn of second degree of multiple left fingers (nail), not including thumb, sequela
T23.241A	Burn of second degree of multiple right fingers (nail), including thumb, initial encounter
T23.241D	Burn of second degree of multiple right fingers (nail), including thumb, subsequent encounter
T23.241S	Burn of second degree of multiple right fingers (nail), including thumb, sequela
T23.242A	Burn of second degree of multiple left fingers (nail), including thumb, initial encounter
T23.242D	Burn of second degree of multiple left fingers (nail), including thumb, subsequent encounter
T23.242S	Burn of second degree of multiple left fingers (nail), including thumb, sequela
T23.251A	Burn of second degree of right palm, initial encounter
T23.251D	Burn of second degree of right palm, subsequent encounter
T23.251S	Burn of second degree of right palm, sequela
T23.252A	Burn of second degree of left palm, initial encounter
T23.252D	Burn of second degree of left palm, subsequent encounter
T23.252S	Burn of second degree of left palm, sequela
T23.261A	Burn of second degree of back of right hand, initial encounter
T23.261D	Burn of second degree of back of right hand, subsequent encounter
T23.261S	Burn of second degree of back of right hand, sequela
T23.262A	Burn of second degree of back of left hand, initial encounter
T23.262D	Burn of second degree of back of left hand, subsequent encounter
T23.262S	Burn of second degree of back of left hand, sequela
T23.271A	Burn of second degree of right wrist, initial encounter
T23.271D	Burn of second degree of right wrist, subsequent encounter
T23.271S	Burn of second degree of right wrist, sequela
T23.272A	Burn of second degree of left wrist, initial encounter
T23.272D	Burn of second degree of left wrist, subsequent encounter
T23.272S	Burn of second degree of left wrist, sequela
T23.291A	Burn of second degree of multiple sites of right wrist and hand, initial encounter
T23.291D	Burn of second degree of multiple sites of right wrist and hand, subsequent encounter
T23.291S	Burn of second degree of multiple sites of right wrist and hand, sequela
T23.292A	Burn of second degree of multiple sites of left wrist and hand, initial encounter
T23.292D	Burn of second degree of multiple sites of left wrist and hand, subsequent encounter
T23.292S	Burn of second degree of multiple sites of left wrist and hand, sequela
T23.311A	Burn of third degree of right thumb (nail), initial encounter
T23.311D	Burn of third degree of right thumb (nail), subsequent encounter
T23.311S	Burn of third degree of right thumb (nail), sequela
T23.312A	Burn of third degree of left thumb (nail), initial encounter
T23.312D	Burn of third degree of left thumb (nail), subsequent encounter
T23.312S	Burn of third degree of left thumb (nail), sequela
T23.321A	Burn of third degree of single right finger (nail) except thumb, initial encounter
T23.321D	Burn of third degree of single right finger (nail) except thumb, subsequent encounter
T23.321S	Burn of third degree of single right finger (nail) except thumb, sequela
T23.322A	Burn of third degree of single left finger (nail) except thumb, initial encounter
T23.322D	Burn of third degree of single left finger (nail) except thumb, subsequent encounter
T23.322S	Burn of third degree of single left finger (nail) except thumb, sequela
T23.331A	Burn of third degree of multiple right fingers (nail), not including thumb, initial encounter
T23.331D	Burn of third degree of multiple right fingers (nail), not including thumb, subsequent encounter
T23.331S	Burn of third degree of multiple right fingers (nail), not including thumb, sequela
T23.332A	Burn of third degree of multiple left fingers (nail), not including thumb, initial encounter
T23.332D	Burn of third degree of multiple left fingers (nail), not including thumb, subsequent encounter
T23.332S	Burn of third degree of multiple left fingers (nail), not including thumb, sequela
T23.341A	Burn of third degree of multiple right fingers (nail), including thumb, initial encounter
T23.341D	Burn of third degree of multiple right fingers (nail), including thumb, subsequent encounter
T23.341S	Burn of third degree of multiple right fingers (nail), including thumb, sequela
T23.342A	Burn of third degree of multiple left fingers (nail), including thumb, initial encounter
T23.342D	Burn of third degree of multiple left fingers (nail), including thumb, subsequent encounter

- T23.342S Burn of third degree of multiple left fingers (nail), including thumb, sequela
- T23.351A Burn of third degree of right palm, initial encounter
- T23.351D Burn of third degree of right palm, subsequent encounter
- T23.351S Burn of third degree of right palm, sequela
- T23.352A Burn of third degree of left palm, initial encounter
- T23.352D Burn of third degree of left palm, subsequent encounter
- T23.352S Burn of third degree of left palm, sequela
- T23.361A Burn of third degree of back of right hand, initial encounter
- T23.361D Burn of third degree of back of right hand, subsequent encounter
- T23.361S Burn of third degree of back of right hand, sequela
- T23.362A Burn of third degree of back of left hand, initial encounter
- T23.362D Burn of third degree of back of left hand, subsequent encounter
- T23.362S Burn of third degree of back of left hand, sequela
- T23.371A Burn of third degree of right wrist, initial encounter
- T23.371D Burn of third degree of right wrist, subsequent encounter
- T23.371S Burn of third degree of right wrist, sequela
- T23.372A Burn of third degree of left wrist, initial encounter
- T23.372D Burn of third degree of left wrist, subsequent encounter
- T23.372S Burn of third degree of left wrist, sequela
- T23.391A Burn of third degree of multiple sites of right wrist and hand, initial encounter
- T23.391D Burn of third degree of multiple sites of right wrist and hand, subsequent encounter
- T23.391S Burn of third degree of multiple sites of right wrist and hand, sequela
- T23.392A Burn of third degree of multiple sites of left wrist and hand, initial encounter
- T23.392D Burn of third degree of multiple sites of left wrist and hand, subsequent encounter
- T23.392S Burn of third degree of multiple sites of left wrist and hand, sequela
- T23.611A Corrosion of second degree of right thumb (nail), initial encounter
- T23.611D Corrosion of second degree of right thumb (nail), subsequent encounter
- T23.611S Corrosion of second degree of right thumb (nail), sequela
- T23.612A Corrosion of second degree of left thumb (nail), initial encounter
- T23.612D Corrosion of second degree of left thumb (nail), subsequent encounter
- T23.612S Corrosion of second degree of left thumb (nail), sequela
- T23.621A Corrosion of second degree of single right finger (nail) except thumb, initial encounter
- T23.621D Corrosion of second degree of single right finger (nail) except thumb, subsequent encounter
- T23.621S Corrosion of second degree of single right finger (nail) except thumb, sequela
- T23.622A Corrosion of second degree of single left finger (nail) except thumb, initial encounter
- T23.622D Corrosion of second degree of single left finger (nail) except thumb, subsequent encounter
- T23.622S Corrosion of second degree of single left finger (nail) except thumb, sequela
- T23.631A Corrosion of second degree of multiple right fingers (nail), not including thumb, initial encounter
- T23.631D Corrosion of second degree of multiple right fingers (nail), not including thumb, subsequent encounter
- T23.631S Corrosion of second degree of multiple right fingers (nail), not including thumb, sequela
- T23.632A Corrosion of second degree of multiple left fingers (nail), not including thumb, initial encounter
- T23.632D Corrosion of second degree of multiple left fingers (nail), not including thumb, subsequent encounter
- T23.632S Corrosion of second degree of multiple left fingers (nail), not including thumb, sequela
- T23.641A Corrosion of second degree of multiple right fingers (nail), including thumb, initial encounter
- T23.641D Corrosion of second degree of multiple right fingers (nail), including thumb, subsequent encounter
- T23.641S Corrosion of second degree of multiple right fingers (nail), including thumb, sequela
- T23.642A Corrosion of second degree of multiple left fingers (nail), including thumb, initial encounter
- T23.642D Corrosion of second degree of multiple left fingers (nail), including thumb, subsequent encounter
- T23.642S Corrosion of second degree of multiple left fingers (nail), including thumb, sequela

