Clinical Policy:
Bio-Engineered Skin & Soft Tissue Substitutes

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Document: BI382:00

Public Statement

Effective Date:

a) This policy will apply to all services performed on or after the above revision date which will become the new effective date.
b) For all services referred to in this policy that were performed before the revision date, contact customer service for the rules that would apply.

1) Bio-engineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), non-human tissue (xenographic), synthetic materials, or a composite of these materials. Bio-engineered skin and soft tissue substitutes are being evaluated for a variety of conditions, including breast reconstruction and to aid healing of lower extremity ulcers and severe burns. Acellular dermal matrix products are also being evaluated in the repair of a variety of soft tissues.

2) Preauthorization is required for Apligraf® and Oasis™ for chronic lower extremity venous ulcers.

3) QualChoice covers the use of the following:
   a) AlloDerm® or DermACELL® for breast reconstruction;
   b) EpiFix®, Apligraf®, DermACELL®, Dermagraft® or Grafix® for noninfected full-thickness diabetic lower extremity ulcers;
   c) Dermagraft® or OrCel™ for dystrophic epidermolysis bullosa, and Integra Dermal Regeneration Template™, TransCyte™, or Epicel® for certain second and third degree burns.
   d) Other products, or use of these products for other purposes, are considered investigational and are not covered. Please see BI383.
   e) Use of noncontact real-time fluorescence wound imaging for bacterial presence (to determine when to apply skin substitutes) is also considered investigational and is not covered.

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Medical Statement

1) AlloDerm is considered medically necessary for prevention of Frey syndrome when performing parotidectomy with preservation of the facial nerve.

2) The use of AlloDerm® or DermACELL for breast reconstruction is considered medically necessary:
   a) When there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; OR
   b) When there is viable but compromised or thin post-mastectomy skin flaps that are at risk of dehiscence or necrosis; OR
   c) When the infra-mammary fold and lateral mammary folds have been undermined during mastectomy and re-establishment of these landmarks is needed.

3) Treatment of chronic, noninfected, full-thickness diabetic lower extremity ulcers (as part of standard wound care) includes optimization of blood sugars, nutritional status, and circulation. Hgb A1C (< 12%), protein, albumin, smoking cessation, and ABIs (≥0.70) should all be adequately addressed. If all of these have been addressed, treatment with the following tissue-engineered skin substitutes is considered medically necessary (in conjunction with standard wound therapy): Apligraf®, DermACELL®, Dermagraft®, EpiFix® or Grafix®.

4) Treatment of chronic, non-infected, partial- or full-thickness lower extremity skin ulcers due to venous insufficiency, which have not adequately responded following a six-month period of conventional ulcer therapy (which includes optimizing nutritional, metabolic and circulatory issues as described above), with the following tissue-engineered skin substitutes is considered medically necessary (requires preauthorization):
   - Apligraf®
   - Oasis™ Wound Matrix

5) Treatment of dystrophic epidermolysis bullosa with the following tissue-engineered skin substitutes is considered medically necessary:
   - Dermagraft®
   - 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 FDA)

6) Treatment of 2nd and 3rd degree burns with the following tissue-engineered skin substitutes is considered medically necessary:
   - Epicel® (for the treatment of deep dermal or full-thickness burns comprising a total body surface area of > or = to 30% when provided in accordance with the HDE specifications of the FDA);
   - Integra Dermal Regeneration Template™;
   - TransCyte™.

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Codes Used In This BI:

