

An Evaluation of Healing Metrics Associated With Commonly Used Advanced Wound Care Products For the Treatment of Chronic Diabetic Foot Ulcers

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ABSTRACT

Purpose: As rates of diabetes escalate worldwide, diabetic foot ulcers are an increasingly significant public health problem. Advanced wound therapies that promote rapid and complete healing, thus reducing the risk for infection and amputation, can substantially improve quality of life while decreasing financial burdens to the individual and health care system. Our purpose is to compare standardized healing metrics in patients with diabetic foot ulcers treated with three widely used advanced wound-healing products.

Design: Retrospective analysis of data collected and reported in published randomized controlled trials, physician product prescribing in-

formation, and premarket approval summary documents from the U.S. Food and Drug Administration.

Methodology: Rates of complete wound closure within 12 weeks, time to healing, number of graft applications to wound closure, durability of healed wounds, and safety were examined for patients with diabetic ulcers treated with Apligraf, Dermagraft, or EpiFix.

Results: Complete wound closure within 12 weeks of treatment initiation occurred in 56%, 30%, and 92% of Apligraf-, Dermagraft-, and EpiFix-treated ulcers, respectively. EpiFix-treated ulcers had the shortest time to healing (median 14 days) and least amount of graft material used (14 cm²) versus comparative products. Rate of ulcer recurrence was 5.9% for Apligraf (after 6 months), 18.8% for Dermagraft (after 8 months), and 5.6% for EpiFix (after 9–12 months).

Conclusion: Although prospective comparative effectiveness trials are needed, the differences recorded suggest EpiFix results in the most rapid improvement and resolution of diabetic foot ulcers.

Key words: advanced wound care; chronic wounds; diabetic foot ulcers

INTRODUCTION

Chronic wounds are defined as those that fail to proceed through an orderly and timely reparative process, which results in anatomic and functional integrity of an injured site (Lazarus 1994). Chronic wounds create a challenging cellular environment characterized by excessive proteases, increased cellular senescence,

and increased bacterial infiltration resulting in a disordered and uncoordinated process of healing. Diabetic foot ulcers, venous leg ulcers, and pressure ulcers are the most common types of chronic wounds, but any time there is a breakdown in the protective function of the skin, by whatever cause, there is a risk for chronicity. Almost 6.5 million people the United States are affected by chronic wounds (Crovetto 2004, Sen 2009). The economic impact is substantial, as more than \$25 billion is spent annually on the treatment of these chronic wounds (Brem 2007, Sen 2009). The cost of treatment for chronic diabetic foot ulcers accounts for one third to one half of this amount, at \$9 billion to \$13 billion annually (Rice 2014). In addition to financial burdens, ulcer-associated personal and societal quality-of-life issues also affect patients with diabetic ulcers (Evans 2005). With an aging population and the sharp rise in the incidence of diabetes and obesity in the United States, the number of chronic wounds and corresponding costs will continue to escalate rapidly.

Approximately one quarter of people with diabetes will develop a foot ulcer over their lifetime (Boulton 2008). Even if a foot ulcer heals, the rate of recurrence is greater than 50% after 3 years (Boulton 2005). Underlying conditions such as peripheral vascular disease, neuropathy, and poor blood glucose control contribute to slow healing rates and recurrence of diabetic ulcers, which in turn increase the risk for wound chronicity, infection, and amputation. Increased

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comorbidity and mortality associated with these wounds are associated with infection, cellulitis, and osteomyelitis. In addition, their presence often suggests important contributing comorbidities, such as peripheral vascular disease, cerebrovascular disease, and renal disease (Rice 2014). More than half of patients have ulcers that become infected, often with osteomyelitis, and up to 20% require some form of amputation (Wu 2005). After new-onset diabetic ulceration, 5-year mortality rates between 43% and 55% have been reported, approaching 74% in patients with lower-extremity amputation (Robbins 2008). These rates are higher than those for several types of cancer, including prostate, breast, colon, and Hodgkin's disease (Robbins 2008). Diabetic foot ulcers precede 85% of lower-extremity amputations, and it is estimated that 49% to 85% of these amputations are preventable (Driver 2008). Diabetes-related amputations cost the health care system approximately \$3 billion per year (\$38,077 per amputation procedure) (Shearer 2003, Gordoio 2003). Underscoring the need for rapid healing, it is reported that ulcer duration of more than 30 days is independently associated with a 4.7-fold increase in infection, and that an infected foot ulcer increases the risk of hospitalization by nearly 56 times and risk for amputation by nearly 155 times (Lavery 2006).