T23.651A	Corrosion of second degree of right palm, initial encounter
T23.651D	Corrosion of second degree of right palm, subsequent encounter
T23.651S	Corrosion of second degree of right palm, sequela
T23.652A	Corrosion of second degree of left palm, initial encounter
T23.652D	Corrosion of second degree of left palm, subsequent encounter
T23.652S	Corrosion of second degree of left palm, sequela
T23.661A	Corrosion of second degree back of right hand, initial encounter
T23.661D	Corrosion of second degree back of right hand, subsequent encounter
T23.661S	Corrosion of second degree back of right hand, sequela
T23.662A	Corrosion of second degree back of left hand, initial encounter
T23.662D	Corrosion of second degree back of left hand, subsequent encounter
T23.662S	Corrosion of second degree back of left hand, sequela
T23.671A	Corrosion of second degree of right wrist, initial encounter
T23.671D	Corrosion of second degree of right wrist, subsequent encounter
T23.671S	Corrosion of second degree of right wrist, sequela
T23.672A	Corrosion of second degree of left wrist, initial encounter
T23.672D	Corrosion of second degree of left wrist, subsequent encounter
T23.672S	Corrosion of second degree of left wrist, sequela
T23.691A	Corrosion of second degree of multiple sites of right wrist and hand, initial encounter
T23.691D	Corrosion of second degree of multiple sites of right wrist and hand, subsequent encounter
T23.691S	Corrosion of second degree of multiple sites of right wrist and hand, sequela
T23.692A	Corrosion of second degree of multiple sites of left wrist and hand, initial encounter
T23.692D	Corrosion of second degree of multiple sites of left wrist and hand, subsequent encounter
T23.692S	Corrosion of second degree of multiple sites of left wrist and hand, sequela
T23.711A	Corrosion of third degree of right thumb (nail), initial encounter
T23.711D	Corrosion of third degree of right thumb (nail), subsequent encounter
T23.711S	Corrosion of third degree of right thumb (nail), sequela
T23.712A	Corrosion of third degree of left thumb (nail), initial encounter
T23.712D	Corrosion of third degree of left thumb (nail), subsequent encounter
T23.712S	Corrosion of third degree of left thumb (nail), sequela
T23.721A	Corrosion of third degree of single right finger (nail) except thumb, initial encounter
T23.721D	Corrosion of third degree of single right finger (nail) except thumb, subsequent encounter
T23.721S	Corrosion of third degree of single right finger (nail) except thumb, sequela
T23.722A	Corrosion of third degree of single left finger (nail) except thumb, initial encounter
T23.722D	Corrosion of third degree of single left finger (nail) except thumb, subsequent encounter
T23.722S	Corrosion of third degree of single left finger (nail) except thumb, sequela
T23.731A	Corrosion of third degree of multiple right fingers (nail), not including thumb, initial encounter
T23.731D	Corrosion of third degree of multiple right fingers (nail), not including thumb, subsequent encounter
T23.731S	Corrosion of third degree of multiple right fingers (nail), not including thumb, sequela
T23.732A	Corrosion of third degree of multiple left fingers (nail), not including thumb, initial encounter
T23.732D	Corrosion of third degree of multiple left fingers (nail), not including thumb, subsequent encounter
T23.732S	Corrosion of third degree of multiple left fingers (nail), not including thumb, sequela
T23.741A	Corrosion of third degree of multiple right fingers (nail), including thumb, initial encounter
T23.741D	Corrosion of third degree of multiple right fingers (nail), including thumb, subsequent encounter
T23.741S	Corrosion of third degree of multiple right fingers (nail), including thumb, sequela
T23.742A	Corrosion of third degree of multiple left fingers (nail), including thumb, initial encounter
T23.742D	Corrosion of third degree of multiple left fingers (nail), including thumb, subsequent encounter
T23.742S	Corrosion of third degree of multiple left fingers (nail), including thumb, sequela
T23.751A	Corrosion of third degree of right palm, initial encounter
T23.751D	Corrosion of third degree of right palm, subsequent encounter
T23.751S	Corrosion of third degree of right palm, sequela

T23.752A	Corrosion of third degree of left palm, initial encounter
T23.752D	Corrosion of third degree of left palm, subsequent encounter
T23.752S	Corrosion of third degree of left palm, sequela
T23.761A	Corrosion of third degree of back of right hand, initial encounter
T23.761D	Corrosion of third degree of back of right hand, subsequent encounter
T23.761S	Corrosion of third degree of back of right hand, sequela
T23.762A	Corrosion of third degree of back of left hand, initial encounter
T23.762D	Corrosion of third degree of back of left hand, subsequent encounter
T23.762S	Corrosion of third degree of back of left hand, sequela
T23.771A	Corrosion of third degree of right wrist, initial encounter
T23.771D	Corrosion of third degree of right wrist, subsequent encounter
T23.771S	Corrosion of third degree of right wrist, sequela
T23.772A	Corrosion of third degree of left wrist, initial encounter
T23.772D	Corrosion of third degree of left wrist, subsequent encounter
T23.772S	Corrosion of third degree of left wrist, sequela
T23.791A	Corrosion of third degree of multiple sites of right wrist and hand, initial encounter
T23.791D	Corrosion of third degree of multiple sites of right wrist and hand, subsequent encounter
T23.791S	Corrosion of third degree of multiple sites of right wrist and hand, sequela
T23.792A	Corrosion of third degree of multiple sites of left wrist and hand, initial encounter
T23.792D	Corrosion of third degree of multiple sites of left wrist and hand, subsequent encounter
T23.792S	Corrosion of third degree of multiple sites of left wrist and hand, sequela
T24.211A	Burn of second degree of right thigh, initial encounter
T24.211D	Burn of second degree of right thigh, subsequent encounter
T24.211S	Burn of second degree of right thigh, sequela
T24.212A	Burn of second degree of left thigh, initial encounter
T24.212D	Burn of second degree of left thigh, subsequent encounter
T24.212S	Burn of second degree of left thigh, sequela
T24.221A	Burn of second degree of right knee, initial encounter
T24.221D	Burn of second degree of right knee, subsequent encounter
T24.221S	Burn of second degree of right knee, sequela
T24.222A	Burn of second degree of left knee, initial encounter
T24.222D	Burn of second degree of left knee, subsequent encounter
T24.222S	Burn of second degree of left knee, sequela
T24.231A	Burn of second degree of right lower leg, initial encounter
T24.231D	Burn of second degree of right lower leg, subsequent encounter
T24.231S	Burn of second degree of right lower leg, sequela
T24.232A	Burn of second degree of left lower leg, initial encounter
T24.232D	Burn of second degree of left lower leg, subsequent encounter
T24.232S	Burn of second degree of left lower leg, sequela
T24.291A	Burn of second degree of multiple sites of right lower limb, except ankle and foot, initial encounter
T24.291D	Burn of second degree of multiple sites of right lower limb, except ankle and foot, subsequent encounter
T24.291S	Burn of second degree of multiple sites of right lower limb, except ankle and foot, sequela
T24.292A	Burn of second degree of multiple sites of left lower limb, except ankle and foot, initial encounter
T24.292D	Burn of second degree of multiple sites of left lower limb, except ankle and foot, subsequent encounter
T24.292S	Burn of second degree of multiple sites of left lower limb, except ankle and foot, sequela
T24.311A	Burn of third degree of right thigh, initial encounter
T24.311D	Burn of third degree of right thigh, subsequent encounter
T24.311S	Burn of third degree of right thigh, sequela
T24.312A	Burn of third degree of left thigh, initial encounter
T24.312D	Burn of third degree of left thigh, subsequent encounter

