Medical Policy

BlueCross BlueShield Kansas
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Title: Bio-Engineered Skin and Soft Tissue Substitutes

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

Professional
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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are undergoing breast reconstruction	Interventions of interest are: • Allogeneic acellular dermal matrix products	Comparators of interest are: • Breast reconstruction without an acellular dermal matrix product	Relevant outcomes include: • Symptoms • Morbid events • Functional outcomes • Quality of life • Treatment-related morbidity
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: • 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: • 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: • 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: • 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: • 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-extremity ulcers and severe burns. Acellular dermal matrix (ADM) products are also being evaluated for soft tissue repair.

Objective

The objective of this review is to determine whether the use of artificial skin and soft-tissue substitutes for reinforcement for surgical procedures, and healing of chronic wounds and burns improves the net health outcome.

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 section summarizes 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 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, not requiring FDA approval for homologous use.

In 2017, FDA published clarification of what is considered minimal manipulation and homologous use for human cells, tissues, and cellular and tissue-based products (HCT/Ps) [1,]

HCT/Ps are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.
An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

1) The HCT/P is minimally manipulated;
2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
4) Either:
    i. The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
    ii. The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and: a) Is for autologous use; b) Is for allogeneic use in a first-degree or second-degree blood relative; or c) Is for reproductive use.

Although frequently used by surgeons for breast reconstruction, FDA does not consider this homologous use and has not cleared or approved any surgical mesh device (synthetic, animal collagen-derived, or human collagen-derived) for use in breast surgery. The indication of surgical

mesh for general use in "Plastic and reconstructive surgery" was cleared by the FDA before surgical mesh was described for breast reconstruction in 2005. FDA states that the specific use of surgical mesh in breast procedures represents a new intended use and that a substantial equivalence evaluation via 510(k) review is not appropriate and a pre-market approval evaluation is required.[2,]

- 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 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; a subsidiary of Integra Life Sciences) 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; a subsidiary of Integra Life Sciences) is a xenogeneic ADM processed from fetal bovine and neonatal 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 American Association of Tissue Banks and FDA guidelines. It is considered a minimally processed human cell, tissue, and cellular- and tissue-based product by FDA.

- Epicel® (Genzyme Biosurgery) is an 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 & 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 the 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[a] may be considered **medically necessary**. (See Policy Guidelines)
1. AlloDerm (Q4116)
2. AlloMend
3. Cortiva [AlloMax]
4. DermACELL (Q4122)
5. DermaMatrix
6. FlexHD (Q4128)
7. FlexHD Pliable
8. 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 [a] (Q4128)
2. Apligraf [b] (Q4101)
3. Dermagraft [b] (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 [b] (Q4101)
2. Oasis Wound Matrix [c] (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]) [d]

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 ≥30% when provided in accordance with the HDE specifications of the FDA) [d]
   2. Integra Dermal Regeneration Template[b] (Q4105)

[a] Banked human tissue
[b] FDA premarket approved
[c] FDA 510(k) clearance
[d] 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:

Experimental / Investigational
1. ACell UBM Hydrated / Lyophilized Wound Dressing
2. AlloSkin (Q4115)
3. AlloSkin AC, per sq cm (Q4141)
4. AlloSkin RT (Q4123)
5. Aongen Collagen Matrix
6. Architect ECM, PX, FX (Q4147)
7. ArthroFlex (Flex Graft) (Q4125)
8. Atlas Wound Matrix
9. Avagen Wound Dressing
10. AxoGuard Nerve Protector (AxoGen)
11. BellaCell HD or Surederm, per square centimeter (Q4220)
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

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. Derm-Maxx, per square centimeter (Q4238)
33. DressSkin
34. Durepair Regeneration Matrix
35. Endoform Dermal Template
36. *ENDURA*Gen
37. Excellagen (Q4149)
38. ExpressGraft
39. E-Z Derm (Q4136)
40. Flowerderm (Q4179)
41. GammaGraft (Q4111)
42. GraftJacket Xpress, injectable (Q4113)
43. Helicoll (Q4164)
44. hMatrix (Q4134)
45. Hyalomatrix (Q4117)
46. Hyalomatrix PA
47. Integra Bilayer Wound Matrix (C9363, Q4104)
48. Integra Matrix, per sq cm (Q4108)
49. Keramatrix or Kerasorb, per sq cm (Q4165)
50. Kerecis Omega3 (Q4158)
51. Keroxx (2.5g/cc), 1cc (Q4202)
52. MariGen / Kerecis Omega3 (Q4158)
53. MatriDerm
54. MatriStem Micromatrix (Q4118)
55. Matrix HD (Q4128)
56. Mediskin (Q4135)
57. MemoDerm (Q4126)
58. Miroderm biologic wound matrix (Q4175)
59. MyOwn skin, includes harvesting and preparation procedures, per square centimeter (Q4226)
60. NeoForm
61. Neopatch (Q4176)
62. NuCel
63. Oasis Burn Matrix (Q4103)
64. Oasis Ultra (Q4124)
65. Pelvicol / PelviSoft

66. Permacol (C9364)
67. PriMatrix (Q4110)
68. Primatrix Dermal Repair Scaffold
69. ProgenaMatrix, per square centimeter (Q4222)
70. Puraply Wound Matrix (previously FortaDerm™), per square centimeter (Q4195)
71. Puraply AM (Antimicrobial Wound Matrix), per square centimeter (Q4196)
72. Puraply XT, per square centimeter (Q4197)
73. Puros Dermis
74. RegenePro
75. Repliform
76. Repriza (Q4143)
77. Revita, per sq cm (Q4180)
78. SkinTE, 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 12, 2019.