Many diabetic foot ulcers will not heal with conventional therapy. The Wound Healing Society guidelines recommend consideration of advanced wound therapies if a diabetic ulcer does not reduce in size by 40% or more after 4 weeks of standard therapy (Steed 2006). Clinical trial results have shown that bioengineered skin substitutes, such as Apligraf (human neonatal fibroblasts in bovine collagen matrix overlaid with neonatal keratinocytes; Organogenesis, Canton, Mass.), Dermagraft (human

neonatal fibroblasts cultured in polyglactin mesh; Organogenesis, Canton, Mass.), and EpiFix (dehydrated human amnion/chorion membrane; MiMedx Group Inc., Marietta, Ga.) promote wound closure, resulting in more frequent and rapid healing of chronic diabetic foot ulcers when compared with standard therapy with moist to dry dressings (Veves 2001, Marston 2003, Zelen 2013a). Determining the cost-effectiveness of any advanced wound care treatment or product in achieving wound closure is a complex calculation and must consider a number of variables. The rate of wound healing, time to healing, complications, and wound reoccurrence are primary cost drivers. Additional factors influencing the cost-effectiveness of any advanced wound product include the amount and cost of product used and the amount of product discarded at each application due to wastage of unused dispensed product.

The purpose of this evaluation is to compare the clinical effectiveness and product attributes of Apligraf, Dermagraft, and EpiFix advanced wound products for the treatment of chronic diabetic foot ulcers.

METHODS

A retrospective evaluation of randomized controlled trial data was performed. Rates of complete wound closure, time to healing, number of graft applications to wound closure, durability of healed wounds, and safety data were examined for three commonly available skin substitutes: Apligraf, Dermagraft, and EpiFix.

Included for analysis were data only from patients receiving the active intervention (Apligraf, Dermagraft, or EpiFix). The Apligraf and Dermagraft study groups were identified from peer-reviewed publications of pivotal clinical study data (Veves 2001, Marston 2003). The pivotal study of Apligraf included 112 Apligraf-treated

patients. The pivotal study of Dermagraft included 163 treated patients overall who were included in the safety analysis; 130 treated patients with ulcer duration of more than 6 weeks were used to determine efficacy. The EpiFix group (n=64) consisted of pooled data from patients enrolled in three separate randomized controlled trials of EpiFix for the management of lower-extremity ulcers (Zelen 2013a, Zelen 2013b, Zelen 2014a). Additional source documents included the product prescribing information and premarket approval summary documents (FDA 2000, FDA 2001). All included studies were industry-sponsored and funded.

Product description: Apligraf, Dermagraft, and EpiFix

Apligraf is supplied as a living, allogeneic bilayered cultured skin substitute: the epidermal layer is formed by human keratinocytes and has a well-differentiated stratum corneum; the dermal layer is composed of human fibroblasts in a bovine Type I collagen lattice. While matrix proteins, cytokines, and growth factors found in human skin are present in Apligraf, it does not contain Langerhans cells, melanocytes, macrophages, lymphocytes, blood vessels, or hair follicles. The cells are originally derived from donated human neonatal male foreskin tissue (FDA 2001). Apligraf is supplied in a sealed, heavy-gauge polyethylene bag with a 10% CO₂/air atmosphere and agarose nutrient medium. Each Apligraf is supplied ready for use and intended for application on a single patient. To maintain cell viability, Apligraf should be kept in the sealed bag at 68–73°F (20–23°C) until use (FDA 2000).

Dermagraft is a cryopreserved human fibroblast-derived dermal substitute; it is composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold. Dermagraft is manufactured from human fibroblast

cells derived from donated newborn foreskin tissue. During the manufacturing process, the human fibroblasts are seeded onto a bioabsorbable polyglactin mesh scaffold. The fibroblasts proliferate to fill the interstices of this scaffold and secrete human dermal collagen, matrix proteins, growth factors and cytokines, to create a three-dimensional human dermal substitute containing metabolically active living cells. Dermagraft does not contain macrophages, lymphocytes, blood vessels, or hair follicles (FDA 2001). Dermagraft is supplied frozen in a clear bag and instructions for use include a 20-step process of thawing and rinsing the product prior to application to the wound (FDA 2001).