T24.312S	Burn of third degree of left thigh, sequela
T24.321A	Burn of third degree of right knee, initial encounter
T24.321D	Burn of third degree of right knee, subsequent encounter
T24.321S	Burn of third degree of right knee, sequela
T24.322A	Burn of third degree of left knee, initial encounter
T24.322D	Burn of third degree of left knee, subsequent encounter
T24.322S	Burn of third degree of left knee, sequela
T24.331A	Burn of third degree of right lower leg, initial encounter
T24.331D	Burn of third degree of right lower leg, subsequent encounter
T24.331S	Burn of third degree of right lower leg, sequela
T24.332A	Burn of third degree of left lower leg, initial encounter
T24.332D	Burn of third degree of left lower leg, subsequent encounter
T24.332S	Burn of third degree of left lower leg, sequela
T24.391A	Burn of third degree of multiple sites of right lower limb, except ankle and foot, initial encounter
T24.391D	Burn of third degree of multiple sites of right lower limb, except ankle and foot, subsequent encounter
T24.391S	Burn of third degree of multiple sites of right lower limb, except ankle and foot, sequela
T24.392A	Burn of third degree of multiple sites of left lower limb, except ankle and foot, initial encounter
T24.392D	Burn of third degree of multiple sites of left lower limb, except ankle and foot, subsequent encounter
T24.392S	Burn of third degree of multiple sites of left lower limb, except ankle and foot, sequela
T24.611A	Corrosion of second degree of right thigh, initial encounter
T24.611D	Corrosion of second degree of right thigh, subsequent encounter
T24.611S	Corrosion of second degree of right thigh, sequela
T24.612A	Corrosion of second degree of left thigh, initial encounter
T24.612D	Corrosion of second degree of left thigh, subsequent encounter
T24.612S	Corrosion of second degree of left thigh, sequela
T24.621A	Corrosion of second degree of right knee, initial encounter
T24.621D	Corrosion of second degree of right knee, subsequent encounter
T24.621S	Corrosion of second degree of right knee, sequela
T24.622A	Corrosion of second degree of left knee, initial encounter
T24.622D	Corrosion of second degree of left knee, subsequent encounter
T24.622S	Corrosion of second degree of left knee, sequela
T24.631A	Corrosion of second degree of right lower leg, initial encounter
T24.631D	Corrosion of second degree of right lower leg, subsequent encounter
T24.631S	Corrosion of second degree of right lower leg, sequela
T24.632A	Corrosion of second degree of left lower leg, initial encounter
T24.632D	Corrosion of second degree of left lower leg, subsequent encounter
T24.632S	Corrosion of second degree of left lower leg, sequela
T24.691A	Corrosion of second degree of multiple sites of right lower limb, except ankle and foot, initial encounter
T24.691D	Corrosion of second degree of multiple sites of right lower limb, except ankle and foot, subsequent encounter
T24.691S	Corrosion of second degree of multiple sites of right lower limb, except ankle and foot, sequela
T24.692A	Corrosion of second degree of multiple sites of left lower limb, except ankle and foot, initial encounter
T24.692D	Corrosion of second degree of multiple sites of left lower limb, except ankle and foot, subsequent encounter
T24.692S	Corrosion of second degree of multiple sites of left lower limb, except ankle and foot, sequela
T24.711A	Corrosion of third degree of right thigh, initial encounter
T24.711D	Corrosion of third degree of right thigh, subsequent encounter
T24.711S	Corrosion of third degree of right thigh, sequela
T24.712A	Corrosion of third degree of left thigh, initial encounter

T24.712D	Corrosion of third degree of left thigh, subsequent encounter
T24.712S	Corrosion of third degree of left thigh, sequela
T24.721A	Corrosion of third degree of right knee, initial encounter
T24.721D	Corrosion of third degree of right knee, subsequent encounter
T24.721S	Corrosion of third degree of right knee, sequela
T24.722A	Corrosion of third degree of left knee, initial encounter
T24.722D	Corrosion of third degree of left knee, subsequent encounter
T24.722S	Corrosion of third degree of left knee, sequela
T24.731A	Corrosion of third degree of right lower leg, initial encounter
T24.731D	Corrosion of third degree of right lower leg, subsequent encounter
T24.731S	Corrosion of third degree of right lower leg, sequela
T24.732A	Corrosion of third degree of left lower leg, initial encounter
T24.732D	Corrosion of third degree of left lower leg, subsequent encounter
T24.732S	Corrosion of third degree of left lower leg, sequela
T24.791A	Corrosion of third degree of multiple sites of right lower limb, except ankle and foot, initial encounter
T24.791D	Corrosion of third degree of multiple sites of right lower limb, except ankle and foot, subsequent encounter
T24.791S	Corrosion of third degree of multiple sites of right lower limb, except ankle and foot, sequela
T24.792A	Corrosion of third degree of multiple sites of left lower limb, except ankle and foot, initial encounter
T24.792D	Corrosion of third degree of multiple sites of left lower limb, except ankle and foot, subsequent encounter
T24.792S	Corrosion of third degree of multiple sites of left lower limb, except ankle and foot, sequela
T25.211A	Burn of second degree of right ankle, initial encounter
T25.211D	Burn of second degree of right ankle, subsequent encounter
T25.211S	Burn of second degree of right ankle, sequela
T25.212A	Burn of second degree of left ankle, initial encounter
T25.212D	Burn of second degree of left ankle, subsequent encounter
T25.212S	Burn of second degree of left ankle, sequela
T25.221A	Burn of second degree of right foot, initial encounter
T25.221D	Burn of second degree of right foot, subsequent encounter
T25.221S	Burn of second degree of right foot, sequela
T25.222A	Burn of second degree of left foot, initial encounter
T25.222D	Burn of second degree of left foot, subsequent encounter
T25.222S	Burn of second degree of left foot, sequela
T25.231A	Burn of second degree of right toe(s) (nail), initial encounter
T25.231D	Burn of second degree of right toe(s) (nail), subsequent encounter
T25.231S	Burn of second degree of right toe(s) (nail), sequela
T25.232A	Burn of second degree of left toe(s) (nail), initial encounter
T25.232D	Burn of second degree of left toe(s) (nail), subsequent encounter
T25.232S	Burn of second degree of left toe(s) (nail), sequela
T25.291A	Burn of second degree of multiple sites of right ankle and foot, initial encounter
T25.291D	Burn of second degree of multiple sites of right ankle and foot, subsequent encounter
T25.291S	Burn of second degree of multiple sites of right ankle and foot, sequela
T25.292A	Burn of second degree of multiple sites of left ankle and foot, initial encounter
T25.292D	Burn of second degree of multiple sites of left ankle and foot, subsequent encounter
T25.292S	Burn of second degree of multiple sites of left ankle and foot, sequela
T25.311A	Burn of third degree of right ankle, initial encounter
T25.311D	Burn of third degree of right ankle, subsequent encounter
T25.311S	Burn of third degree of right ankle, sequela
T25.312A	Burn of third degree of left ankle, initial encounter
T25.312D	Burn of third degree of left ankle, subsequent encounter
T25.312S	Burn of third degree of left ankle, sequela

T25.321A	Burn of third degree of right foot, initial encounter
T25.321D	Burn of third degree of right foot, subsequent encounter
T25.321S	Burn of third degree of right foot, sequela
T25.322A	Burn of third degree of left foot, initial encounter
T25.322D	Burn of third degree of left foot, subsequent encounter
T25.322S	Burn of third degree of left foot, sequela
T25.331A	Burn of third degree of right toe(s) (nail), initial encounter
T25.331D	Burn of third degree of right toe(s) (nail), subsequent encounter
T25.331S	Burn of third degree of right toe(s) (nail), sequela
T25.332A	Burn of third degree of left toe(s) (nail), initial encounter
T25.332D	Burn of third degree of left toe(s) (nail), subsequent encounter
T25.332S	Burn of third degree of left toe(s) (nail), sequela
T25.391A	Burn of third degree of multiple sites of right ankle and foot, initial encounter
T25.391D	Burn of third degree of multiple sites of right ankle and foot, subsequent encounter
T25.391S	Burn of third degree of multiple sites of right ankle and foot, sequela
T25.392A	Burn of third degree of multiple sites of left ankle and foot, initial encounter
T25.392D	Burn of third degree of multiple sites of left ankle and foot, subsequent encounter
T25.392S	Burn of third degree of multiple sites of left ankle and foot, sequela
T25.611A	Corrosion of second degree of right ankle, initial encounter
T25.611D	Corrosion of second degree of right ankle, subsequent encounter
T25.611S	Corrosion of second degree of right ankle, sequela
T25.612A	Corrosion of second degree of left ankle, initial encounter
T25.612D	Corrosion of second degree of left ankle, subsequent encounter
T25.612S	Corrosion of second degree of left ankle, sequela
T25.621A	Corrosion of second degree of right foot, initial encounter
T25.621D	Corrosion of second degree of right foot, subsequent encounter
T25.621S	Corrosion of second degree of right foot, sequela
T25.622A	Corrosion of second degree of left foot, initial encounter
T25.622D	Corrosion of second degree of left foot, subsequent encounter
T25.622S	Corrosion of second degree of left foot, sequela
T25.631A	Corrosion of second degree of right toe(s) (nail), initial encounter
T25.631D	Corrosion of second degree of right toe(s) (nail), subsequent encounter
T25.631S	Corrosion of second degree of right toe(s) (nail), sequela
T25.632A	Corrosion of second degree of left toe(s) (nail), initial encounter
T25.632D	Corrosion of second degree of left toe(s) (nail), subsequent encounter
T25.632S	Corrosion of second degree of left toe(s) (nail), sequela
T25.691A	Corrosion of second degree of right ankle and foot, initial encounter
T25.691D	Corrosion of second degree of right ankle and foot, subsequent encounter
T25.691S	Corrosion of second degree of right ankle and foot, sequela
T25.692A	Corrosion of second degree of left ankle and foot, initial encounter
T25.692D	Corrosion of second degree of left ankle and foot, subsequent encounter
T25.692S	Corrosion of second degree of left ankle and foot, sequela
T25.711A	Corrosion of third degree of right ankle, initial encounter
T25.711D	Corrosion of third degree of right ankle, subsequent encounter
T25.711S	Corrosion of third degree of right ankle, sequela
T25.712A	Corrosion of third degree of left ankle, initial encounter
T25.712D	Corrosion of third degree of left ankle, subsequent encounter
T25.712S	Corrosion of third degree of left ankle, sequela
T25.721A	Corrosion of third degree of right foot, initial encounter
T25.721D	Corrosion of third degree of right foot, subsequent encounter
T25.721S	Corrosion of third degree of right foot, sequela
T25.722A	Corrosion of third degree of left foot, initial encounter
T25.722D	Corrosion of third degree of left foot, subsequent encounter
T25.722S	Corrosion of third degree of left foot, sequela