15777	Implantation of biologic implant
19357	Tissue expander placement in breast reconstruction, including subsequent expansion(s)
19361	Breast reconstruction; with latissimus dorsi flap
19364	Breast reconstruction; with free flap
19366	Breast reconstr w/other technique (code deleted 01-01-2021)
19367	Breast reconstruction; with single-pedicled transverse rectus abdominis myocutaneous (TRAM) flap
19368	Breast reconstruction; with single-pedicled transverse rectus abdominis myocutaneous (TRAM) flap, requiring separate microvascular anastomosis
19369	Breast reconstruction; with bipedicled transverse rectus abdominis myocutaneous (TRAM) flap
19370	Revision of peri-implant capsule, breast, including capsulotomy, capsulorrhaphy, and/or partial capsulectomy
19371	Peri-implant capsulectomy, breast, complete, including removal of all intracapsular contents
19380	Revision of reconstructed breast (eg, significant removal of tissue, re-advancement and/or re-inset of flaps in autologous reconstruction or significant capsular revision combined with soft tissue excision in implant-based reconstruction)
C1849	Skin substitute, synthetic, resorbable, per sq cm (new code 7/1/2020): E/I
C9354	Acellular pericardial tissue matrix of nonhuman origin (Veritas), 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 sq 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
Q4105	Integra dermal regeneration template (DRT), 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	Gamma Graft, per sq cm
Q4112	Cymetra, injectable, 1 cc
Q4113	GRAFTJACKET XPRESS, injectable, 1 cc
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 micro matrix, 1 mg
Q4119	MatriStem wound matrix, per sq cm (code deleted 01-01-2017)
Q4120	MatriStem burn matrix, per sq cm (code deleted 01-01-2017)
Q4121	Thera Skin, per sq cm
Q4122	DermACELL, per sq cm
Q4123	AlloSkin RT, per sq cm
Q4124	OASIS ultra tri-layer wound matrix, per sq cm
Q4126	MemoDerm, DermaSpan, TranZgraft or IntéguPly, per sq cm
Q4127	Talymed, per sq cm
Q4129	Unite biomatrix, per sq cm (code deleted 01-01-2017)
Q4130	Strattice TM, per sq cm
Q4131	EpiFix per sq cm (code deleted 1/1/19)
Q4132	Grafix Core per sq cm
Q4133	Grafix PRIME, GrafixPL PRIME, Stravix & StravixPL, per sq cm (code revised 1/1/19)
Q4176	Neopatch, per sq cm
Q4177	FlowerAmnioFlo, 0.1cc
Q4178	FlowerAmnioPatch, per sq cm
Q4179	FlowerDerm, per sq cm
Q4180	Revita, per sq cm
Q4181	Amnio Wound, per sq cm
Q4182	TransCyte, per sq cm
Q4183	SURGIGRAFT PER SQ CM (new code 1/1/19)

Q4184	CELLESTA PER SQ CM (new code 1/1/19)
Q4185	CELLESTA FLOWABLE AMNION; PER 0.5 CC (new code 1/1/19)
Q4186	EPIFIX PER SQ CM (new code 1/1/19)
Q4187	EPICORD PER SQ CM (new code 1/1/19)
Q4188	AMNIOARMOR PER SQ CM (new code 1/1/19)
Q4189	ARTACENT AC 1 MG (new code 1/1/19)
Q4190	ARTACENT AC PER SQ CM (new code 1/1/19)
Q4191	RESTORIGIN PER SQ CM (new code 1/1/19)
Q4192	RESTORIGIN 1 CC (new code 1/1/19)
Q4193	COLL-E-DERM PER SQ CM (new code 1/1/19)
Q4194	NOVACHOR PER SQ CM (new code 1/1/19)
Q4195	PURAPLY PER SQ CM (new code 1/1/19)
Q4196	PURAPLY AM PER SQ CM (new code 1/1/19)
Q4197	PURAPLY XT PER SQ CM (new code 1/1/19)
Q4198	GENESIS AMNIOTIC MEMBRANE PER SQ CM (new code 1/1/19)
Q4200	SKINTE PER SQ CM (new code 1/1/19)
Q4201	MATRION PER SQ CM (new code 1/1/19)
Q4202	KEROXX (2.5G/CC) 1CC (new code 1/1/19)
Q4203	DERMA-GIDE PER SQ CM (new code 1/1/19)
Q4204	XWRAP PER SQ CM (new code 1/1/19)
Q4227	AmnioCoreTM, per sq cm (new code 7/1/2020): E/I
Q4228	BioNextPATCH, per sq cm (new code 7/1/2020): E/I
Q4229	Cogenex Amniotic Membrane, per sq cm (new code 7/1/2020): E/I
Q4230	Cogenex Flowable Amnion, per 0.5 cc (new code 7/1/2020): E/I
Q4231	Corplex P, per cc (new code 7/1/2020): E/I
Q4232	Corplex, per sq cm (new code 7/1/2020): E/I
Q4233	SurFactor or NuDyn, per 0.5 cc (new code 7/1/2020): E/I
Q4234	XCellerate, per sq cm (new code 7/1/2020): E/I
Q4235	AMNIOREPAIR or AltiPly, per sq cm (new code 7/1/2020): E/I
Q4236	carePATCH, per sq cm (new code 7/1/2020): E/I