EpiFix is a dehydrated human amnion/chorion membrane allograft. Human amniotic membrane comprises the innermost layer of the placenta and lines the amniotic cavity. The allograft consists of layers of the amniotic sac, including an epithelial lining, amnion, and chorion, which contain important biological molecules such as collagen, connective tissue, cytokines, and growth factors. Although it contains no living cells, EpiFix provides a biologically active matrix and growth factors for cellular ingrowth. Processed through a proprietary Purion method that combines cleaning, dehydration, and sterilization, EpiFix has been shown to contain growth factors that help in wound healing, as well as such cytokines including anti-inflammatory interleukins and tissue inhibitors of metalloproteinase (TIMPs), which help regulate the matrix metalloproteinase (MMP) activity, the key to extracellular matrix remodeling (Koob 2013). In vitro and in vivo experiments established that EpiFix contains one or more soluble factors capable of stimulating mesenchymal stem cell migration and recruitment (Koob 2013). EpiFix is supplied in a sterile

package and is stored under ambient conditions. It is clearly embossed to aid in identification of proper orientation for placement on the wound. EpiFix can be applied dry into the moistened wound bed, or moistened with sterile saline (Zelen 2013a, Zelen 2013b, Zelen 2014a).

Description of patient population used in analysis

The population of this analysis consisted of patients with type 1 or type 2 diabetes enrolled in randomized controlled trials who received one of the advanced wound therapies, Apligraf, Dermagraft, or EpiFix, for the treatment of a chronic foot ulcer (Veves 2001, Marston 2003, Zelen 2013a, Zelen 2013b, Zelen 2014a). Prior to study enrollment and receiving advanced wound therapy, all patients were required to have a noninfected foot ulcer that had not responded to standard wound care, and all had adequate circulation to the affected extremity. In all studies, infection was assessed by clinical evaluation of the enrolling physician. In both the Apligraf and Dermagraft studies, wound duration of at least 2 weeks was required for study inclusion (Veves 2001, Marston 2003), while in the EpiFix studies wound duration of at least 4 weeks was required (Zelen 2013a, Zelen 2013b, Zelen 2014a). Treatments consisted of Apligraf (up to 5 weekly applications), Dermagraft (up to 8 weekly applications), or EpiFix (weekly applications, n=20, or every-2-week applications, n=44) applied until wound closure or up to 12 weeks, whichever came first. In all studies, standard principles of diabetic foot care were adhered to. Products were applied after sharp debridement followed by moist-to-dry dressings. In each study, various methods were used to relieve areas of elevated plantar pressure (offloading), which has been shown to help prevent or heal plantar ulceration (Cavanagh

2010). Apligraf-treated patients were required to use crutches or a wheelchair for the first 6 weeks of the study and were fitted for customized tridensity sandals to be worn throughout the study (Veves 2001). Dermagraft-treated patients were allowed to be ambulatory using extra-depth diabetic footwear with custom inserts or healing sandals (Marston 2003). EpiFix-treated patients' wounds were offloaded using a removable cast walker (Active Offloading Walker; Darco, Huntington, W.V.). All studies followed patients with weekly visits until complete healing was verified or up to 12 weeks.

Data analysis

Statistical analysis was limited in that patient-level data were not available for the Apligraf or Dermagraft groups. Patient-level data were available for EpiFix-treated patients enrolled prospectively in three published studies, N=13, N=11, and N=40 (Zelen 2013b, Zelen 2013a, Zelen 2014a). These data were aggregated into one dataset and a pooled analysis was performed. Rates of wound closure after 6 and 12 weeks of treatment were compared with a Fisher's exact test. Adjusted *P* values of <.017 were considered significant, as the risk of making erroneous false-positive conclusions is increased when testing multiple hypotheses on a single set of data, and the Bonferonni correction was applied. GraphPad InStat v3 was used to perform statistical testing.