T25.731A	Corrosion of third degree of right toe(s) (nail), initial encounter
T25.731D	Corrosion of third degree of right toe(s) (nail), subsequent encounter
T25.731S	Corrosion of third degree of right toe(s) (nail), sequela
T25.732A	Corrosion of third degree of left toe(s) (nail), initial encounter
T25.732D	Corrosion of third degree of left toe(s) (nail), subsequent encounter
T25.732S	Corrosion of third degree of left toe(s) (nail), sequela
T25.791A	Corrosion of third degree of multiple sites of right ankle and foot, initial encounter
T25.791D	Corrosion of third degree of multiple sites of right ankle and foot, subsequent encounter
T25.791S	Corrosion of third degree of multiple sites of right ankle and foot, sequela
T25.792A	Corrosion of third degree of multiple sites of left ankle and foot, initial encounter
T25.792D	Corrosion of third degree of multiple sites of left ankle and foot, subsequent encounter
T25.792S	Corrosion of third degree of multiple sites of left ankle and foot, sequela
T26.71xA	Corrosion with resulting rupture and destruction of right eyeball, initial encounter
T26.71xD	Corrosion with resulting rupture and destruction of right eyeball, subsequent encounter
T26.71xS	Corrosion with resulting rupture and destruction of right eyeball, sequela
T26.72xA	Corrosion with resulting rupture and destruction of left eyeball, initial encounter
T26.72xD	Corrosion with resulting rupture and destruction of left eyeball, subsequent encounter
T26.72xS	Corrosion with resulting rupture and destruction of left eyeball, sequela
T31.0	Burns involving less than 10% of body surface
T31.10	Burns involving 10-19% of body surface with 0% to 9% third degree burns
T31.11	Burns involving 10-19% of body surface with 10-19% third degree burns
T31.20	Burns involving 20-29% of body surface with 0% to 9% third degree burns
T31.21	Burns involving 20-29% of body surface with 10-19% third degree burns
T31.22	Burns involving 20-29% of body surface with 20-29% third degree burns
T31.30	Burns involving 30-39% of body surface with 0% to 9% third degree burns
T31.31	Burns involving 30-39% of body surface with 10-19% third degree burns
T31.32	Burns involving 30-39% of body surface with 20-29% third degree burns
T31.33	Burns involving 30-39% of body surface with 30-39% third degree burns
T31.40	Burns involving 40-49% of body surface with 0% to 9% third degree burns
T31.41	Burns involving 40-49% of body surface with 10-19% third degree burns
T31.42	Burns involving 40-49% of body surface with 20-29% third degree burns
T31.43	Burns involving 40-49% of body surface with 30-39% third degree burns
T31.44	Burns involving 40-49% of body surface with 40-49% third degree burns
T31.50	Burns involving 50-59% of body surface with 0% to 9% third degree burns
T31.51	Burns involving 50-59% of body surface with 10-19% third degree burns
T31.52	Burns involving 50-59% of body surface with 20-29% third degree burns
T31.53	Burns involving 50-59% of body surface with 30-39% third degree burns
T31.54	Burns involving 50-59% of body surface with 40-49% third degree burns
T31.55	Burns involving 50-59% of body surface with 50-59% third degree burns
T31.60	Burns involving 60-69% of body surface with 0% to 9% third degree burns
T31.61	Burns involving 60-69% of body surface with 10-19% third degree burns
T31.62	Burns involving 60-69% of body surface with 20-29% third degree burns
T31.63	Burns involving 60-69% of body surface with 30-39% third degree burns
T31.64	Burns involving 60-69% of body surface with 40-49% third degree burns
T31.65	Burns involving 60-69% of body surface with 50-59% third degree burns
T31.66	Burns involving 60-69% of body surface with 60-69% third degree burns
T31.70	Burns involving 70-79% of body surface with 0% to 9% third degree burns
T31.71	Burns involving 70-79% of body surface with 10-19% third degree burns
T31.72	Burns involving 70-79% of body surface with 20-29% third degree burns
T31.73	Burns involving 70-79% of body surface with 30-39% third degree burns
T31.74	Burns involving 70-79% of body surface with 40-49% third degree burns
T31.75	Burns involving 70-79% of body surface with 50-59% third degree burns
T31.76	Burns involving 70-79% of body surface with 60-69% third degree burns
T31.77	Burns involving 70-79% of body surface with 70-79% third degree burns

T31.80	Burns involving 80-89% of body surface with 0% to 9% third degree burns
T31.81	Burns involving 80-89% of body surface with 10-19% third degree burns
T31.82	Burns involving 80-89% of body surface with 20-29% third degree burns
T31.83	Burns involving 80-89% of body surface with 30-39% third degree burns
T31.84	Burns involving 80-89% of body surface with 40-49% third degree burns
T31.85	Burns involving 80-89% of body surface with 50-59% third degree burns
T31.86	Burns involving 80-89% of body surface with 60-69% third degree burns
T31.87	Burns involving 80-89% of body surface with 70-79% third degree burns
T31.88	Burns involving 80-89% of body surface with 80-89% third degree burns
T31.90	Burns involving 90% or more of body surface with 0% to 9% third degree burns
T31.91	Burns involving 90% or more of body surface with 10-19% third degree burns
T31.92	Burns involving 90% or more of body surface with 20-29% third degree burns
T31.93	Burns involving 90% or more of body surface with 30-39% third degree burns
T31.94	Burns involving 90% or more of body surface with 40-49% third degree burns
T31.95	Burns involving 90% or more of body surface with 50-59% third degree burns
T31.96	Burns involving 90% or more of body surface with 60-69% third degree burns
T31.97	Burns involving 90% or more of body surface with 70-79% third degree burns
T31.98	Burns involving 90% or more of body surface with 80-89% third degree burns
T31.99	Burns involving 90% or more of body surface with 90% or more third degree burns
T32.0	Corrosions involving less than 10% of body surface
T32.10	Corrosions involving 10-19% of body surface with 0% to 9% third degree corrosion
T32.11	Corrosions involving 10-19% of body surface with 10-19% third degree corrosion
T32.20	Corrosions involving 20-29% of body surface with 0% to 9% third degree corrosion
T32.21	Corrosions involving 20-29% of body surface with 10-19% third degree corrosion
T32.22	Corrosions involving 20-29% of body surface with 20-29% third degree corrosion
T32.30	Corrosions involving 30-39% of body surface with 0% to 9% third degree corrosion
T32.31	Corrosions involving 30-39% of body surface with 10-19% third degree corrosion
T32.32	Corrosions involving 30-39% of body surface with 20-29% third degree corrosion
T32.33	Corrosions involving 30-39% of body surface with 30-39% third degree corrosion
T32.40	Corrosions involving 40-49% of body surface with 0% to 9% third degree corrosion
T32.41	Corrosions involving 40-49% of body surface with 10-19% third degree corrosion
T32.42	Corrosions involving 40-49% of body surface with 20-29% third degree corrosion
T32.43	Corrosions involving 40-49% of body surface with 30-39% third degree corrosion
T32.44	Corrosions involving 40-49% of body surface with 40-49% third degree corrosion
T32.50	Corrosions involving 50-59% of body surface with 0% to 9% third degree corrosion
T32.51	Corrosions involving 50-59% of body surface with 10-19% third degree corrosion
T32.52	Corrosions involving 50-59% of body surface with 20-29% third degree corrosion
T32.53	Corrosions involving 50-59% of body surface with 30-39% third degree corrosion
T32.54	Corrosions involving 50-59% of body surface with 40-49% third degree corrosion
T32.55	Corrosions involving 50-59% of body surface with 50-59% third degree corrosion
T32.60	Corrosions involving 60-69% of body surface with 0% to 9% third degree corrosion
T32.61	Corrosions involving 60-69% of body surface with 10-19% third degree corrosion
T32.62	Corrosions involving 60-69% of body surface with 20-29% third degree corrosion
T32.63	Corrosions involving 60-69% of body surface with 30-39% third degree corrosion
T32.64	Corrosions involving 60-69% of body surface with 40-49% third degree corrosion
T32.65	Corrosions involving 60-69% of body surface with 50-59% third degree corrosion
T32.66	Corrosions involving 60-69% of body surface with 60-69% third degree corrosion
T32.70	Corrosions involving 70-79% of body surface with 0% to 9% third degree corrosion
T32.71	Corrosions involving 70-79% of body surface with 10-19% third degree corrosion
T32.72	Corrosions involving 70-79% of body surface with 20-29% third degree corrosion
T32.73	Corrosions involving 70-79% of body surface with 30-39% third degree corrosion
T32.74	Corrosions involving 70-79% of body surface with 40-49% third degree corrosion
T32.75	Corrosions involving 70-79% of body surface with 50-59% third degree corrosion
T32.76	Corrosions involving 70-79% of body surface with 60-69% third degree corrosion

