A Review of Bioactive Materials and Chronic Wounds

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An increasing number of bioactive materials are indicated for the treatment of chronic lower extremity ulcers. They are promising adjuncts to standard therapy. When used in conjunction with standard therapy for venous leg ulcers and diabetic foot ulcers, bioactive materials may increase the likelihood and rate of healing. This review compares commonly available bioactive materials indicated for chronic wound healing and provides an overview of the relevant Current Procedural Terminology *(CPT) and Healthcare Common Procedure Coding System (HCPCS) codes for these products.*

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Lower extremity ulcers are challenging to treat; however, bioactive materials are promising adjuncts to standard therapy. In this article, we review the treatment of chronic venous and diabetic ulcers with representative bioactive materials and the costs associated with these therapies.

Venous Ulcers

Of the 2.5 million cases of leg ulcers in the United States, up to 80%[1] are estimated to be venous ulcers, and the number of affected individuals is expected to increase with the growth of the older population. Venous ulcers are caused by chronic venous insufficiency and hypertension due to venous valve incompetence and/or deep venous obstruction. Chronic nonhealing venous ulcers present a substantial challenge to physicians, as an estimated 50% of patients have ulcers that persist for more than 1 year.[2,3] Patients with chronic venous ulcers experience pain, decreased productivity, and lost work days,[4] as well as decreased quality of life.[5] Venous ulcers are healed primarily by compression dressings, but ablation of incompetent perforating vessels and biological dressings may be adjunct therapeutic interventions.

Diabetic Ulcers

Of the 17.4 million individuals with diabetes in the United States,[6] 15% to 20% eventually develop a chronic wound.[7] As with venous ulcers, the prevalence of diabetic ulcers is expected to increase in the next several years because of the growing aging population as well as the obesity epidemic, which has an associated increase in the prevalence of type 2 diabetes mellitus. Anesthesia allows repeated insensible trauma to tissues, especially at sites of pressure. In addition, reduced resistance to infection and comorbid venous and arterial insufficiency may further contribute to this process. A substantial cause and consequence of morbidity for many diabetic patients with nonhealing ulcers is lower limb amputation. An estimated 92,000 amputations were performed on diabetic patients in 1999,[8] and it is believed that approximately 27% of diabetic foot ulcers are associated with amputation.[9] Diabetic ulcers are healed primarily through off-loading pressure.

Arterial Ulcers

Arterial, or ischemic, ulcers most commonly occur in patients with peripheral artery disease or may be caused by an atheroembolism; both mechanisms lead to decreased perfusion of distal tissues resulting in ischemia and ulceration. Although arterial insufficiency may complicate both venous and diabetic ulcers, in one epidemiologic study of 259 patients with lower extremity ulcers, 10% of patients had peripheral artery disease as the only identifiable etiology.[10] There are limited and inconclusive data regarding the use of bioactive materials as adjunct therapy for arterial ulcers; however, differentiation must