Q4237	Cryo-Cord, per sq cm (new code 7/1/2020): E/I
Q4238	Derm-Maxx, per sq cm (new code 7/1/2020): E/I
Q4239	Amnio-Maxx or Amnio-Maxx Lite, per sq cm (new code 7/1/2020): E/I
Q4240	CoreCyte, for topical use only, per 0.5 cc (new code 7/1/2020): E/I
Q4241	PolyCyte, for topical use only, per 0.5 cc (new code 7/1/2020): E/I
Q4242	AmnioCyte Plus, per 0.5 cc (new code 7/1/2020): E/I
Q4244	Procenta, per 200 mg (new code 7/1/2020): E/I
Q4245	AmnioText, per cc (new code 7/1/2020): E/I
Q4246	CoreText or ProText, per cc (new code 7/1/2020): E/I
Q4247	Amniotext patch, per sq cm (new code 7/1/2020): E/I
Q4248	Dermacyte Amniotic Membrane Allograft, per sq cm
Q4249	AMNIPLY, for topical use only, per sq cm
Q4250	AmnioAmp-MP, per sq cm
Q4254	NovaFix DL, per sq cm
Q4255	REGUaRD, for topical use only, per sq cm
0598T	Noncontact real-time fluorescence wound imaging for bacterial presence, 1st anatomic site (new code 7/1/2020): E/I
0599T	Noncontact real-time fluorescence wound imaging for bacterial presence. Each additional anatomic site (new code 7/1/2020): E/I

Limits

All other uses of bio-engineered skin and soft tissue substitutes are considered experimental or investigational because of lack of scientific literature to support other uses.

Similarly, noncontact real-time fluorescence wound imaging for bacterial presence is considered experimental or investigational.

Background

BREAST RECONSTRUCTION

AlloDerm

Controlled Studies: Preminger and colleagues (2008) evaluated the impact of AlloDerm on expansion rates in immediate tissue expander/implant reconstruction in a retrospective matched cohort study. Forty-five patients had reconstruction with AlloDerm and 45 had

standard reconstruction. Subjects were matched for expander size (+/-100 mL), history of irradiation, and indication for mastectomy. There were no significant differences in initial filling volume, mean number of postoperative expansions, mean rate of postoperative tissue expansion, or in the incidence of postoperative complications. Aesthetic outcomes were not addressed.

Colwell and Breuing (2008) reported on 10 patients who had mastopexy with dermal slings, 5 patients were given AlloDerm and 5 were given autologous tissue. Patients have maintained projection and breast base width after 6 months to 3 years.

AlloDerm has been reported in nipple reconstructive surgery (Garramone and Lam, 2007). This report involves a case series on 30 nipple reconstructive procedures performed at one institution. The authors conclude that use of an AlloDerm graft core is a safe technique for "improving the long-term maintenance of nipple projection."

DIABETIC LOWER EXTREMITY ULCERS

Apligraf

Veves and colleagues (2001) reported on a randomized prospective study on the effectiveness of Graftskin (Apligraf), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers. The study involved 24 centers in the U.S.; 208 patients were randomly assigned to ulcer treatment either with Graftskin (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical debridement and adequate foot off-loading, was provided in both groups. Graftskin 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%) Graftskin-treated patients achieved complete wound healing compared with 36 (38%) in the control group (p=0.0042). The Kaplan-Meier median time to complete closure was 65 days for Graftskin, significantly lower than the 90 days observed in the control group (p=0.0026). The rate of adverse reactions was similar between the 2 groups with the exception of osteomyelitis and lower-limb amputations, both of which were less frequent in the Graftskin group. The authors concluded that application of Graftskin for a maximum of 4 weeks resulted in a higher healing rate when compared with state-of-the-art treatment and was not associated with any significant side effects.