- T32.77 Corrosions involving 70-79% of body surface with 70-79% third degree corrosion
- T32.80 Corrosions involving 80-89% of body surface with 0% to 9% third degree corrosion
- T32.81 Corrosions involving 80-89% of body surface with 10-19% third degree corrosion
- T32.82 Corrosions involving 80-89% of body surface with 20-29% third degree corrosion
- T32.83 Corrosions involving 80-89% of body surface with 30-39% third degree corrosion
- T32.84 Corrosions involving 80-89% of body surface with 40-49% third degree corrosion
- T32.85 Corrosions involving 80-89% of body surface with 50-59% third degree corrosion
- T32.86 Corrosions involving 80-89% of body surface with 60-69% third degree corrosion
- T32.87 Corrosions involving 80-89% of body surface with 70-79% third degree corrosion
- T32.88 Corrosions involving 80-89% of body surface with 80-89% third degree corrosion
- T32.90 Corrosions involving 90% or more of body surface with 0% to 9% third degree corrosion
- T32.91 Corrosions involving 90% or more of body surface with 10-19% third degree corrosion
- T32.92 Corrosions involving 90% or more of body surface with 20-29% third degree corrosion
- T32.93 Corrosions involving 90% or more of body surface with 30-39% third degree corrosion
- T32.94 Corrosions involving 90% or more of body surface with 40-49% third degree corrosion
- T32.95 Corrosions involving 90% or more of body surface with 50-59% third degree corrosion
- T32.96 Corrosions involving 90% or more of body surface with 60-69% third degree corrosion
- T32.97 Corrosions involving 90% or more of body surface with 70-79% third degree corrosion
- T32.98 Corrosions involving 90% or more of body surface with 80-89% third degree corrosion
- T32.99 Corrosions involving 90% or more of body surface with 90% or more third degree corrosion
- Z15.01 Genetic susceptibility to malignant neoplasm of breast
- Z85.3 Personal history of malignant neoplasm of breast
- Z90.11 Acquired absence of right breast and nipple
- Z90.12 Acquired absence of left breast and nipple
- Z90.13 Acquired absence of bilateral breasts and nipples

<b>REVISIONS</b>	
04-30-2015	Policy published 03-31-2015
	Description section updated
	<p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item A added "allogeneic" and "products*" to read, "...using the following allogeneic acellular dermal matrix products* may be considered medically necessary..."</li> <li>▪ In Item A added the following four medically necessary skin substitutes: AlloMax, DermaMatrix, FlexHD, and GrafJacket.</li> <li>▪ In Item B added the following medically necessary skin substitute: Epifix.</li> <li>▪ In Item G moved the following experimental / investigational skin and soft tissue substitutes to be medically necessary: AlloMax, DermaMatrix Acellular Dermis, EpiFix (Q4131) (Q4145), FlexHD Acellular Hydrated Dermis (Q4128), GraftJacket (Q4107).</li> <li>▪ In Item G added the following experimental / investigational skin and soft tissue substitutes: ACell UBM Hydated Wound Dressing, ACell UBM Lyophilized Wound Dressing, Affinity (Q4159), Allowrap (Q4150), Alphaplex with MariGen Omega3, AmnioBand (Q4151), Aongen Collagen Matrix, Atlas Wound Matrix, Avagen Wound Dressing, Biovance (Q4154), Clarix Flo, Collagen Sponge (Innocoll), Collagen Wound Dressing (Oasis Research), Collaguard, CollaSorb, CollaWound, Collexa, Collieva, Coreleader Colla-Pad, Dermadapt Wound Dressing, Dermapure (Q4152), Dermavest (Q4153), DressSkin, FortaDerm Wound Dressing (C9349), GUARDIAN (Q4151), HA Absorbent Wound Dressing, Helicoll, Hyalomatrix (Laserskin), Jaloskin, MariGen (Q4158), Matrix Collagen Wound Dressing, Neox Flo (Q4155), Primatrix Dermal Repair Scaffold, Puros Dermis, Repliform, Revitalon (Q4157), SIS Wound Dressing II, Solana, SS Matrix, Stimulen Collagen, Suprathel, TheraForm Standard/Sheet.</li> <li>▪ In Item G removed reference to the following experimental / investigational skin and soft tissue substitutes: Allograft, Allopatch, Alloskin AC (Q4141), AmnioExCel (Q4137), Aminomatrix (Q4139), Architect Extracellular Matrix (Q4147), Artelon, Arthres GraftRope,</li> </ul>