RESULTS

Product attributes are compared in Table 1. Both Apligraf and Dermagraft were determined by the FDA to be Class III medical devices and were required to undergo a premarket approval (PMA) process before being available for clinical care. EpiFix, regulated by the FDA as a Human Cells, Tissues, and Cellular and Tissue-Based Product (HCT/P, 21

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TABLE 1

Product comparisons

	Apligraf	Dermagraft	EpiFix
Product description	Neonatal fibroblasts cultured in bovine collagen matrix overlaid with neonatal keratinocytes	Neonatal fibroblasts cultured in polyglactin mesh	Dehydrated human amnion/chorion membrane allograft
Regulatory pathway	Premarket approval	Premarket approval	HCT/P; PHS Act Section 361
Graft sizes available	One 44 cm ² disc	One 37.5 cm ² sheet	Multiple sizes: 14 mm diameter disc (1.54 cm ²) to 9 cm x 20 cm (180 cm ²) sheet
Cost per graft¹	\$1,806.14	\$1,688.34	Various costs depending on graft size, starting at \$329.70 for 14 mm disc
Storage considerations	Consists of living cells that must be kept sealed in nutrient medium and 10% CO ₂ /air atmosphere under controlled temperature 68–73°F (20–23°C). Shelf life 15 days.	Must be stored continuously at minus 75°C ± 10°C. For continuous storage, transfer of Dermagraft from shipping container into freezer must take ≤60 seconds to ensure cell viability. Frozen 6-month shelf life.	Sterilized tissue that may be stored at ambient conditions for up to 5 years.
Wound application instructions	Remove from liquid-filled pouch. Use within 15 minutes.	20-step application process including thawing.	Remove from dry pouch.

HCT/P=Human Cells, Tissue, and Cellular and Tissue-Based Product, PHS=Public Health Service.

¹CMS Reimbursement Schedule at <http://www.cms.gov/apps/ama/license.asp?file=/hospitaloutpatientpps/downloads/October-2013-Web-Addendum-B.zip>. Accessed June 20, 2014.

TABLE 2

Wound area and healing metrics

(Veves 2001, Marston 2003, Zelen 2013a, Zelen 2013b, Zelen 2014a, Zelen 2014b)

	Apligraf (n=112)	Dermagraft (n=130)	EpiFix (n=64)
Wound area (cm ²)	2.97 ± 3.10	2.31	2.72 ± 2.6
Mean grafts received ^a	3.9	5.7	2.4
Complete wound closure within 12 weeks	56% 63/112	30% 39/130	92% 59/64
Median days to closure	65 (7, 88) (n=63)	NR	14 (7, 77) (n=59)
Ulcer recurrence	5.9% ^b	18.8% ^c	5.6% ^d
Adverse events ^e (infection, cellulitis, osteomyelitis)	22.3%	19%	1.6%

Data reported as mean ± SD, percentage, or median (min, max) as indicated.

^aTo healing or to maximum allowed during 12-week study period.

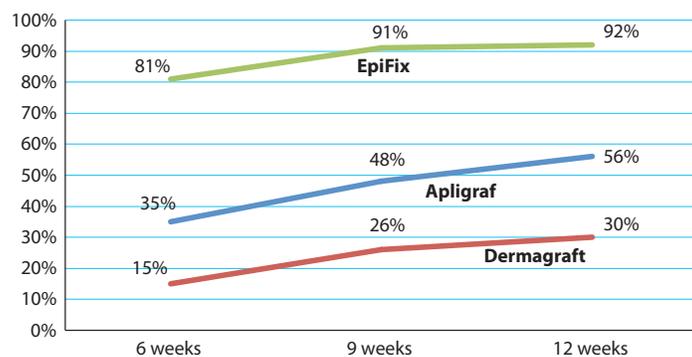
^bAt 6 months.

^cAt 8 months (32 weeks).

^dAt 9–12 months.

^eOf study wound.

FIGURE 1
Rates of complete healing at 6, 9, and 12 weeks for Apligraf, Dermagraft, and EpiFix groups



CFR 1271) and by Section 361 of the Public Health Service Act, does not require premarket approval but does come under other FDA and regulatory pathways as described above. In each study, mean wound size at treatment initiation was between 2 and 3 cm². Mean wound size was 2.97 cm², 2.31 cm², and 2.72 cm², for Apligraf, Dermagraft, and EpiFix groups, respectively. Healing metrics reported in the studies evaluated are shown in Table 2.

Complete wound closure

For each product evaluated, the definition of complete wound healing was defined as full epithelialization of the wound with the absence of drainage. Healing rates at 6, 9, and 12 weeks are presented in Figure 1. Of the products evaluated, wounds treated with EpiFix had the highest rate of complete closure (92%) at the end of the 12-week study period, compared with a 56% closure rate with Apligraf and a 30% closure rate with Dermagraft (all pairwise comparisons $P < .001$). Within 6 weeks of the first graft application, 81% of ulcers treated with EpiFix were closed versus 35% and 15% of Apligraf- and Dermagraft-treated wounds, respectively (all pairwise

comparisons $P \leq .003$).