Steinberg and colleagues (2010) reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of non-infected diabetic foot ulcers. The design and patient population of this study were similar to the 208-subject United States study (described above) which led to FDA-approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with a non-infected neuropathic diabetic foot ulcer present for at least 2 weeks were enrolled in these prospective, multicenter, randomized, controlled, open-label studies that compared Apligraf use in conjunction with standard therapy (sharp debridement, standard wound care, and off-loading) against 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 that was significantly longer in the European study (21 months, compared to 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 to 34.3% (46/134) of control subjects (p=0.0005), and Apligraf subjects had a significantly shorter time to complete wound closure (p=0.0004). The authors concluded that both the EU and U.S. studies exhibited superior efficacy and comparable safety for subjects treated with Apligraf compared to control subjects, and the studies provide evidence of the benefit of Apligraf in treating diabetic foot ulcer (DFU).

Kirsner and colleagues (2010) reported on analysis of 2,517 patients with diabetic neuropathic foot ulcers who were treated between 2001 and 2004. The study was a retrospective analysis using a wound-care database; the patients received advanced biological therapy i.e., Apligraf (446 patients), Regranex, or Procuren. In this study, advanced biological therapy was used, on average, within 28 days from the first wound clinic visit and associated with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biological therapy were 31.2% more likely to heal than wounds first treated with topical recombinant growth factor (p<0.001) and 40.0% 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 biological therapy affected the time to healing.

Dermagraft

A pivotal multi-center FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft or control. Over the course of 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 to 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 to 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%).

GraftJacket Regenerative Tissue Matrix

Brigido et al. (2004) reported a small (n=40) randomized pilot study of GraftJacket compared with conventional treatment for chronic non-healing diabetic foot ulcers in 2004. Control patients received conventional therapy with debridement, 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%). All of the grafts incorporated into the host tissue.

Reyzelman et al. (2009) reported an industry-sponsored multicenter randomized study that compared a single application of GraftJacket versus standard of care in 86 patients with diabetic foot ulcers. Offloading was performed using a removable cast walker. Ulcer size at presentation was 3.6 cm2 in the GraftJacket group and 5.1 cm2 in the control group. 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 non-healing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks versus 6.8 weeks for the control group. The authors did not report if this difference was statistically significant. The 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 survivorship analysis for time to complete healing at 12 weeks showed a significantly lower non-healing rate for the study group (30.4%) compared with the control group (53.9%). The authors commented that a single application of GraftJacket, as used in this study, is often sufficient for complete healing. This study is limited by the small study population, differences in ulcer size at baseline, and the difference in the percentage of patients censored in each group. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant. Additional trials with a larger number of subjects are needed to evaluate if GraftJacket Regenerative Tissue Matrix improves health outcomes in this population.

Oasis Wound Matrix

Niezgoda and colleagues (2005) compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix, an acellular wound care product, versus Regranex Gel. This was an industry-sponsored randomized controlled multicenter trial conducted at 9 outpatient wound care clinics and involved 73 patients with at least 1 diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix (n=37) or Regranex Gel (n=36) and a secondary dressing. Wounds were cleansed and debrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks of treatment, 18 (49%) Oasis-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients. Oasis treatment met the non-inferiority 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 a significant improvement in patients with type 2 diabetes (63% vs. 29%). There was also an increased healing of plantar ulcers in the Oasis group (52% vs. 14%). These post-hoc findings are considered hypothesis-generating. Additional study with a larger number of subjects is needed to evaluate the effect of Oasis treatment in comparison with the current standard of care.

PriMatrix
Karr (2011) published a retrospective comparison of PriMatrix (a xenograft fetal bovine dermal collagen matrix) and Apligraf in 40 diabetic foot ulcers. The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. Included were diabetic foot ulcers of 4 weeks' duration, at least 1 sq. cm and depth to subcutaneous tissue, healthy tissue at the ulcer, adequate arterial perfusion to heal, and able to off-load the diabetic ulcer. The products were placed on the wound with clean technique, overlapping the edges of the wound, and secured with sutures or staples. The time to complete healing for PriMatrix was 38 days with 1.5 applications compared to 87 days with 2 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

The ASPS endorsed guidelines from the Wound Healing Society on the treatment of diabetic ulcers in 2006 (Steed). The guidelines state that healthy living skin cells assist in healing diabetic foot ulcers by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed. Guideline #7.2.2 states that living skin equivalents may be of benefit in healing diabetic foot ulcers. (Level I)