<b>REVISIONS</b>	
	<p>Avotermin, BioDfence Dryflex (Q4138), Biostat Biologx, Biotape, C-QUR, CollaFix, Collamend, CorMatrix Patch, Cuffpatch, Cymetra Injectable Allograft (Q4112), Dermacell (Q4122), DermaClose RC Continuous External Tissue Expander, DuraGen Plus, EpiDex, Evicel, GraftJacket Regenerative Tissue Matrix , Inforce, Integra Neural Wrap, Integra Matrix Wound Dressing (Q4108), Medeor, Meso BioMatrix, Neuragen, NeuraWrap, Neuroflex, NeuroMatrix Collagen Nerve Cuff (C9355), NeuroMend Collagen Nerve Wrap (C9361), NuCel, OrthADAPT Bioimplant, Ovation, Pelvicol, Pelvisoft, Peri-Strips Dry, Permacol Biologic Implant, PriMatrix Acellular Dermal Tissue Matrix, Promogran, PTFE felt, Puracol, Seamguard, SportMatrix, SportMesh, Strattice Tissue Matrix, TenSIX (Q4146), TheraSkin, TissueMend (Q4109), X-Repair, XenMatrix (Removal of these products does not mean they are considered medically necessary, rather they were not considered to be appropriate for this policy at this time)</p>
	Rational section updated
	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added HCPCS Codes: C9349, Q4150, Q4151, Q4152, Q4153, Q4154, Q4155, Q4157, Q4158, Q4159, Q4160.</li> <li>▪ Removed HCPCS Codes: C9355, C9361, C9367, Q4108, Q4109, Q4122, q4137, Q4138, Q4139, Q4141, Q4142, Q4146, Q4147.</li> <li>▪ Revised HCPCS Codes: Q4113, Q4119, Q4123, Q4124, Q4125, q4127, Q4128, Q4129, Q4130, Q4140, Q4143, Q4148</li> </ul>
	<p>In Revision section:</p> <ul style="list-style-type: none"> <li>▪ Removed revision details for: 08-03-2010, 02-01-2012.</li> </ul>
	References updated
05-01-2016	Published 03-31-2016. Effective 05-01-2016
	Description section updated
	<p>In Policy section:</p> <ul style="list-style-type: none"> <li>▪ In Item B added "Integra Dermal Regeneration Template (Q4105)"</li> <li>▪ In Item B added "Biovance (Q4154)" and "Grafix (Q4132) (Q4133)" and "(Amniotic Membrane Grafts*)" to read "Biovance (Q4154), Epifix (Q4131) (Q4145), Grafix (Q4132) (Q4133) (Amniotic Membrane Grafts*)"</li> <li>▪ In Item G removed the following products from the E/I list: "AmnioBand (Q4151), Biovance (Q4154), Grafix Core (Q4132), Grafix Prime (Q4133), NEOX 1K (Q4148), Solana"</li> <li>▪ In Item G removed "Unite" to read "TheraSkin (Q4121)"</li> <li>▪ In Item G added the following products to the E/I list (these are products in the HCPCS code list that were not referenced in the policy statement): "AlloSkin AC, per sq cm (Q4141), AmnioExcel, per sq cm (Q4137), Amniogen-45, Amniogen-200, per sq cm (Q4163), AmnioMatrix, injectable, 1 cc (Q4139), AmnioPro, per sq cm Q4163), Architect, Architect PX, or Architect FX, extracellular matrix, per sq cm (Q4147), Bio-ConneKt wound matrix, per sq cm (Q4161), BioDExCel, per sq cm (Q4137), BioDFence DryFlex, per sq cm (Q4138), BioDMatrix, injectable, 1 cc (Q4139), BioSkin, per sq cm (Q4163), BioRenew, per sq cm (Q4163), DermACELL, per sq cm (Q4122), Integra matrix, per sq cm (Q4108), Keramatrix, per sq cm (Q4165), Neox 100, per sq cm (Q4156), Plurinvest, per sq cm (Q4153), Tensix, per sq cm (Q4146), WoundEx, per sq cm (Q4163), XCM biologic tissue matrix, per sq cm (Q4142)"</li> <li>▪ In Item G added "(Q4164) to read "Helicoll (Q4164)"</li> </ul>
	Rationale section updated
	<p>In Coding section:</p> <ul style="list-style-type: none"> <li>▪ Added HCPCS Codes: Q4161, Q4163, Q4164, Q4165 (Effective January 1, 2016)</li> <li>▪ Added HCPCS Codes: Q4108, Q4122, Q4137, Q4138, Q4139, Q4141, Q4142, Q4146, Q4147, Q4156</li> <li>▪ Revised HCPCS Code Nomenclature: Q4153 (Effective January 1, 2016)</li> <li>▪ Revised HCPCS Code Nomenclature: C9349</li> </ul>

<b>REVISIONS</b>	
	References updated
03-20-2017	In Title section added "See Also: Amniotic Membrane and Amniotic Fluid medical policy"
	Description section updated
	In Policy section: <ul style="list-style-type: none"> <li>▪ In Item A added "AlloMend"</li> <li>▪ In Item B added "AlloPatch*" and removed "Biovance (Q4154), Epifix (Q4131) (Q4145), Grafix (Q4132) (Q4133) (Amniotic Membrane Grafts*)"</li> <li>▪ In Item 3 removed "TransCyte**"</li> <li>▪ Updated asterisk Key</li> <li>▪ In Item G moved the following E/I skin and soft tissue substitute to be medically necessary: AlloPatch HD (Q4128).</li> <li>▪ In Item G revised the following E/I skin and soft tissue substitutes: combined "ACell UBM Lyophilized Wound Dressing" and "ACell UBM Hydrated Wound Dressing" to read "ACell UBM Hydrated / Lyophilized Wound Dressing"; "Architect, Architect PX, or Architect FX, extracellular matrix" to "Architect ECM, PX, FX"; "BioDFenceDryFlex" to "BioDryFlex"; revised "CellerateRX" to "CellerateRX (CRXa)"; "Hyalomatrix (Laserskin)" to "Hyalomatrix"; "MariGen" to "MariGen / Kerecis Omega3"; "Oasis Ultra Tri-Layer Matrix" to "Oasis Ultra"; "TenSix" to "TenSix Acellular Dermal Matrix"</li> <li>▪ In Item G added the following E/I skin and soft tissue substitutes: AxoGuard Nerve Protector (AxoGen), CollaCare, CollaCare Dental, CollaMend, Cytal, DermaSpan, ExpressGraft, FlexiGraft, Integra Omnigraft, Miroderm biologic wound matrix, NeoForm, NuCel, Oasis Wound Matrix, Pelvicol / PelviSoft, PuraPly Wound Matrix, PuraPly AM (Antimicrobial Wound Matrix), RegenePro, TissueMend, TruSkin, XenMatrix AB</li> <li>▪ In Item G removed the following E/I skin and soft tissue substitutes: Affinity, AlloPatch HD, Allowrap, Alphaplex with MariGen Omega3, AmnioExcel, AmnioFix, Amniogen-45, Amniogen-200, AmnioMatrix, injectable, AmnioPro, Avaulta Plus, BioDExCel, BioDFence/BioDFactor, BioDMatrix, injectable, BioSkin, BioRenew, Clarix Flo, Collagen Sponge (Innocoll), CollaSorb, CRXa, Dermavest, FortaDerm Wound Dressing, GUARDIAN, HA Absorbent Wound Dressing, Jaloskin, MatriStem Burn Matrix, MatriStem Wound Matrix, Matrix Collagen Wound Dressing, MediHoney, Neox 100, Neox Flo, NuShield, Plurivest, Revitalon, SIS Wound Dressing II, SS Matrix, Stimulen Collagen, Unite Biomatrix, WoundEx</li> <li>▪ Policy Guidelines added</li> </ul>
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> <li>▪ Revised HCPCS code nomenclature: Q4105</li> <li>▪ Added HCPCS codes: Q4166, Q4167, Q4172, Q4175 (Effective 01-01-2017)</li> <li>▪ Removed HCPCS codes: C9349, Q4119, Q4120, Q4129 (Termed 12-31-2016)</li> <li>▪ Removed HCPCS codes: Q4131, Q4132, Q4133, Q4137, Q4138, Q4139, Q4140, Q4145, Q4148, Q4150, Q4151, Q4153, Q4154, Q4155, Q4156, Q4157, Q4159, Q4160, Q4163</li> </ul>
	In Revision section: <ul style="list-style-type: none"> <li>▪ Removed revision details for the following dates: 01-15-2016, 12-12-2013, 01-01-2014.</li> </ul>
	References updated
04-19-2017	In Policy section: <ul style="list-style-type: none"> <li>▪ Removed "CellerateRX (CRXa)" from the policy due to the product not being a skin or soft tissue substitute and not relevant to the policy.</li> </ul>
07-18-2018	Description section updated
	In Policy section: <ul style="list-style-type: none"> <li>▪ In Item A added "Cortiva", "DermACELL", and "FlexHDPliable"</li> <li>▪ In Items B and E updated "Integra Derma Regeneration Template" to "Integra Omnigraft Dermal Regeneration Matrix (also known as Omnigraft)"</li> <li>▪ In Item B added "Integra Flowable Wound Matrix"</li> </ul>