Time to closure

For those wounds that closed in the study period, median days to closure were 14 days in the EpiFix group and 65 days in the Apligraf group. Days to closure was not reported for the Dermagraft study patients. Overall, within 2 weeks of the first application of EpiFix, median percent wound closure was 94%. A similar reduction in size (91%) was not achieved in the Dermagraft group until study completion at 12 weeks. This metric was not reported for the Apligraf group.

Number of graft applications and estimated costs

During the 12-week study period, Apligraf was applied at weekly intervals for a maximum of 5 applications. Total number of grafts used in the study was 440, and the mean number of Apligraf discs used per patient was 3.9 (minimum 1, maximum 5). Each Apligraf 44 cm² disc was trimmed to fit the ulcer and remaining material was discarded (Veves 2001). We calculated the cost of Apligraf and the other 2 products using allowable charges for each product from the Centers for Medicare & Medicaid Services (CMS) product reimbursement

schedule found at <http://www.cms.gov/apps/ama/license.asp?file=/hospitaloutpatientpps/downloads/October-2013-Web-Addendum-B.zip>. Overall cost for Apligraf product used in the study is estimated at \$794,922 or \$7,097 per patient.

In the published study of Dermagraft, patients received 1 to 8 weekly applications. Mean number of applications was not reported in the published manuscript (Marston 2003), although it is documented in the FDA PMA summary that a total of 927 devices, equating to a mean of 5.7 grafts per study patient, were used. Dermagraft is supplied in a 37.5cm² sheet frozen in a clear bag for a single-use application. Overall cost for Dermagraft product used in the study is estimated at \$1,544,499, or \$11,881 per patient.

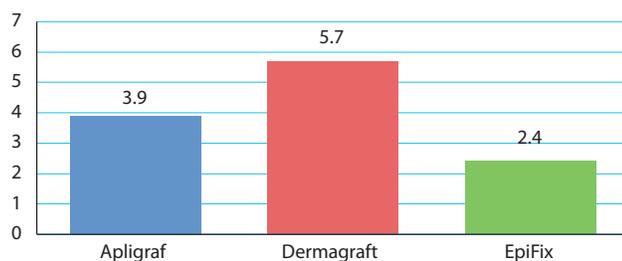
EpiFix allografts were applied weekly or every 2 weeks, according to study protocol. Twenty patients received weekly application and 44 received EpiFix every 2 weeks. Patients received a minimum of 1 application to a maximum of 8. Overall, 154 EpiFix allografts were applied and a mean of 2.4 grafts were used per study patient. Total cost for EpiFix allograft material used in the study is estimated to be \$197,819 or \$3,091 per patient. Although grafts were trimmed to approximate wound size, the size of the packaged graft used depended on wound measurements at time of application, minimizing wastage. The number of product applications per healed wound is not able to be compared between treatment regimens, as this information is available only for the EpiFix pooled data (2.2 ± 1.5 grafts per healed wound). Based on available data, the average amount of graft material used per treated patient is presented in Figure 2.

Durability of healed wounds

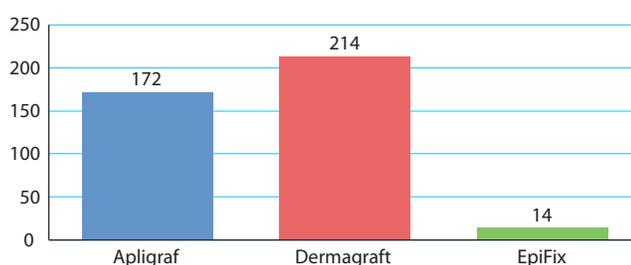
An important consideration of advanced wound care product effective-

FIGURE 2
Comparison of quantity and estimated cost of products used per patient

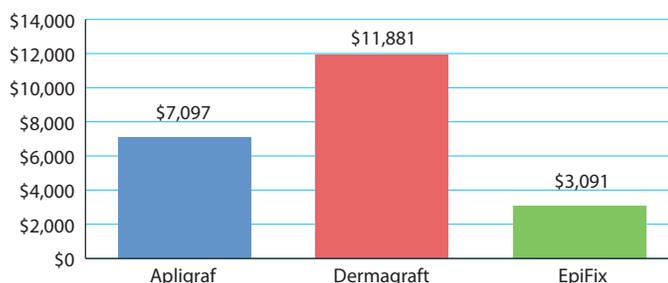
Mean number of grafts per patient



Total product used (sq cm)