The original review focused on the use of 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 technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 technology, 2 domains are examined: the relevance, and 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 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 following is a summary of key literature to date.

Breast Reconstruction

Clinical Context and Therapy Purpose

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 purpose of bioengineered soft tissue substitutes in patients who are undergoing breast reconstruction is to provide a treatment option that is an alternative to or an improvement on breast reconstruction without use of a biological or biosynthetic matrix.

The question addressed in this evidence review is: Do bio-engineered soft tissue substitutes in patients who are undergoing breast reconstruction improve the net health outcome?

The following PICO was used to select literature to inform this review.

Patients

The relevant population of interest is patients who are undergoing breast reconstruction, typically following mastectomy.

Interventions
The therapy being considered is bioengineered soft tissue substitutes as a biological matrix that is used to facilitate one-stage tissue expander reconstruction. As noted in the regulatory status section, the FDA has not cleared or approved any surgical mesh device (synthetic, animal collagen-derived, or human collagen-derived) for use in breast surgery.

Comparators
The following therapies are currently being used to make decisions about soft tissue substitutes or biological matrices: 2-stage tissue expander reconstruction without a biological matrix.

Outcomes
The general outcomes of interest are symptoms, morbid events, functional outcomes, QOL, and treatment-related morbidity. Specific outcomes are the time to permanent implant, pain during and after the procedure, and adverse events including seroma, infection, and necrosis rates, rates of capsular contracture, and malposition of implants. Short-term outcomes would be measured within 3 months with longer-term outcomes apparent by 2 years.

Study Selection Criteria
1. To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for RCTs*.
2. In the absence of such trials, we sought comparative observational studies, with preference for prospective studies.
3. To assess longer-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.
4. Within each category of study design, we prefer larger sample size studies and longer duration studies.
5. We excluded studies with duplicative or overlapping populations.

* Includes various RCT designs such as adaptive trials, pragmatic trials, and cluster trials.

Evidence Review
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.[3,] 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 meta-analysis by Lee and Mun (2016) included 23 studies (total N=6199 cases) on implant-based breast reconstruction that were published between February 2011 and December 2014.[4,] 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, 79.63; 95% confidence interval [CI], 41.99 to 117.26; p<0.001) and percentage of intraoperative filling (mean difference=13.30;

95% CI, 9.95 to 16.65; p<0.001), and reduced the frequency of injections to complete expansion (mean difference=-1.56; 95% CI, -2.77 to -0.35; p=0.01).

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

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

Adapted from Lee and Mun (2016).[4,]
ADM: acellular dermal matrix; *NS*: not significant.

AlloDerm

Randomized Controlled Trials

McCarthy et al (2012) reported on a multicenter, blinded RCT of AlloDerm in 2-stage expander/implant reconstruction.[5,] 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 endpoint 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 Versus AlloMax

Hinchcliff et al (2017) conducted an RCT that compared AlloDerm with AlloMax (n=15 each) for implant-based breast reconstruction.[6,] 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 Versus DermaMatrix

Mendenhall et al (2017) conducted an RCT that compared AlloDerm with DermaMatrix in 111 patients (173 breasts).[7,] There were no significant differences in overall rates of complications (AlloDerm, 15.4%; DermaMatrix, 18.3%; p=0.8) or implant loss (AlloDerm, 2.2%; DermaMatrix, 3.7%; p=0.5) between the 2 ADMs.

AlloDerm Versus FlexHD

A retrospective review by Liu et al (2014) compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts).[8,] 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 Versus 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.[9,] 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).[10,] 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).[11,] One-stage breast reconstruction with porcine ADM was associated with a higher risk of surgical complications, reoperation, and with removal of implant, ADM, or both (see Table 3). The trial was stopped early due to safety concerns, but it cannot be determined from this study design whether the increase in complications was due to the use of the xenogenic ADM or to the comparison between 1-stage and 2-stage reconstruction.

Table 2. Summary of Key RCT Characteristics

					Interventions	
Author	**Countries**	**Sites**	**Dates**	**Participants**	**Active**	**Comparator**
Dikmans et al (2017)[11,]	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)[11,]				
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

Clinical Context and Therapy Purpose

The purpose of bio-engineered soft tissue substitutes in patients who are undergoing tendon repair is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Do bio-engineered soft tissue substitutes in patients undergoing tendon repair improve the net health outcome?

The following PICO was used to select literature to inform this review.