<b>REVISIONS</b>	
	<ul style="list-style-type: none"> <li>▪ In Item G removed "BioDDryFlex (Q4138), DermACELL, per sq cm (Q4122), Integra Flowable Wound Matrix (Q4114), Integra Omnigraft (Q4105), Oasis Wound Matrix (Q4102)"</li> <li>▪ In Item G added "Kerecis (Q4158), NeoPatch, per sq cm (Q4176), FlowerAmnioFlo, 0.1 cc (Q4177), FlowerAmnioPatch, per sq cm (Q4178), FlowerDerm, per sq cm (Q4179), Revita, per sq cm (Q4180), Amnio Wound, per sq cm (Q4181), TransCyte, per sq cm (Q4182)"</li> <li>▪ In Item G revised "Biobrane" to "Biobrane / Biobrane-L" and "Cymetra (Q4112)" to "Cymetra (Micronized AlloDerm) (Q4112)"</li> </ul>
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> <li>▪ Added CPT Codes: 15200, 15201, 15220, 15221, 15240, 15241, 15260, 15261</li> <li>▪ Added HCPCS Codes: Q4176, Q4177, Q4178, Q4179, Q4180, Q4181, Q4182 (Effective January 1, 2018)</li> </ul>
	References updated
01-01-2019	In Policy section: <ul style="list-style-type: none"> <li>▪ In Item G removed the following experimental / investigational products: "PuraPly Wound Matrix (previously FortaDerm) (Q4172) PuraPly AM (Antimicrobial Wound Matrix) (Q4172)" and added the following experimental / investigational products:               <ul style="list-style-type: none"> <li>20. Coll-e-derm, per square centimeter (Q4193)</li> <li>29. Derma-gide, per square centimeter (Q4203)</li> <li>53. Keroxx (2.5g/cc), 1cc (Q4202)</li> <li>70. Puraply, per square centimeter (Q4195)</li> <li>71. Puraply am, per square centimeter (Q4196)</li> <li>72. Puraply xt, per square centimeter (Q4197)</li> <li>78. Skin te, per square centimeter (Q4200)"</li> </ul> </li> </ul>
	In Coding section: <ul style="list-style-type: none"> <li>▪ Added HCPCS Codes: Q4193, Q4195, Q4196, Q4197, Q4200, Q4202, Q4203</li> <li>▪ Removed HCPCS Code: Q4172</li> </ul>

## **REFERENCES**

1. Davila AA, Seth AK, Wang E, et al. Human acellular dermis versus submuscular tissue expander breast reconstruction: a multivariate analysis of short-term complications. Arch Plast Surg. Jan 2013;40(1):19-27. PMID 23362476
2. Lee KT, Mun GH. Updated evidence of acellular dermal matrix use for implant-based breast reconstruction: a meta-analysis. Ann Surg Oncol. Feb 2016;23(2):600-610. PMID 26438439
3. McCarthy CM, Lee CN, Halvorson EG, et al. The use of acellular dermal matrices in two-stage expander/implant reconstruction: a multicenter, blinded, randomized controlled trial. Plast Reconstr Surg. Nov 2012;130(5 Suppl 2):57S-66S. PMID 23096987
4. Hinchcliff KM, Orbay H, Busse BK, et al. Comparison of two cadaveric acellular dermal matrices for immediate breast reconstruction: A prospective randomized trial. J Plast Reconstr Aesthet Surg. May 2017;70(5):568-576. PMID 28341592
5. Mendenhall SD, Anderson LA, Ying J, et al. The BREASTrial Stage II: ADM breast reconstruction outcomes from definitive reconstruction to 3 months postoperative. Plast Reconstr Surg Glob Open. Jan 2017;5(1):e1209. PMID 28203509
6. Liu DZ, Mathes DW, Neligan PC, et al. Comparison of outcomes using AlloDerm versus FlexHD for implant-based breast reconstruction. Ann Plast Surg. May 2014;72(5):503-507. PMID 23636114
7. Chang EI, Liu J. Prospective unbiased experience with three acellular dermal matrices in breast reconstruction. J Surg Oncol. Sep 2017;116(3):365-370. PMID 28444764

8. Pittman TA, Fan KL, Knapp A, et al. Comparison of Different Acellular Dermal Matrices in Breast Reconstruction: The 50/50 Study. *Plast Reconstr Surg.* Mar 2017;139(3):521-528. PMID 28234811
9. Dikmans RE, Negenborn VL, Bouman MB, et al. Two-stage implant-based breast reconstruction compared with immediate one-stage implant-based breast reconstruction augmented with an acellular dermal matrix: an open-label, phase 4, multicentre, randomised, controlled trial. *Lancet Oncol.* Feb 2017;18(2):251-258. PMID 28012977
10. Barber FA, Burns JP, Deutsch A, et al. A prospective, randomized evaluation of acellular human dermal matrix augmentation for arthroscopic rotator cuff repair. *Arthroscopy.* Jan 2012;28(1):8-15. PMID 21978432
11. Bellows CF, Smith A, Malsbury J, et al. Repair of incisional hernias with biological prosthesis: a systematic review of current evidence. *Am J Surg.* Jan 2013;205(1):85-101. PMID 22867726
12. Espinosa-de-los-Monteros A, de la Torre JI, Marrero I, et al. Utilization of human cadaveric acellular dermis for abdominal hernia reconstruction. *Ann Plast Surg.* Mar 2007;58(3):264-267. PMID 17471129
13. Gupta A, Zahriya K, Mullens PL, et al. Ventral herniorrhaphy: experience with two different biosynthetic mesh materials, Surgisis and Alloderm. *Hernia.* Oct 2006;10(5):419-425. PMID 16924395
14. Bochicchio GV, De Castro GP, Bochicchio KM, et al. Comparison study of acellular dermal matrices in complicated hernia surgery. *J Am Coll Surg.* Oct 2013;217(4):606-613. PMID 23973102
15. Roth JS, Zachem A, Plymale MA, et al. Complex ventral hernia repair with acellular dermal matrices: clinical and quality of life outcomes. *Am Surg.* Feb 1 2017;83(2):141-147. PMID 28228200
16. Bellows CF, Shaddock P, Helton WS, et al. Early report of a randomized comparative clinical trial of Strattice reconstructive tissue matrix to lightweight synthetic mesh in the repair of inguinal hernias. *Hernia.* Apr 2014;18(2):221-230. PMID 23543334
17. Fleshman JW, Beck DE, Hyman N, et al. A prospective, multicenter, randomized, controlled study of non-cross-linked porcine acellular dermal matrix fascial sublay for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies. *Dis Colon Rectum.* May 2014;57(5):623-631. PMID 24819103
18. Santema TB, Poyck PP, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev.* Feb 11 2016;2:CD011255. PMID 26866804
19. Martinson M, Martinson N. A comparative analysis of skin substitutes used in the management of diabetic foot ulcers. *J Wound Care.* Oct 2016;25(Sup10):S8-S17. PMID 27681811
20. Guo X, Mu D, Gao F. Efficacy and safety of acellular dermal matrix in diabetic foot ulcer treatment: A systematic review and meta-analysis. *Int J Surg.* Apr 2017;40:1-7. PMID 28232031
21. Veves A, Falanga V, Armstrong DG, et al. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care.* Feb 2001;24(2):290-295. PMID 11213881
22. Blue Cross and Blue Shield Technology Evaluation Center (TEC). Graftskin for the treatment of skin ulcers. *TEC Assessments.* 2001;Volume 16:Tab 12.
23. Steinberg JS, Edmonds M, Hurley DP, Jr., et al. Confirmatory data from EU study supports Apligraf for the treatment of neuropathic diabetic foot ulcers. *J Am Podiatr Med Assoc.* Jan-Feb 2010;100(1):73-77. PMID 20093548
24. Kirsner RS, Warriner R, Michela M, et al. Advanced biological therapies for diabetic foot ulcers. *Arch Dermatol.* Aug 2010;146(8):857-862. PMID 20713816
25. Marston WA, Hanft J, Norwood P, et al. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care.* Jun 2003;26(6):1701-1705. PMID 12766097
26. Frykberg RG, Marston WA, Cardinal M. The incidence of lower-extremity amputation and bone resection in diabetic foot ulcer patients treated with a human fibroblast-derived dermal substitute. *Adv Skin Wound Care.* Jan 2015;28(1):17-20. PMID 25407083
27. Zelen CM, Orgill DP, Serena T, et al. A prospective, randomised, controlled, multicentre clinical trial examining healing rates, safety and cost to closure of an acellular reticular allogenic human dermis versus standard of care in the treatment of chronic diabetic foot ulcers. *Int Wound J.* Apr 2017;14(2):307-315. PMID 27073000