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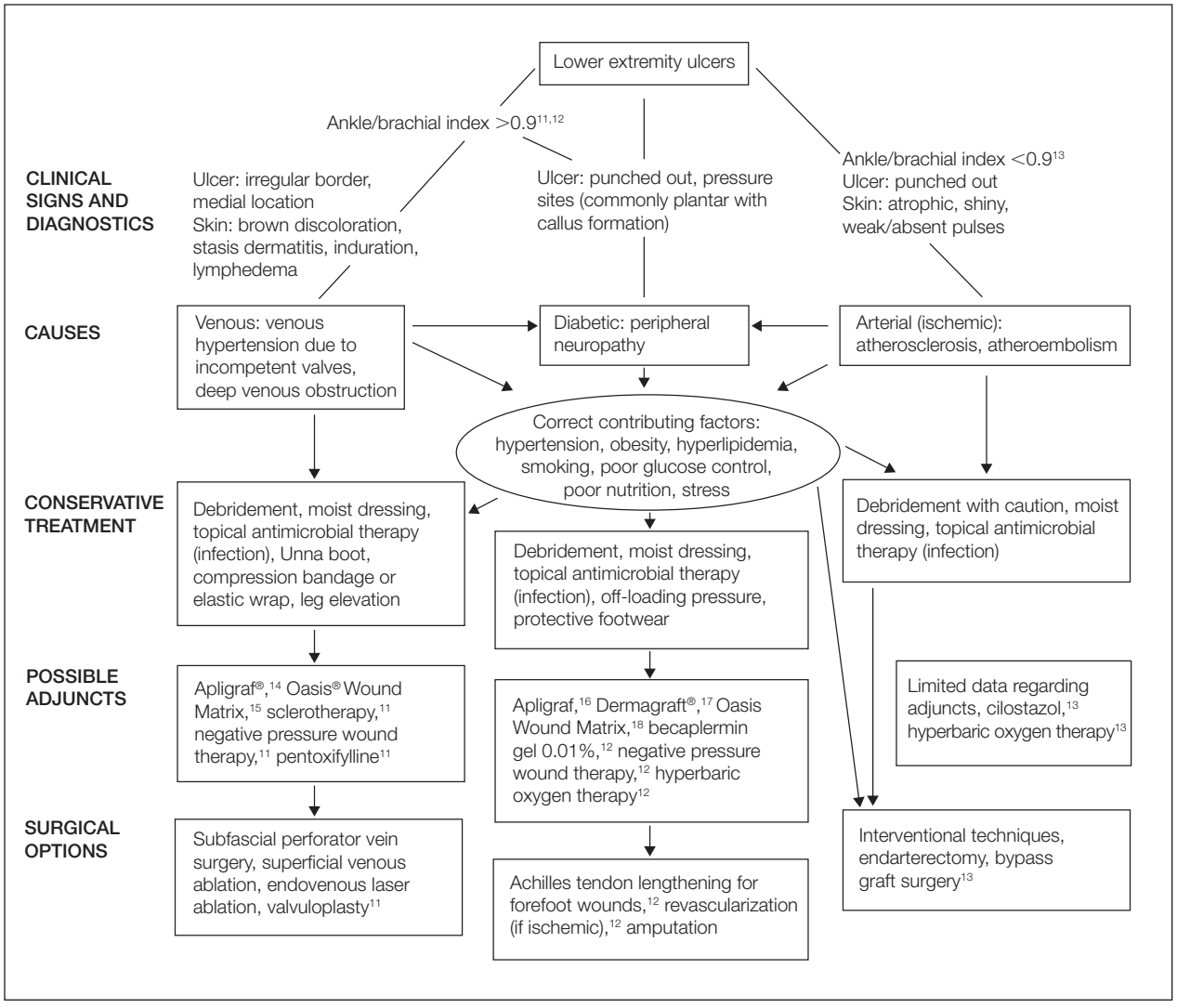

Characteristics and management of lower extremity ulcers. Only the 3 most common types of lower extremity ulcers are included.

be made early because first-line therapy for an arterial ulcer is surgical intervention to reestablish arterial perfusion, while conservative and adjunct therapies are initially used for venous and diabetic ulcers. The Figure outlines the characteristics and management of the 3 most common types of lower extremity ulcers.

Traditional Therapy

Treatment of nonhealing venous and diabetic ulcers is expensive because of frequent hospitalizations and office visits, use of home healthcare, costs of wound care products, and costs associated with common complications (eg, wound infection, sepsis, lower limb amputation). One retrospective study determined the average cost per month per nonhealing venous ulcer to be approximately $2400,[19] and another study of the economic impact of diabetic foot ulcers found the attributable cost of a new ulcer in a middle-aged man to be almost $28,000 in the 2 years immediately following diagnosis.[20] In addition, the US healthcare expenditure is estimated to be as much as $1 billion annually for chronic wounds.[1]

The standard of care for venous ulcers typically includes debridement and compression therapy involving an antimicrobial product if there is clinical evidence of infection or colonization, moist gauze, tape, and a compression bandage or elastic wrap.[21] Compression therapy reduces venous pressure in the lower extremity, thereby controlling edema and improving venous return. Unfortunately, 30% to 50% of all venous ulcers fail to respond to this therapy.[22]