Patients

The relevant population(s) of interest is patients undergoing tendon repair.

Interventions

The therapy being considered is bioengineered soft-tissue substitutes.

Comparators

The following therapies are currently being used to make decisions about tendon repair: tendon repair without bioengineered soft-tissue substitutes.

Outcomes

The general outcomes of interest are symptoms, morbid events, functional outcomes, QOL, and treatment-related morbidity. Short-term outcomes would be measured within 3 months with longer-term outcomes apparent by 2 years.

Study Selection Criteria

1. To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for RCTs*.
2. In the absence of such trials, we sought comparative observational studies, with preference for prospective studies.
3. To assess longer-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.
4. Within each category of study design, prefer larger sample size studies and longer duration studies.
5. We excluded studies with duplicative or overlapping populations.

* Includes various RCT designs such as adaptive trials, pragmatic trials, and cluster trials.

Evidence Review

Graftjacket

Barber et al(2012) 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.[12,] 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 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 corroborate these findings and determine the effects of this technology with greater certainty.

Surgical Repair of Hernias or Parastomal Reinforcement

Clinical Context and Therapy Purpose

The purpose of bio-engineered soft tissue substitutes in patients who are undergoing surgical repair of hernias or require parastomal reinforcement is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Do bioengineered soft tissue substitutes in patients undergoing surgical repair of hernias or require parastomal reinforcement improve the net health outcome?

The following PICO was used to select literature to inform this review.

Patients

The relevant population(s) of interest is undergoing surgical repair of hernias or require parastomal reinforcement.

Interventions
The therapy being considered is bioengineered matrix support.

Comparators
The following therapies are currently being used for surgical repair of hernias or parastomal reinforcement: synthetic mesh.

Outcomes
The general outcomes of interest are symptoms, morbid events, functional outcomes, QOL, and treatment-related morbidity. Specific outcomes are surgical site occurrence of postoperative infection, seroma/hematoma, pain, bulging, dehiscence, fistula, or mechanical failure. Short-term outcomes would be measured within 3 months with longer-term outcomes apparent by 2 years.

Study Selection Criteria
1. To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for RCTs*.
2. In the absence of such trials, we sought comparative observational studies, with preference for prospective studies.
3. To assess longer-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.
4. Within each category of study design, prefer larger sample size studies and longer duration studies.
5. We excluded studies with duplicative or overlapping populations.

* Includes various RCT designs such as adaptive trials, pragmatic trials, and cluster trials.

A 2013 systematic review evaluated the clinical effectiveness of acellular collagen-based scaffolds for the repair of incisional hernias.[13,] 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
Espinosa-de-los-Monteros et al (2007) retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases.[14,] They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

Comparisons Between Products

AlloDerm Versus Surgisis Gold

Gupta et al (2006) compared the efficacy and complications associated with use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair.[15,] 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 Versus FlexHD

A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery.[16,] From 2005 to 2007, AlloDerm was used to repair large (>200 cm^2) 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 Versus Strattice

Roth et al (2017) reported on a prospective study assessing clinical and QOL outcomes following complex hernia repair with a human (FlexHD) or porcine (Strattice) ADM.[17,] The study was funded by the Musculoskeletal Transplant Foundation, which prepares and supplies FlexHD. Patients were enrolled if they had a hernia at least 6 cm in the transverse dimension, active or prior infection of the abdominal wall, and/or enterocutaneous fistula requiring mesh removal. Eighteen (51%) of the 35 patients had undergone a previous hernia repair. After abdominal wall repair with the ADM, 20 (57%) patients had a surgical site occurrence, and nearly one-third had hospital readmission. The type of biologic material did not impact hernia outcomes. There was no comparison with synthetic mesh in this study, limiting interpretation.

Strattice Versus Synthetic Mesh

Bellows et al (2014) 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.[18,] 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 Versus No Reinforcement

Also in 2014, the Parastomal Reinforcement With Strattice (PRISM) Study Group reported a multicenter, double-blinded, randomized trial of Strattice for parastomal reinforcement in patients

undergoing surgery for permanent abdominal wall ostomies.[19,] 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
Clinical Context and Therapy Purpose
The purpose of bio-engineered soft tissue substitutes in patients who have diabetic lower extremity ulcers is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Do bio-engineered soft tissue substitutes in patients with diabetic lower extremity ulcers improve the net health outcome?

The following PICO was used to select literature to inform this review.

Patients
The relevant population(s) of interest is patients with diabetic lower extremity ulcers.

Interventions
The therapy being considered is bioengineered skin substitutes.

Comparators
The following therapies are currently being used: standard wound care which involves regular debridement and moist wound covering.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, and QOL.

The primary endpoints of interest for trials of wound closure are as follows, consistent with guidance from the FDA 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.

Time to wound closure can be measured at 6 months with longer-term outcomes apparent by 1 year. More complex wounds may require more than 6 months to heal.