EpiFix
Zelen and colleagues (2016) enrolled 100 patients with diabetic lower extremity ulcers in a prospective, randomized, controlled, parallel group, multi-center clinical trial that showed dHACM (EpiFix, MiMedx Group Inc., Marietta, GA) was superior to BSS (Apligraf, Organogenesis, Inc., Canton, MA) and standard wound care (SWC) in achieving complete wound closure within 12 weeks (97%, 73% and 51% with EpiFix, Apligraf and SWC respectively, P = 0.00019 with substantially lower costs per patient).

LOWER EXTREMITY ULCERS DUE TO VENOUS INSUFFICIENCY

Apligraf
Falanga and colleagues (1998) reported a multicenter randomized trial of Apligraf (human skin equivalent). A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or 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 months' follow-up, the percentage of patients healed was increased with Apligraf (63% vs. 49%), and the median time to complete wound closure was reduced (61 vs. 181 days). Treatment with Apligraf was found to be superior to compression therapy in healing larger (>1000 mm2) and deeper ulcers and ulcers of more than 6 months' duration. There were no symptoms or signs of rejection, and the occurrence of adverse events was similar in both groups.

Oasis Wound Matrix

Mostow et al. (2005) reported an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment with Oasis Wound Matrix versus standard of care in 120 patients with chronic ulcers due to venous insufficiency that were not adequately responding to conventional therapy. 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 achieve healing than those in the standard care group. Patients in the standard care group whose wounds did not heal by the 12th week were given the option to cross over to Oasis treatment. None of the healed patients treated with Oasis wound matrix and 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 arterial venous and venous ulcers. Romanelli et al. (2007) in a quasi-randomized study compared the efficacy of 2 extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid). A total of 54 patients with mixed arterial/venous leg ulcers were assigned to the 2 arms based on order of entry into the study; 50 patients completed the study. Patients were followed up twice a week, and the dressings were 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 of 6.4 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 in 23 patients with mixed arterial/venous ulcers and 27 patients with venous ulcers. The study was described as randomized, but the method of randomization was not described. After the 8-week study period, patients were followed up monthly for 6 months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis-treated ulcers at 8 weeks, compared to 65% of the standard of care group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks as compared with 8.3 weeks for the standard of care group. Treatment with Oasis also increased the time to dressing change (5.2 vs. 2.1 days) and the percentage of granulation tissue formed (65% vs. 38%).

PriMatrix

Karr (2011) published a retrospective comparison of PriMatrix and Apligraf in 28 venous stasis ulcers. The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Included were venous stasis ulcers of 4 weeks' duration, at least 1 sq. cm and depth to subcutaneous tissue, healthy tissue at the ulcer, adequate arterial perfusion to heal, and able to tolerate compression therapy. The products were placed on the wound with clean technique, overlapping the edges of the wound, and secured with sutures or staples. The

time to complete healing for PriMatrix was 32 days with 1.3 applications compared to 63 days with 1.7 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current standard of care.

The ASPS endorsed guidelines from the Wound Healing Society on the treatment of venous ulcers in 2006 (Robson). The guidelines state that various skin substitutes or biologically active dressings are emerging that provides temporary wound closure and serve as a source of stimuli (e.g., growth factors) for healing of venous ulcers. Guideline #7b.1 states that there is evidence that a bilayered artificial skin (biologically active dressing), used in conjunction with compression bandaging, increases the chance of healing a venous ulcer compared with compression and a simple dressing (Level I).

DYSTROPHIC EPIDERMOLYSIS BULLOSA

Dermagraft is FDA approved by a Humanitarian Device Exemption (HDE) for the treatment of dystrophic epidermolysis bullosa.

OrCel is approved by 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.

As this is a rare disorder, it is unlikely that there will be randomized controlled trials to evaluate whether Dermagraft or OrCel improve health outcomes for this condition.