For diabetic ulcers, the standard of care has been debridement, application of a moist dressing, and off-loading pressure from the wounded foot.[23] Of the 370 diabetic patients referred to a specialist

center and treated with standard therapy for at least 6 months in one study, 32.7% (121/370) never became ulcer free and 15% (56/370) remained unhealed from their initial ulcers. Most notably, only 35.9% (133/370) of the patients in this study healed completely without recurrence or amputation.[24]

Historically, surgical intervention has been the next step in treating ulcers that do not respond to these initial therapies. In venous ulcers, the venous insufficiency itself is corrected or the wound site is targeted for repair by skin grafting.[21,25] Diabetic ulcers also are amenable to surgical repair by autograft and vascular intervention techniques to restore blood flow in the setting of concomitant ischemia.[8] These procedures are costly because they often require hospitalization and anesthesia. The autograft creates a new donor wound site that also may be painful, difficult to heal, and susceptible to secondary infection, which are major downfalls of this therapy.[25] Certain bioactive materials have been found to be equally effective to autograft for the treatment of venous ulcers.[26,27] Studies have not been conducted to directly compare bioactive materials to autograft for diabetic ulcers, but studies comparing these products with standard nonsurgical therapy alone show promising results that are discussed in detail below. Bioactive materials serve as an effective adjunct to standard compression therapy and dressings as well as a suitable alternative to relatively expensive surgical procedures.

Bioactive Materials

For the purpose of this article, we define *bioactive material* as a substance derived from living tissue that maintains conformational integrity and elicits a specific biological response from live human tissue at the application site. Several bioactive materials have been demonstrated in randomized controlled clinical trials to increase the likelihood of healing and expedite healing time in patients with venous or diabetic ulcers, or both. Living bilayered products, acellular matrix, and dermal substitute are indicated for use as adjuncts to standard therapy. Clinical characteristics, cost, and clinical study data from a representative member of each type of bioactive material are discussed below. Table 1 lists 3 commonly used bioactive materials approved by the US Food and Drug Administration (FDA) for the treatment of chronic venous and diabetic ulcers.

Living Bilayered Products—A living bilayered skin substitute, Apligraf® is indicated as an adjunct therapy for both chronic venous (>1 month's duration) and diabetic (>3 weeks' duration) ulcers. Living bilayered skin substitutes are created using cells from neonatal foreskin tissue and have been determined to produce the cytokines and growth factors that are present during healing in healthy skin.[33] Chronic wound sites are deficient in certain growth factors and receptors,[34,35] and although growth factors may be present, they could be bound by leaked macromolecules, prohibiting their healing function.[36] Therefore, the living bilayered skin substitute may deliver these necessary materials to the wound site. For product safety, screening for infectious agents is performed on maternal blood prepartum and postpartum and on the harvested cells. Apligraf, which has been studied in many clinical trials, obtained FDA approval in 1998 for venous leg ulcers and in 2000 for diabetic ulcers and has since been used in more than 150,000 patients.[37] Disadvantages of living bilayered products include the short 10-day shelf life, fragile handling, and expense.

Acellular Matrix—An acellular porcine small intestinal submucosa product, Oasis® Wound Matrix is a bioactive material of particular interest because of its relatively low cost, effectiveness, and novelty as an adjunct in the treatment of both venous and diabetic ulcers. Small intestinal submucosa has been used for years in various surgical procedures, including reconstruction of urethral slings and repair of inguinal hernias. Clinical trials have found Oasis Wound Matrix to be effective in increasing healing rate and decreasing healing time in patients with nonhealing venous ulcers.[15] The submucosa is a naturally occurring, 3-dimensional, collagenous scaffold that contains growth factors, cytokines, and cell adhesion molecules that seem to create conditions conducive to wound repair.[38] The product is unlike purified collagen-derived products in that it has been determined to retain important matrix components such as glycosaminoglycans[29] and glycoproteins.[30] Cells from adjacent tissues invade the product, allowing capillary growth that increases delivery of nutrients and reconstruction of the damaged site with host tissue.[39] Ultimately, the explanation for this product's actions may be related to the repair or replacement of an impaired extracellular matrix that has resulted in a nonhealing or slow-healing wound. Other bioactive materials have had similar success rates (Table 1); however, Oasis Wound Matrix remains advantageous because of its 24-month shelf life, ability to be stored at room temperature, and low cost.[40]

Dermal Substitute—Human fibroblast-derived dermis, commercially available as Dermagraft®, is FDA approved for the treatment of diabetic foot ulcers persisting more than 6 weeks. This product has not been approved for venous ulcers. Dermagraft is available in a cryopreserved form allowing a long shelf life. Dermagraft costs slightly more than

Table 1.