Study Selection Criteria

1. To assess efficacy outcomes, we sought comparative controlled prospective trials, with preference for RCTs*.
2. In the absence of such trials, we sought comparative observational studies, with preference for prospective studies.
3. To assess longer-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.
4. Within each category of study design, prefer larger sample size studies and longer duration studies.
5. We excluded studies with duplicative or overlapping populations.

* Includes various RCT designs such as adaptive trials, pragmatic trials, and cluster trials.

Evidence Review

Systematic Reviews

A 2016 Cochrane review evaluated skin substitutes for the treatment of diabetic foot ulcers.[20,] 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 (13193 treatment episodes) to compare efficacy and cost of skin substitutes for the management of diabetic foot ulcers.[21,] 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 of diabetic foot ulcers.[22,]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.[23,] 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.[24,]

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.[25,] Study design and patient population were similar to the 208-subject U.S. study (previously described), which led to 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.

Kirsner et al (2010) analyzed 2517 patients with diabetic neuropathic foot ulcers treated between 2001 and 2004.[26,] 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.[27,] 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).[28,] 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 an industry-sponsored multicenter trial by Zelen et al (2017, 2018).[29,30,] The initial trial with 20 patients per group was extended to determine the percent healing at 6 weeks with 40 patients per group. Healing was evaluated by the site investigator and confirmed by an independent panel. At 6 weeks, 68% (27/40) of wounds treated using AlloPatch had healed compared with 15% (6/40) in the SOC-alone group (p<0.001). At 12 weeks, 80% (32/40) of patients in the AlloPatch group had healed compared to 30% (12/40) in the control group. Mean time to heal within 12 weeks was 38 days (95% CI: 29-47 days) for the HR-ADM group and 72 days (95% CI: 66-78 days) for the SOC group (p < 0.001).

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.[31,] 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 intention-to-treat (ITT) analysis.

Integra Flowable Wound Matrix is composed of a porous matrix of cross-linked bovine tendon collagen and glycosaminoglycan. It is supplied as a granular product that is mixed with saline. Campitiello et al (2017) published an RCT that compared the flowable matrix with wet dressing in 46 patients who had Wagner grade 3 diabetic foot ulcers.[32,] 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 Versus SOC

Study	Complete Wound Healing	Rehospitalization	Major Amputation
Campitiello et al (2017)[32,]			
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.[33,] 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 1-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 4 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.[34,] Eight patients, 6 in the study group and 2 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 versus 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.

Reyzelman and Bazarov (2015)[35,] 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)[36,] with 28 patients (total N=154 patients). The time to heal was estimated for the Brigido (2004) 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 (2006) 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 (2015), included publication and reporting biases, study selection biases, incomplete data selection, post hoc manipulation of data, and subjective choice of analytic methods. Overall, results of these studies do not provide convincing evidence that Graftjacket is more effective than SOC for healing diabetic foot ulcers.

DermACELL Versus Graftjacket Regenerative Tissue Matrix or SOC

DermACELL and Graftjacket are both composed of human ADM.Walters et al(2016) reported on a multicenter randomized comparison of DermACELL, Graftjacket, or SOC (2:1:2 ratio) in 168 patients with diabetic foot ulcers.[37,] The study was sponsored by LifeNet Health, a nonprofit organ procurement association and processor for DermACELL. At 16 weeks, the proportion of completely healed ulcers was 67.9% for DermACELL, 47.8% for Graftjacket, and 48.1% for SOC. The 20% difference in completely healed ulcers was statistically significant for DermACELL versus SOC (p=0.039). The mean time to complete wound closure did not differ significantly for DermACELL (8.6 weeks), Graftjacket (8.6 weeks), and SOC (8.7 weeks).

A second report from this study was published in 2017.[38,] 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 ITT. 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 Versus SOC

	% 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)[38,]						
DermACELL, %	65.0%	82.5%	89.7%	NR	67.9%	83.7%
SOC, %	41.1%	48.1%	67.3%	NR	48.1%	67.3%
HR (95% CI)	1.97 (1.1 to 3.5)	2.40 (1.4 to 4.1)	2.11 (1.3 to 3.5)		1.72 (1.04 to 2.83)	1.55 (0.98 to 2.44)
p	0.012	<0.001	<0.001	*NS*	0.028	0.049

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

TheraSkin Versus Dermagraft

Sanders et al (2014) reported 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.[39,] Wound size at baseline ranged from 0.5 to 18.02 cm^2; the average wound size was about 5 cm^2 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 Versus Apligraf

DiDomenico et al (2011) compared TheraSkin with Apligraf for the treatment of diabetic foot ulcers in a small (N=29) RCT.[40,] 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) Versus Dermagraft

Frykberg et al (2017) reported a prespecified interim analysis of an industry-funded multicenter noninferiority trial of Cytal (a porcine urinary bladder–derived extracellular matrix) versus Dermagraft in 56 patients with diabetic foot ulcers.[41,]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. ITT analysis found complete wound closure in 5 (18.5%) wounds treated with Cytal compared with 2 (6.9%) wounds treated with Dermagraft ($p=NS$). QOL, 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.[42,] Average duration of ulcers before treatment was 286 days, and average wound area was 4.34 cm^2. 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.[43,] 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^2 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 Versus 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.[44,] 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 secondary dressing. Wounds were cleaned 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 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.