28. Driver VR, Lavery LA, Reyzelman AM, et al. A clinical trial of Integra Template for diabetic foot ulcer treatment. *Wound Repair Regen.* Nov 12 2015;23(6):891-900. PMID 26297933
29. Campitiello F, Mancone M, Della Corte A, et al. To evaluate the efficacy of an acellular Flowable matrix in comparison with a wet dressing for the treatment of patients with diabetic foot ulcers: a randomized clinical trial. *Updates Surg.* Dec 2017;69(4):523-529. PMID 28497218
30. Brigido SA, Boc SF, Lopez RC. Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. *Orthopedics.* Jan 2004;27(1 Suppl):s145-149. PMID 14763548
31. Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *Int Wound J.* Jun 2009;6(3):196-208. PMID 19368581
32. Reyzelman AM, Bazarov I. Human acellular dermal wound matrix for treatment of DFU: literature review and analysis. *J Wound Care.* Mar 2015;24(3):128; 129-134. PMID 25764957
33. Brigido SA. The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. *Int Wound J.* Sep 2006;3(3):181-187. PMID 16984575
34. Walters J, Cazzell S, Pham H, et al. Healing rates in a multicenter assessment of a sterile, room temperature, acellular dermal matrix versus conventional care wound management and an active comparator in the treatment of full-thickness diabetic foot ulcers. *Eplasty.* Mar 2016;16:e10. PMID 26933467
35. Cazzell S, Vayser D, Pham H, et al. A randomized clinical trial of a human acellular dermal matrix demonstrated superior healing rates for chronic diabetic foot ulcers over conventional care and an active acellular dermal matrix comparator. *Wound Repair Regen.* May 2017;25(3):483-497. PMID 28544150
36. Sanders L, Landsman AS, Landsman A, et al. A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. *Ostomy Wound Manage.* Sep 2014;60(9):26-38. PMID 25211605
37. DiDomenico L, Landsman AR, Emch KJ, et al. A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. *Wounds.* Jul 2011;23(7):184-189. PMID 25879172
38. Frykberg RG, Cazzell SM, Arroyo-Rivera J, et al. Evaluation of tissue engineering products for the management of neuropathic diabetic foot ulcers: an interim analysis. *J Wound Care.* Jul 2016;25 Suppl 7:S18-25. PMID 27410467
39. Kavros SJ, Dutra T, Gonzalez-Cruz R, et al. The use of PriMatrix, a fetal bovine acellular dermal matrix, in healing chronic diabetic foot ulcers: a prospective multicenter study. *Adv Skin Wound Care.* Aug 2014;27(8):356-362. PMID 25033310
40. Karr JC. Retrospective comparison of diabetic foot ulcer and venous stasis ulcer healing outcome between a dermal repair scaffold (PriMatrix) and a bilayered living cell therapy (Apligraf). *Adv Skin Wound Care.* Mar 2011;24(3):119-125. PMID 21326023
41. Niezgoda JA, Van Gils CC, Frykberg RG, et al. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care.* Jun 2005;18(5 Pt 1):258-266. PMID 15942317
42. Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. *Arch Dermatol.* Mar 1998;134(3):293-300. PMID 9521027
43. Mostow EN, Haraway GD, Dalsing M, et al. Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. *J Vasc Surg.* May 2005;41(5):837-843. PMID 15886669
44. Romanelli M, Dini V, Bertone M, et al. OASIS wound matrix versus Hyaloskin in the treatment of difficult-to-heal wounds of mixed arterial/venous aetiology. *Int Wound J.* Mar 2007;4(1):3-7. PMID 17425543
45. Romanelli M, Dini V, Bertone MS. Randomized comparison of OASIS wound matrix versus moist wound dressing in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. *Adv Skin Wound Care.* Jan 2010;23(1):34-38. PMID 20101114

46. Harding K, Sumner M, Cardinal M. A prospective, multicentre, randomised controlled study of human fibroblast-derived dermal substitute (Dermagraft) in patients with venous leg ulcers. *Int Wound J*. Apr 2013;10(2):132-137. PMID 23506344
47. Fivenson DP, Scherschun L, Cohen LV. Apligraf in the treatment of severe mitten deformity associated with recessive dystrophic epidermolysis bullosa. *Plast Reconstr Surg*. Aug 2003;112(2):584-588. PMID 12900618
48. Carsin H, Ainaud P, Le Bever H, et al. Cultured epithelial autografts in extensive burn coverage of severely traumatized patients: a five year single-center experience with 30 patients. *Burns*. Jun 2000;26(4):379-387. PMID 10751706
49. Lagus H, Sarlomo-Rikala M, Bohling T, et al. Prospective study on burns treated with Integra(R), a cellulose sponge and split thickness skin graft: comparative clinical and histological study--randomized controlled trial. *Burns*. Dec 2013;39(8):1577-1587. PMID 23880091
50. Branski LK, Herndon DN, Pereira C, et al. Longitudinal assessment of Integra in primary burn management: a randomized pediatric clinical trial. *Crit Care Med*. Nov 2007;35(11):2615-2623. PMID 17828040
51. Heimbach DM, Warden GD, Luterman A, et al. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. *J Burn Care Rehabil*. Jan-Feb 2003;24(1):42-48. PMID 12543990
52. Lukish JR, Eichelberger MR, Newman KD, et al. The use of a bioactive skin substitute decreases length of stay for pediatric burn patients. *J Pediatr Surg*. Aug 2001;36(8):1118-1121. PMID 11479839
53. Amani H, Dougherty WR, Blome-Eberwein S. Use of Transcyte and dermabrasion to treat burns reduces length of stay in burns of all size and etiology. *Burns*. Nov 2006;32(7):828-832. PMID 16997480
54. Baldursson BT, Kjartansson H, Konradsdottir F, et al. Healing rate and autoimmune safety of full-thickness wounds treated with fish skin acellular dermal matrix versus porcine small-intestine submucosa: a noninferiority study. *Int J Low Extrem Wounds*. Mar 2015;14(1):37-43. PMID 25759413
55. Still J, Glat P, Silverstein P, et al. The use of a collagen sponge/living cell composite material to treat donor sites in burn patients. *Burns*. Dec 2003;29(8):837-841. PMID 14636761
56. Lazic T, Falanga V. Bioengineered skin constructs and their use in wound healing. *Plast Reconstr Surg*. Jan 2011;127 Suppl 1:75S-90S. PMID 21200276
57. Saffle JR. Closure of the excised burn wound: temporary skin substitutes. *Clin Plast Surg*. Oct 2009;36(4):627-641. PMID 19793557
58. American Society of Plastic Surgeons. Evidence-Based Clinical Practice Guideline: Breast Reconstruction with Expanders and Implants. 2013; <http://www.plasticsurgery.org/Documents/medical-professionals/health-policy/evidence-practice/breast-reconstruction-expanders-with-implants-guidelines.pdf>. Accessed January 2, 2018.
59. National Institute for Health and Care Excellence (NICE). Diabetic Foot Problems: Prevention and Management [NG19]. 2016; <https://www.nice.org.uk/guidance/ng19/evidence>. Accessed January 2, 2018.
60. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. Jun 2012;54(12):e132-173. PMID 22619242
61. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Porcine Skin and Gradient Pressure Dressings (270.5). n.d.; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=139&ncdver=1&bc=AgAAQAAAAAAAA&>. Accessed January 2, 2018.
62. Centers for Medicare & Medicaid Services (CMS). Fact Sheet: CMS issues hospital outpatient department and ambulatory surgical center policy and payment changes for 2014. 2013; <http://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-Sheets/2013-Fact-Sheets-Items/2013-11-27-3.html>. Accessed January 2, 2018.

Other References:

1. National Medical Consultant Board Certified in Plastic Surgery and Surgery of the Hand (ID 1079-0258) May 21, 2008.
2. C&A practicing board certified Plastic Surgeon (462), June 9, 2008.
3. C&A practicing board certified Ear Nose and Throat Surgeon (440), June 17, 2008.
4. C&A board certified General Surgeon (520), June 30, 2009.
5. C&A practicing board certified General Surgeon (405), August 18, 2009.
6. MCOP board certified in Plastic Surgery and Surgery of the Hand, MCOP ID 2065-3191, Reviewer ID 2259, February 23, 2010.
7. C&A practicing board certified Plastic Surgeon (418), March 2, 2010.
8. C&A practicing board certified Podiatrist (544), April 13, 2010.
9. AMR practicing physician and board certified in General Surgery, Hand Surgery, and Plastic Surgery (47013), January 26, 2012.