FDA-Approved Bioactive Materials for Chronic Wounds

Product	Description	FDA Indication	Clinical Trials	Cost Evaluation
Apligraf®	Living bilayered skin substitute consisting of keratinocytes and fibroblasts derived from neonatal foreskin; fibroblasts combined with type I collagen form a matrix; keratinocytes cultured on surface	Partial- and full-thickness venous ulcers persisting >1 mo; full-thickness neuropathic diabetic foot ulcers persisting >3 wk	Venous ulcers (N=120)[14]: Apligraf + compression therapy was significantly more effective than compression therapy alone in percentage of participants healed at 12 weeks (40% vs 13%, respectively; *P*<.001) and time to healing (181 days vs not attained, respectively; *P*<.005); Apligraf + compression therapy was >60% more effective in achieving wound closure; maximum applications per participant during the study, 5 Diabetic ulcers (N=208)[16]: Apligraf + standard dressing was significantly more effective than saline-moistened gauze dressing alone in percentage of participants healed at 12 weeks (56% vs 38%, respectively; *P*=.0042) and time to healing (65 vs 90 days, respectively; *P*=.0026); patients had a 1.59-fold better chance for closure per unit time; average number of applications, 3.9	Annual cost of venous ulcer treatment per patient using Apligraf was ≈$20,000 vs ≈$27,000 using compression therapy[28]
Oasis® Wound Matrix	Porcine SIS; acellular 3-dimensional matrix consisting of collagens and other extracellular matrix proteins[29,30]	Partial and full-thickness wounds, venous and diabetic ulcers, and other wounds	Venous ulcers (N=120)[15]: SIS + compression therapy was significantly more effective than compression therapy alone in percentage of participants healed at 12 weeks (55% vs 34%, respectively; *P*=.0196) and time to healing (*P*=.0226); SIS participants were 2.3 times more likely to heal; average number of applications, 8	

Product	Description	FDA Indication	Clinical Trials	Cost Evaluation
Oasis® Wound Matrix (continued)			Diabetic ulcers (N=73)[18,a]: SIS + standard dressing was statistically similar in healing rates to becaplermin gel 0.01%[b] + standard dressing (49% vs 28%, respectively; *P*=.055); average number of applications, 10	Average cost of diabetic ulcer treatment per patient was $250 with SIS and $1070 with becaplermin gel 0.01% (30 g)[18]
Dermagraft®	Living dermal substitute; fibroblasts derived from human neonatal fibroblasts are seeded onto a biodegradable polyglactin mesh	Full-thickness diabetic foot ulcers persisting >6 wk	Venous ulcers (not an FDA-approved indication) (N=18)[31]: Dermagraft + compression therapy was significantly more effective than compression therapy alone in reducing ulcer area (*P*=.001); no significant difference in percentage of participants healed at 12 weeks (50% vs 12.5%, respectively; *P*=.15); number of applications, 4	
			Diabetic ulcers (N=314)[17]: Dermagraft + standard dressing was significantly more effective than dressing alone in percentage of participants healed at 12 weeks (30% vs 18%, respectively; *P*=.023) and time to healing (*P*=.04); participants had a 1.6- to 1.7-fold better chance of healing at any time during the study; maximum applications per participant during the study, 7	Annual cost of diabetic ulcer treatment per patient using Dermagraft equaled cost of standard therapy alone ($17,000); annual cost per healed ulcer using Dermagraft was $17,800 vs $24,400 for standard therapy alone[32]

Abbreviations: FDA, US Food and Drug Administration; SIS, small intestinal submucosa.

[a]There is no published study comparing SIS to standard care only for diabetic ulcers.