Autologous Grafting on HYAFF Scaffolds

Uccioli et al (2011) reported a multicenter RCT of cultured expanded fibroblasts and keratinocytes grown on an HYAFF scaffold (benzyl ester of hyaluronic acid) compared with paraffin gauze for difficult diabetic foot ulcers.[45,] A total of 180 patients were randomized. At 12 weeks, complete ulcer healing was similar for the 2 groups (24% treated vs. 21% controls). At 20 weeks, complete ulcer healing was achieved in

a similar proportion of the treatment group (50%) and the control group (43%, log-rank test = 0.344). Subgroup analysis, adjusted for baseline factors and possibly post-hoc, found a statistically significant benefit of treatment on dorsal ulcers but not plantar ulcers.

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

Clinical Context and Therapy Purpose

The purpose of bio-engineered soft tissue substitutes in patients who have lower extremity ulcers due to venous insufficiency is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Do bio-engineered soft tissue substitutes in patients with venous ulcers improve the net health outcome?

The following PICO was used to select literature to inform this review.

Patients
The relevant population(s) of interest is patients who have lower extremity ulcers due to venous insufficiency.

Interventions
The therapy being considered is bioengineered skin substitutes.

Comparators
The following therapies are currently being used: SOC which includes debridement of necrotic tissue and compression.

A Cochrane review by O<92>Meara et al (2012) that evaluated compression for venous leg ulcers included 48 RCTs with 59 different comparisons.[46,] Most RCTs were small. Measures of healing were the time to complete healing, the proportion of ulcers healed within the trial period (typically 12 weeks), the change in ulcer size, and the rate of change in ulcer size. Evidence from 8 trials indicated that venous ulcers healed more rapidly with compression than without. Findings suggested that multicomponent systems (bandages or stockings) were more effective than single-component compression. Also, multicomponent systems containing an elastic bandage appeared more effective than those composed mainly of inelastic constituents. Although these meta-analyses did not include time to healing, studies included in the review reported the mean time to ulcer healing was approximately 2 months, while the median time to healing in other reports was 3 to 5 months.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, and QOL.

The primary endpoints of interest for trials of wound closure are as follows, consistent with guidance from the FDA 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.

Time to wound closure can be measured at 6 months with longer-term outcomes apparent by 1 year. Complex wounds may require more than 6 months to heal.

Study Selection Criteria
As described above.

Evidence Review
Apligraf
Falanga et al (1998) reported on a multicenter randomized trial of Apligraf living cell therapy.[47,] 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 endpoints 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^2) 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.[24,]

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 responded to conventional therapy.[48,] 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 quasirandomized study, Romanelli et al(2007) compared the efficacy of 2 extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid).[49,] 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).

Romanelli et al(2010) compared Oasis with a moist wound dressing (SOC) in 23 patients with mixed arteriovenous ulcers and 27 patients with venous ulcers.[50,] 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 the FDA for repair of diabetic foot ulcers. Use of Dermagraft for venous ulcers is an off-label indication.Harding et al (2013) reported an open-label multicenter RCT that compared Dermagraft plus compression therapy (n=186) with compression therapy alone (n=180).[51,] 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

Karr (2011) published a retrospective comparison of PriMatrix (xenogenic ADM) and Apligraf in 28 venous stasis ulcers.[43,] 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^2 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.

DermACELL

Cazzell (2019) published an RCT on DermACELL ADM for venous leg ulcers in 18 patients (see Table 6).[52,] This was part of a larger study of the acellular dermal matrix for chronic wounds of the lower extremity in 202 patients; the component on diabetic lower extremity ulcers was previously reported by Cazzell et al (2017) and is described above.[38,] When including patients who required more than 1 application of the ADM, the percent of wounds closed at 24 weeks was 29.4% with DermACELL and 33.3% with SOC, suggesting no benefit DermACELL for the treatment of venous ulcers in this small substudy.

Table 6. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Cazzell (2019) NCT01970163	US	7	2013-2016	Venous leg ulcer present for at least 60 days (n=18)	1 or 2 applications of DermACELL plus SOC (n=18)	SOC (debridement and compression, n=10)

RCT: randomized controlled trial; SOC: standard of care

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 endpoints 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. An initial study with 18 patients found that and DermACELL (ADM) was not more effective than SOC. Additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment compared with current SOC.

Deep Dermal Burns

Clinical Context and Therapy Purpose

The purpose of bio-engineered soft tissue substitutes in patients who have deep dermal burns is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Do bio-engineered soft tissue substitutes in patients with deep dermal burns improve the net health outcome?

The following PICO was used to select literature to inform this review.

Patients

The relevant population(s) of interest is patients with deep dermal burns.

Interventions

The therapy being considered is bioengineered skin substitutes.

Comparators

The following therapies are currently being used; standard therapy for burns.

Outcomes

The general outcomes of interest are disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, QOL, and treatment-related morbidity.