BURNS

Epicel

Epicel is FDA-approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a total body surface area of greater than or equal to 30%. It is unlikely that there will be randomized controlled trials (RCTs) to evaluate whether Epicel® will improve health outcomes for this condition. One case series described the treatment of 30 severely burned patients with Epicel® (Carsin 2000). The cultured epithelial autografts were applied to a mean 37% of total body surface area. Epicel® achieved permanent coverage of a mean 26% of total body surface area, an area greater than that covered by conventional autografts (a mean 25%). Survival was 90% in these severely burned patients.

Integra Dermal Regeneration Template

Branski et al. (2007) reported a randomized trial of Integra compared with a standard autograft-allograft technique in 20 children with an average burn size of 73% total body surface area (71% full-thickness burns). 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% total body surface area), mortality (40% vs. 30%), and 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 (12 months and

18-24 months) in the Integra group. No differences were observed between the groups in the time to first reconstructive procedure, cumulative reconstructive procedures required during 2 years, and the 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.

Heimback and colleagues (2003) reported a multicenter (13 U.S. burn care facilities) post approval study involving 222 burn injury patients (36.5% total body surface area, range 1-95%) who were treated with Integra® Dermal Regeneration Template. Within 2 to 3 weeks, the dermal layer regenerated, and a thin epidermal autograft was placed. 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%.

OrCel

There is limited evidence to support the efficacy of OrCel compared to the standard of care for the treatment of split-thickness donor sites. 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. Each patient had 2 designated donor sites that were randomized to receive a single treatment of either OrCel or the 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 non-significant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

TransCyte

Lukish et al. (2001) compared 20 consecutive cases of pediatric burns greater than 7% total body surface area that underwent wound closure with TransCyte with the previous 20 consecutive burn cases greater than 7% total body surface area that received standard therapy. Standard therapy consisted of application of antimicrobial ointments and hydro debridement. Only 1 child in the TransCyte group required autografting (5%), compared with 7 children in the standard therapy group (35%). Children treated with TransCyte had a statistically significant decreased length of stay compared with those receiving standard therapy, 5.9 days versus 13.8 days, respectively.

Amani et al. (2006) compared results from 110 consecutive patients with deep partial-thickness burns who were treated with Transcyte with data from the American Burn Association Patient Registry. Significant differences were found in patients who were treated with dermabrasion and Transcyte compared to the population in the Registry. Patients with 0-19.9% total body surface area burn treated with dermabrasion and Transcyte had length of stay of 6.1 days versus 9.0 days ($p<0.001$). Those with 20-39.9% total body surface area burn had length of stay of 17.5 days versus 25.5 days. Patients who had 40-59.9% total body surface area burn had length of stay of 31 versus 44.6 days. The authors found this new method of managing patients

with partial-thickness burns to be more efficacious and to significantly reduce length of stay compared to traditional management.

SURGICAL REPAIR OF HERNIAS

AlloDerm

Gupta et al. (2006) compared the efficacy and complications associated with the use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair in 2006. 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 7-10 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 hernia recurrences (24%). Fifteen of the AlloDerm patients (45%) developed a diastasis or bulging at the repair site. Seroma formation was only a problem in 2 patients.

Espinosa-de-los-Monteros and colleagues (2007) retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases. 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.

The limited evidence available at this time does not support the use of AlloDerm in hernia repair.

ORAL SURGERY

AlloDerm

Novaes and de Barros (2008) described 3 randomized trials from their research group that examined use of acellular dermal matrix in root coverage therapy and alveolar ridge augmentation. Two trials used acellular dermal matrix in both the study and control groups and are not described here. A third trial compared acellular dermal matrix with sub epithelial connective tissue graft in 30 gingival recessions (9 patients). At 6 months post-surgery, the acellular dermal matrix showed recession reduction of 1.83 mm while sub epithelial connective tissue graft showed recession reduction of 2.10 mm; these were not significantly different.

A nonrandomized cohort study compared AlloDerm with the gold standard of split thickness skin grafts in 34 patients who underwent oral cavity reconstruction following surgical removal of tumors (Girod 2009). Patients were enrolled after surgical treatment for evaluation at a tertiary care center and divided into 2 cohorts according to the reconstruction method used, which was based on surgeon preference. Twenty-two patients had been treated with AlloDerm, and 12 had been treated with split thickness skin grafts. The location of the grafts (AlloDerm vs. autograft) were on the tongue (54% vs. 25%), floor of mouth (9% vs. 50%), tongue and floor of

mouth (23% vs. 8%), buccal (9% vs. 0%), or other (5% vs. 17%). More patients in the AlloDerm group were treated with radiation therapy (45% vs. 17%), and the graft failure rate was higher (14% vs. 0%). Radiation therapy had a significantly negative impact for both groups. Histology on a subset of the patients showed increased inflammation, fibrosis, and elastic fibers with split thickness skin grafts. Functional status and quality of life were generally similar in the 2 groups. Interpretation of these results is limited by the differences between the groups at baseline.