[b]The investigators chose becaplermin gel 0.01% as a control because "it is one of the few wound care products on the market that had an indication for increasing the incidence of complete healing of diabetic ulcers."[18]

Apligraf per square centimeter and is more than 8 times more expensive than Oasis Wound Matrix for an equivalent-sized piece. Although Dermagraft is FDA approved only for the treatment of diabetic foot ulcers, a pilot study of 18 participants that investigated the efficacy of the product as an adjunct to standard care in treating venous ulcers did not show a significant difference in the percentage of participants healed, but it did show an increased reduction of ulcer area ($P=.001$).[31]

Current Procedural Terminology Codes

Use of bioactive materials in clinical care requires knowledge of the relevant *Current Procedural Terminology* (CPT) codes created by the American Medical Association and the Healthcare Common Procedure Coding System (HCPCS) codes that the Centers for Medicare and Medicaid Services has assigned to the products. Table 2 reviews the relevant CPT and HCPCS codes, the 2010 national average Medicare payment rates for office-based and facility-based wound care departments, and the global periods that pertain to Medicare payments for physicians. Physicians and other providers must confirm or clarify coding and coverage from their respective payers because each payer may have a different Local Coverage Determination. Physicians and providers are responsible for the accurate documentation of patient conditions and the reporting of procedures and products in accordance with particular payer requirements.

Comment

The objective of this article is to review the efficacy and cost of selected bioactive materials available to treat chronic wounds. Studies have shown that Apligraf, Oasis Wound Matrix, and Dermagraft may increase the likelihood and rate of healing when used as indicated compared with standard therapy alone. In addition, using a bioactive material to aid in healing of a chronic ulcer may actually be more cost-effective than other therapeutic interventions, despite the high cost of some products mentioned.

Managing a patient with chronic ulcers is often a matter of control rather than cure because the patient's underlying disease (ie, vascular insufficiency, diabetes mellitus) predisposes wounds that will never close, related to physiology as well as compliance, cost, and psychosocial issues. Therefore, studies investigating the long-term cost of managing chronic ulcers are useful evaluations of the financial burdens of chronic ulcers and suggest economic advantages of adjunctive therapy. One study reported that the annual cost of managing a patient's

Table 2.

Overview of 2010 CPT and HCPCS Codes for Bioactive Material Procedures and Products[41-43]

Product	Skin Replacement Surgery and Skin Substitute CPT Codes	National Average RBRVS Office-Based Fee	National Average RBRVS Facility-Based Fee	National APC Payment Rate	HCPCS Codes	Average Sales Price 2010 Second Quarter
Apligraf®	15340	$292.65	$252.59	$212.38	Q4101	$32.71/cm^2
	15341	$43.30	$25.62	$212.38	Q4101	$32.71/cm^2
Dermagraft®	15365	$320.79	$278.21	$212.38	Q4106	$40.10/cm^2
	15366	$79.03	$72.53	$212.38	Q4106	$40.10/cm^2
Oasis® Wound Matrix	15430	$496.88	$478.84	$299.19	Q4102	$4.62/cm^2
	15431	Carrier priced	Carrier priced	$299.19	Q4102	$4.62/cm^2

Abbreviations: CPT, *Current Procedural Terminology;* HCPCS, Healthcare Common Procedure Coding System; RBRVS, resource-based relative value scale; APC, Ambulatory Payment Classification.

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chronic venous ulcers was approximately $7000 less with Apligraf compared to standard therapy alone.[28] This lower expense may be attributed to the patient healing more quickly and therefore requiring less treatment (ie, fewer services and products purchased). Furthermore, Oasis Wound Matrix has been shown to be similarly effective in healing venous ulcers, is less expensive than Apligraf, and would therefore likely result in a similar economic advantage over standard care. The same holds true for diabetic ulcers. The annual cost per patient using Dermagraft as an adjunct to standard therapy is about the same as managing a patient's chronic diabetic ulcers with standard therapy[32]; however, use of the adjunct therapy results in more probable and more rapid healing. In addition, Apligraf and Oasis Wound Matrix have been shown in clinical trials to perform similarly to Dermagraft, which was the most expensive bioactive material per square centimeter in 2010.[16-18]

Oasis Wound Matrix stands out as the least expensive, effective bioactive material currently available. However, comparing the total cost of treating a chronic wound with Apligraf, Oasis Wound Matrix, or Dermagraft is not possible because some studies report average number of applications of product and others report maximum applications of product allowed over the study duration (Table 1). Therefore, research that takes into account product cost as well as the number of applications of product required to achieve healing would allow more accurate determination of the total cost of care with each product.