The primary endpoints of interest for trials of wound closure are as follows, consistent with guidance from the FDA 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.

Time to wound closure can be measured at 6 months with longer-term outcomes apparent by 1 year.

Study Selection Criteria

As described above.

Evidence Review

Epicel

One case series from 2000 has described the treatment of 30 severely burned patients with Epicel.[53,] 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.[54,] 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).[55,] 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.[56,] 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 report by Lukish et al(2001) 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.[57,]Amani et al(2006) 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.[58,]

Section Summary: Deep Dermal Burns

Epicel is FDA-approved under a humanitarian device exemption (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

Dystrophic Epidermolysis Bullosa

OrCel was approved under an HDE for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites. 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.[59,]

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.

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).[60,] 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.Still et al(2003) (examined the safety and efficacy of bilayered OrCel to facilitate wound closure of split-thickness donor sites in 82 severely burned patients.[61,] 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.

Pressure Ulcers

Brown-Etris et al (2019) reported an RCT of 130 patients with stage 3 or stage 4 pressure ulcers who were treated with Oasis Wound Matrix (extracellular collagen matrix derived from porcine small intestinal submucosa) plus SOC or SOC alone.[62,] At 12 weeks, the proportion of wounds healed in the collagen matrix group was 40% compared to 29% in the SOC group. This was not statistically significant (p=0.111). There was a statistical difference in the proportion of patients who achieved 90% wound healing (55% vs. 38% p=0.037), but complete wound healing is the preferred and most reliable measure. It is possible that longer follow-up may have identified a significant improvement in the percent of wounds healed. The study did include 6-month follow-up, but there was high loss to follow-up and an insufficient number of patients at this time point for statistical comparison.

Miscellaneous

In addition to indications previously reviewed, off-label uses of bioengineered skin substitutes have included inflammatory ulcers (eg, pyoderma gangrenosum, vasculitis), scleroderma digital ulcers, postkeloid removal wounds, genetic conditions, and variety of other conditions.[63,] 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).[64,]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 (QOL), 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, QOL, and treatment-related morbidity. The RCT identified found 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, QOL, 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 symptoms, change in disease status, morbid events, and QOL. RCTs have demonstrated the efficacy of AlloPatch (reticular ADM), Apligraf and Dermagraft (living cell therapy), and Integra (biosynthetic) over the standard of care (SOC). 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 symptoms, change in disease status, morbid events, and QOL. 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 symptoms, change in disease status, morbid events, and QOL. RCTs have demonstrated the efficacy of Apligraf living cell therapy and xenogenic Oasis Wound Matrix over the SOC. 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 QOL. In a moderately large RCT, Dermagraft was not shown to be more effective than controls for the primary or secondary endpoints in the entire population and was only slightly more effective than controls (an 8%-15% increase in healing) in subgroups of patients with ulcer durations of 12 months or less or size of 10 cm or less. Additional study with a larger number of subjects is needed to evaluate the effect of the xenogenic PriMatrix skin substitute versus the current SOC. 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 QOL. 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 symptoms, change in disease status, morbid events, functional outcomes, QOL, 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

National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems.[65,]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."

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 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03285698	A Randomized, Prospective Trial Comparing the Clinical Outcomes for DermACELL® Compared With Integra® Bilayer Wound Matrix	100	Oct 2020
NCT02587403[a]	A Randomized, Prospective Study Comparing Fortiva™ Porcine Dermis vs. Strattice™ Reconstructive Tissue Matrix in Patients Undergoing Complex Open Primary Ventral Hernia Repair	120	Oct 2020
NCT02322554	The Registry of Cellular and Tissue Based Therapies for Chronic Wounds and Ulcers	50,000	Jan 2020
Unpublished			
NCT01987700[a]	Multi-Center Study To Examine The Use Of Flex HD® And Strattice In The Repair Of Large Abdominal Wall Hernias	120	Aug 2018 (completed)

NCT: national clinical trial.
[a] 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

A2002 Mirragen advanced wound matrix, per square centimeter (effective 01-01-22)
A2003 Bio-connekt wound matrix, per square centimeter (effective 01-01-22)
A2004 Xcellistem, per square centimeter (effective 01-01-22)
A2005 Microlyte matrix, per square centimeter (effective 01-01-22)
A2006 Novosorb synpath dermal matrix, per square centimeter (effective 01-01-22)
A2007 Restrata, per square centimeter (effective 01-01-22)
A2008 Theragenesis, per square centimeter (effective 01-01-22)
A2009 Symphony, per square centimeter (effective 01-01-22)
A2010 Apis, per square centimeter (effective 01-01-22)