Jamal et al. (2010) performed a prospective, randomized trial comparing primary and AlloDerm closure of buccal mucosal sites used to harvest graft for substitution urethroplasty. AlloDerm was an effective means of closing the harvest site, but offered no significant advantages when compared with primary closure.

TYMPANOPLASTY

Vos et al. (2005) reported a retrospective non-randomized comparison of AlloDerm versus native tissue grafts for type I tympanoplasty. Included in the study were 108 patients (25 AlloDerm, 53 fascia reconstruction, and 30 fascia plus cartilage reconstruction) treated between 2001 and 2004. One surgeon had performed 96% of the AlloDerm tympanoplasties. Operative time was reduced in the AlloDerm group (82 minutes for AlloDerm, 114 minutes for fascial cases, and 140 minutes for fascia plus cartilage). There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia). There was no significant difference in hearing between the groups at follow-up (time not specified). Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure.

TRAUMATIC WOUNDS

Use of Integra Dermal Regeneration Template has been reported in small case series (<20 patients) for the treatment of severe wounds with exposed bone, joint and/or tendon (Helgeson, 2007, Taras 2010, Weigert 2011). No controlled trials were identified.

OTHER USES

In 2006, the American Society of Plastic Surgeons (ASPS) endorsed guidelines from the Wound Healing Society on the treatment of arterial insufficiency ulcers (Hopf, 2006). The Guidelines state that extracellular matrix replacement therapy appears to be promising for mixed ulcers and may have a role as an adjuvant agent in arterial ulcers, but further study is required. (Level IIIC) “Despite the existence of animal studies, case series, and a small number of random control trials to support biomaterial use for pressure ulcers, diabetic ulcers, and venous ulcers; there are no studies specifically on arterial ulcers. Therefore, studies in arterial ulcers must be conducted before the recommendation can be made.”

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Addendums:

1) **Effective 05/01/2017:** Added EpiFix and DermACELL for diabetic lower extremity ulcers and DermACELL for breast reconstruction.
2) **Effective 02/01/2018:** Added AlloDerm indication for prevention of Frey syndrome with nerve-sparing parotidectomy.
3) **Effective 03/06/2018:** Added new 2018 codes
4) **Effective 09/01/2018:** Added Grafix for diabetic lower extremity ulcers.
5) **Effective 01/01/2019:** *2019 Code Updates.* Deleted HCPCS code Q4131 and updated code description for Q4133. Also added the following new HCPCS codes to policy: Q4183 – Q4204. Also, CPT codes updated and aligned with BI383.
6) **Effective 07/01/2020:** New codes added (C1849, Q4227 – Q4249, 0598T and 0599T) as experimental.
7) **Effective 10/01/2020:** New codes added (Q4249, Q4250, Q4254, Q4255) as non-covered.
8) **Effective 01/01/2021:** Updated codes 19357, 19361, 19364, 19367, 19368, 19369, 19370, 19371 & 19380 as well as updated deleted codes that were eff 01-01-2017: Q4119, Q4120 & Q4129.

Application to Products

This policy applies to all health plans administered by QualChoice, both those insured by QualChoice and those that are self-funded by the sponsoring employer, unless there is indication in this policy otherwise or a stated exclusion in your medical plan booklet. Consult the individual plan sponsor Summary Plan Description (SPD) for self-insured plans or the specific Evidence of Coverage (EOC) for those plans insured by QualChoice. In the event of a discrepancy between this policy and a self-insured customer's SPD or the specific QualChoice EOC, the SPD or EOC, as applicable, will prevail. State and federal mandates will be followed as they apply.

Changes: QualChoice reserves the right to alter, amend, change or supplement benefit interpretations as needed.