Because of the substantial economic burden of chronic wounds on the healthcare system, financial expense is a major consideration in this review. Aside from healthcare dollars paid by Medicare, Medicaid, and private health insurance providers, patients often are forced to pay out of pocket for part or all of the services provided because of high co-pays or lack of insurance. Therefore, the physician must be informed on all aspects of available products and treatment modalities so that the best option may be selected for a particular patient.

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REFERENCES

1. Phillips TJ, Dover JS. Leg ulcers. *J Am Acad Dermatol*. 1991;25(6, pt 1):965-987.
2. Callam MJ, Harper DR, Dale JJ, et al. Chronic ulcer of the leg: clinical history. *Br Med J (Clin Res Ed)*. 1987;294:1389-1391.
3. Cornwall JV, Doré CJ, Lewis JD. Leg ulcers: epidemiology and aetiology. *Br J Surg*. 1986;73:693-696.
4. Phillips T, Stanton B, Provan A, et al. A study of the impact of leg ulcers on quality of life: financial, social and psychologic implications. *J Am Acad Dermatol*. 1994;31:49-53.
5. Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. *Lancet*. 2004;363:1854-1859.
6. National surveillance data: number (in millions) of civilian/noninstitutionalized persons with diagnosed diabetes, United States, 1980-2007. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm. Updated July 23, 2009. Accessed April 2, 2010.
7. Reiber GE, Boyko EJ, Smith DG. Lower extremity foot ulcers and amputations in diabetics. In: Harris MI, Cowie C, Stern MP, eds. *Diabetes in America*. 2nd ed. Bethesda, MD: NIH Publications No. 95-1468; 1995:409-428.
8. Bloomgarden ZT. American Diabetes Association 60th Scientific Sessions, 2000: the diabetic foot. *Diabetes Care*. 2001;24:946-951.
9. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. the contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care*. 1998;21:855-859.
10. Baker SR, Stacey MC, Singh G, et al. Aetiology of chronic leg ulcers. *Eur J Vasc Surg*. 1992;6:245-251.
11. Robson MC, Cooper DM, Aslam R, et al. Guidelines for the treatment of venous ulcers. *Wound Repair Regen*. 2006;14:649-662.
12. Steed DL, Attinger C, Colaizzi T, et al. Guidelines for the treatment of diabetic ulcers. *Wound Repair Regen*. 2006;14:680-692.
13. Hopf HW, Ueno C, Aslam R, et al. Guidelines for the treatment of arterial insufficiency ulcers. *Wound Repair Regen*. 2006;14:693-710.
14. Falanga V, Sabolinski M. A bilayered living skin construct (APLIGRAF) accelerates complete closure of hard-to-heal venous ulcers. *Wound Repair Regen*. 1999;7:201-207.
15. Mostow EN, Haraway GD, Dalsing M, et al; OASIS Venous Ulcer Study Group. Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. *J Vasc Surg*. 2005;41:837-843.
16. Veves A, Falanga V, Armstrong DG, et al; Apligraf Diabetic Foot Ulcer Study. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care*. 2001;24:290-295.
17. Marston WA, Hanft J, Norwood P, et al; Dermagraft Diabetic Foot Ulcer Study Group. The efficacy and safety of Dermagraft in improving the healing of chronic

diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care*. 2003;26:1701-1705.
18. Niezgoda JA, Van Gils CC, Frykberg RG, et al. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care*. 2005;18(5, pt 1):258-266.
19. Olin JW, Beusterien KM, Childs MB, et al. Medical costs of treating venous stasis ulcers: evidence from a retrospective cohort study. *Vasc Med*. 1999;4:1-7.
20. Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care*. 1999;22:382-387.
21. Wipke-Tevis DD, Sae-Sia W. Management of vascular leg ulcers. *Adv Skin Wound Care*. 2005;18:437-445.
22. Kantor J, Margolis DJ. A multicentre study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. *Br J Dermatol*. 2000;142:960-964.
23. American Diabetes Association. Consensus Development Conference on Diabetic Foot Wound Care: 7-8 April 1999, Boston, Massachusetts. *Diabetes Care*. 1999;22:1354-1360.
24. Pound N, Chipchase S, Treece K, et al. Ulcer-free survival following management of foot ulcers in diabetes. *Diabet Med*. 2005;22:1306-1309.
25. Phillips TJ. Successful methods of treating leg ulcers. the tried and true, plus the novel and new. *Postgrad Med*. 1999;105:159-161, 165-166, 173-174 passim.
26. Jones JE, Nelson EA. Skin grafting for venous leg ulcers. *Cochrane Database Syst Rev*. 2005;(1):CD001737.
27. Muhart M, McFalls S, Kirsner RS, et al. Behavior of tissue-engineered skin: a comparison of a living skin equivalent, autograft, and occlusive dressing in human donor sites. *Arch Dermatol*. 1999;135:913-918.
28. Schonfeld WH, Villa KF, Fastenau JM, et al. An economic assessment of Apligraf (Graftskin) for the treatment of hard-to-heal venous leg ulcers. *Wound Repair Regen*. 2000;8:251-257.
29. Hodde JP, Badylak SF, Brightman AO, et al. Glycosaminoglycan content of small intestinal submucosa: a bioscaffold for tissue replacement. *Tissue Eng*. 1996;2:209-217.
30. McPherson TB, Badylak SF. Characterization of fibronectin derived from porcine small intestinal submucosa. *Tissue Eng*. 1998;4:75-83.
31. Omar AA, Mavor AI, Jones AM, et al. Treatment of venous leg ulcers with Dermagraft. *Eur J Vasc Endovasc Surg*. 2004;27:666-672.
32. Sustainability report 2003. Smith & Nephew Web site. http://www.global.smith-nephew.com/cps/rde/xbcr/smithnephewls_master/sustainability2003.pdf. Updated April 28, 2003. Accessed August 3, 2006.
33. Eaglstein WH, Iriondo M, Laszlo K. A composite skin substitute (graftskin) for surgical wounds. a clinical experience. *Dermatol Surg*. 1995;21:839-843.
34. Cooper DM, Yu EZ, Hennessey P, et al. Determination of endogenous cytokines in chronic wounds. *Ann Surg*. 1994;219:688-691, discussion 691-692.
35. Cowin AJ, Hatzirodos N, Holding CA, et al. Effect of healing on the expression of transforming growth factor beta(s) and their receptors in chronic venous leg ulcers. *J Invest Dermatol*. 2001;117:1282-1289.
36. Falanga V, Eaglstein WH. The "trap" hypothesis of venous ulceration. *Lancet*. 1993;341:1006-1008.
37. What is Apligraf? safety considerations. Apligraf Web site. http://www.apligraf.com/professional/what_is_apligraf/safety_information/index.html. Accessed April 5, 2010.
38. Bello YM, Falabella AF, Eaglstein WH. Tissue-engineered skin: current status in wound healing. *Am J Clin Dermatol*. 2001;2:305-313.
39. Brown-Etris M, Cutshall WD, Hiles MC. A new biomaterial derived from small intestine submucosa and developed into a wound matrix device. *Wounds*. 2002;14:150-166.
40. About Oasis® Wound Matrix. http://www.oasiswoundmatrix.com/about. Accessed April 5, 2010.
41. Physician fee schedule look-up. Centers for Medicare & Medicaid Services Web site. http://www.cms.gov/PfsLookup/. Updated December 16, 2009. Accessed April 14, 2010.
42. Hospital outpatient PPS: addendum A and addendum B updates. Centers for Medicare & Medicaid Services Web site. http://www.cms.gov/HospitalOutpatientPPS/AU/list.asp#TopOfPage. Updated April 20, 2010. Accessed April 22, 2010.
43. Medicare Part B drug average sales price: manufacturer reporting of average sales price data. Centers for Medicare & Medicaid Services Web site. http://www.cms.gov/McrPartBDrugAvgSalesPrice/01a19_2010aspfiles.asp#TopOfPage. Updated April 1, 2010. Accessed April 22, 2010.