C1831 Personalized, anterior and lateral interbody cage (implantable) Effective 10-01-2021
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 (BMWD), per sq cm
Q4105	Integra dermal regeneration template (DRT) or Integra Omnigraft dermal regeneration matrix, per sq cm
Q4106	Dermagraft, per sq cm
Q4107	GRAFTJACKET, per sq cm
Q4108	Integra matrix, per sq cm
Q4110	PriMatrix, per sq cm
Q4111	GammaGraft, per sq cm
Q4112	Cymetra, injectable, 1 cc
Q4113	GRAFTJACKET 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, DermACELL AWM or DermACELL AWM Porous, 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 InteguPly, or SimpliDerm 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	Kerecis Omega3, per sq cm
Q4161	Bio-ConneKt wound matrix, per sq cm
Q4164	Helicoll, per sq cm
Q4165	Keramatrix or Kerasorb, per sq cm
Q4166	Cytal, per sq cm
Q4167	Truskin, per sq cm
Q4175	Miroderm, per sq cm
Q4176	NeoPatch, per sq cm
Q4179	FlowerDerm, per sq cm
Q4180	Revita, 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	SkinTE, per square centimeter
Q4202	Keroxx (2.5g/cc), 1cc

Q4203	Derma-Gide, per square centimeter
Q4220	BellaCell HD or Surederm, per square centimeter
Q4222	Progenamatrix, per square centimeter
Q4226	MyOwn skin, includes harvesting and preparation procedures, per square centimeter
Q4238	Derm-Maxx, 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)
L89.006	Pressure-induced deep tissue damage of unspecified elbow
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
L89.016	Pressure-induced deep tissue damage of right elbow
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
L89.026 Pressure-induced deep tissue damage of left elbow
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
L89.116 Pressure-induced deep tissue damage of right upper back
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
L89.126 Pressure-induced deep tissue damage of left upper back
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
L89.136 Pressure-induced deep tissue damage of right lower back
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
L89.146 Pressure-induced deep tissue damage of left lower back
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
L89.156 Pressure-induced deep tissue damage of sacral region
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
L89.216 Pressure-induced deep tissue damage of right hip
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
L89.226 Pressure-induced deep tissue damage of left hip
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
L89.316 Pressure-induced deep tissue damage of right buttock
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
L89.326 Pressure-induced deep tissue damage of left buttock
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
L89.46 Pressure-induced deep tissue damage of contiguous site of back, buttock and hip
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
L89.516	Pressure-induced deep tissue damage of right ankle
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
L89.526	Pressure-induced deep tissue damage of left ankle
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
L89.616	Pressure-induced deep tissue damage of right heel
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
L89.626	Pressure-induced deep tissue damage of left heel
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
L89.816	Pressure-induced deep tissue damage of head
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
L89.896	Pressure-induced deep tissue damage of other site
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

REVISIONS	
04-30-2015	Policy published 03-31-2015
	Description section updated
	In Policy section: ▪ In Item A added "allogeneic" and "products*" to read, "…using the following allogeneic acellular dermal matrix products* may be considered medically necessary…" ▪ In Item A added the following four medically necessary skin substitutes: AlloMax, DermaMatrix, FlexHD, and GrafJacket. ▪ In Item B added the following medically necessary skin substitute: Epifix. ▪ 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). ▪ 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. ▪ 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, 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)
	Rational section updated
	In Coding section: ▪ Added HCPCS Codes: C9349, Q4150, Q4151, Q4152, Q4153, Q4154, Q4155, Q4157, Q4158, Q4159, Q4160. ▪ Removed HCPCS Codes: C9355, C9361, C9367, Q4108, Q4109, Q4122, q4137, Q4138, Q4139, Q4141, Q4142, Q4146, Q4147. ▪ Revised HCPCS Codes: Q4113, Q4119, Q4123, Q4124, Q4125, q4127, Q4128, Q4129, Q4130, Q4140, Q4143, Q4148
	In Revision section: ▪ Removed revision details for: 08-03-2010, 02-01-2012.
	References updated
05-01-2016	Published 03-31-2016. Effective 05-01-2016

REVISIONS	
	Description section updated
	In Policy section: ▪ In Item B added "Integra Dermal Regeneration Template (Q4105)" ▪ 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*)" ▪ 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" ▪ In Item G removed "Unite" to read "TheraSkin (Q4121)" ▪ 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), Plurivest, per sq cm (Q4153), Tensix, per sq cm (Q4146), WoundEx, per sq cm (Q4163), XCM biologic tissue matrix, per sq cm (Q4142)" ▪ In Item G added "(Q4164) to read "Helicoll (Q4164)"
	Rationale section updated
	In Coding section: ▪ Added HCPCS Codes: Q4161, Q4163, Q4164, Q4165 (Effective January 1, 2016) ▪ Added HCPCS Codes: Q4108, Q4122, Q4137, Q4138, Q4139, Q4141, Q4142, Q4146, Q4147, Q4156 ▪ Revised HCPCS Code Nomenclature: Q4153 (Effective January 1, 2016) ▪ Revised HCPCS Code Nomenclature: C9349
	References updated
03-20-2017	In Title section added "See Also: Amniotic Membrane and Amniotic Fluid medical policy"
	Description section updated
	In Policy section: ▪ In Item A added "AlloMend" ▪ In Item B added "AlloPatch*" and removed "Biovance (Q4154), Epifix (Q4131) (Q4145), Grafix (Q4132) (Q4133) (Amniotic Membrane Grafts*)" ▪ In Item 3 removed "TransCyte**" ▪ Updated asterisk Key ▪ In Item G moved the following E/I skin and soft tissue substitute to be medically necessary: AlloPatch HD (Q4128). ▪ 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" ▪ 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

REVISIONS	
	▪ 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 ▪ Policy Guidelines added
	Rationale section updated
	In Coding section: ▪ Revised HCPCS code nomenclature: Q4105 ▪ Added HCPCS codes: Q4166, Q4167, Q4172, Q4175 (Effective 01-01-2017) ▪ Removed HCPCS codes: C9349, Q4119, Q4120, Q4129 (Termed 12-31-2016) ▪ Removed HCPCS codes: Q4131, Q4132, Q4133, Q4137, Q4138, Q4139, Q4140, Q4145, Q4148, Q4150, Q4151, Q4153, Q4154, Q4155, Q4156, Q4157, Q4159, Q4160, Q4163
	In Revision section: ▪Removed revision details for the following dates: 01-15-2016, 12-12-2013, 01-01-2014.
	References updated
04-19-2017	In Policy section: ▪ Removed "CellerateRX (CRXa)" from the policy due to the product not being a skin or soft tissue substitute and not relevant to the policy.
07-18-2018	Description section updated
	In Policy section: ▪ In Item A added "Cortiva", "DermACELL", and "FlexHDPliable" ▪ In Items B and E updated "Integra Derma Regeneration Template" to "Integra Omnigraft Dermal Regeneration Matrix (also known as Omnigraft)" ▪ In Item B added "Integra Flowable Wound Matrix" ▪ In Item G removed "BioDDryFlex (Q4138), DermACELL, per sq cm (Q4122), Integra Flowable Wound Matrix (Q4114), Integra Omnigraft (Q4105), Oasis Wound Matrix (Q4102)" ▪ 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)" ▪ In Item G revised "Biobrane" to "Biobrane / Biobrane-L" and "Cymetra (Q4112)" to "Cymetra (Micronized AlloDerm) (Q4112)"
	Rationale section updated
	In Coding section: ▪ Added CPT Codes: 15200, 15201, 15220, 15221, 15240, 15241, 15260, 15261 ▪ Added HCPCS Codes: Q4176, Q4177, Q4178, Q4179, Q4180, Q4181, Q4182 (Effective January 1, 2018)
	References updated
01-01-2019	In Policy section: ▪ 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: "20. Coll-e-derm, per square centimeter (Q4193) 29. Derma-gide, per square centimeter (Q4203)

REVISIONS	
	53. Keroxx (2.5g/cc), 1cc (Q4202) 70. Puraply, per square centimeter (Q4195) 71. Puraply am, per square centimeter (Q4196) 72. Puraply xt, per square centimeter (Q4197) 78. Skin te, per square centimeter (Q4200)"
	In Coding section: ▪ Added HCPCS Codes: Q4193, Q4195, Q4196, Q4197, Q4200, Q4202, Q4203 ▪ Removed HCPCS Code: Q4172
11-26-2019	Description section updated
	In Policy section: ▪ In Item A moved AlloMax to be with Cortiva to read "Cortiva [AlloMax]) ▪ In Item E w removed "Omnigraft", and "Matrix (also known as Omnigraft and added "Template" to read "Integra Dermal Regeneration Template (Q4105)" In Item G removed "FlexiGraft"; added "BellaCell HD or Surederm, per square centimeter (Q4220)", "MyOwn skin, includes harvesting and preparation procedures, per square centimeter (Q4226)", "Progenamatrix, per square centimeter (Q4222)"; and revised "Puraply" to read "Puraply Wound Matrix (previously FortaDerm™), per square centimeter (Q4195)", "Puraply AM" to read "Puraply AM (Antimicrobial Wound Matrix), per square centimeter (Q4196)"
	Rationale section updated
	In Coding Section: ▪ Added HCPCS Codes (Effective 10-01-2019): Q4220, Q4222, Q4226 ▪ Revised HCPCS Codes: Q4122, Q4158, Q4165 Added ICD-10 Codes (Effective 10-01-2019): L89.016, L89.026, L89.116, L89.126, L89.136, L89.146, L89.156, L89.216, L89.226, L89.316, L89.326, L89.46, L89.516, L89.526, L89.616, L89.626, L89.816, L89.896
	References updated
07-01-2020	Description section updated
	Rationale section updated
	In coding section: ▪ Added HCPCS Code: Q4239 ▪ Removed HCPCS Codes: Q4177, Q4178, Q4181 (These codes are more appropriately placed in the Amniotic Membrane and Amniotic Fluid medical policy) ▪ Revised HCPCS Codes: Q4126
	References updated
10-08-2021	In Coding section Added HCPCS code C1831
01-01-2022	In Coding section • Added HCPCS Code: A2002, A2003, A2004, A2005, A2005, A2006, A2007, A2008, A2009, A2010 (effective 01-01-22)

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