Cost of product used per patient



ness is ulcer recurrence after primary healing. In patients treated with Apligraf, ulcers healed by 12 weeks were reassessed at 4, 5, and 6 months. Within the 6-month follow-up period, the reported incidence of recurrence was 12.5%, 2%, and 5.9% at 4, 5, and 6 months, respectively (Veves 2001, FDA 2000). In the Dermagraft FDA PMA summary, ulcer recurrence is reported for 2 separate studies of Dermagraft-treated patients. In a dataset of 139 patients treated with Dermagraft, all patients were followed

to Week 32. Ulcer recurrence (defined as ulcers that healed by Week 12 and reopened on or before Week 32) was 26% (11/42). A retrospective analysis was also performed on the subset of patients enrolled in the published study (Marston 2003) who had ulcer duration of more than 6 weeks and who received Dermagraft that met the final metabolic release criterion used to determine consistency of the product; in this population, ulcer recurrence was 19% (3/16) at Week 32 (FDA 2001). In a long-term follow-up

report of patients with ulcers treated with EpiFix, 94% (17/18) of wounds remained fully healed 9 to 12 months following primary healing (Zelen 2014b).

Safety

Although all patient clinical events during treatment were recorded in the three studies, for this investigation we chose to examine only those adverse events that were reported to be associated with ulcer complications. The incidence of serious wound complications (infection, cellulitis, osteomyelitis) was reported individually or in aggregate form for all studies. Percent of patients with serious wound complications during the study periods ranged from 1.6% (EpiFix) to 22% (Apligraf) (Table 2). Infection was the most common adverse event in all studies.

DISCUSSION

The pathogenesis of foot ulcers is often complex and their management is difficult. Knowledge of new techniques, technology, and products can allow clinicians to excel in their effort to provide optimal care and promote positive outcomes for these challenging patients. With standard wound care, healing can be slow and many ulcers remain unhealed over a long period. Prolonged care and associated morbidity often generate a burden to the health care system and to patients. Advanced therapies have been shown to accelerate the healing process in many patients, yet there is no perfect treatment for all patients in all situations (Shores 2007). Therapies that promote rapid and complete healing of foot ulcers can reduce the risk for infection and amputation and may substantially improve quality of life while decreasing financial burdens to the individual and to society overall (Albert 2002).

Advanced wound care products have been demonstrated to be ben-

eficial in the treatment of diabetic foot ulcers. Indeed, statistically significant differences in rates of wound healing were observed versus controls for Apligraf (56% vs. 38%, $P=.004$), Dermagraft (30% vs. 18%, $P=.02$), and EpiFix (92% vs. 8%, $P<.001$). A meta-analysis provided additional support that 12-week treatment of diabetic ulcers with either Apligraf or Dermagraft increases the chance of healing over standard care alone (Ho 2005). Both products are widely used in the clinical setting. The purpose of the present analysis was to compare healing metrics between Apligraf, Dermagraft, and the more newly available allograft EpiFix for the treatment of diabetic foot ulcers. These comparisons suggest that diabetic foot ulcers treated with EpiFix have higher closure rates and heal more rapidly than ulcers treated with Apligraf or Dermagraft.

Skin substitutes may follow multiple regulatory pathways to reach market, and all of them are regulated by the FDA. One route is to qualify for regulation solely under Section 361 of the Public Health Service Act and 21 CFR 1271 in the Code of Federal Regulations, which is the regulation governing many human tissue products on the market today. If tissue qualifies for regulation solely under Section 361, it is not required to be licensed by the FDA and, in fact, no license is available. This is true not just of placental tissue, but also of many cornea, dermis, tendon, and bone products, which may also qualify as Section 361 tissues that do not require FDA clearance, approval, or licenses.

Both clinical effectiveness and cost-effectiveness are important considerations when choosing an advanced wound care product. Rates of healing, time to healing, number of grafts applied, costs per treatment, and ease of use must all be evaluated when determining if a treatment is cost-effective. For example, the utiliza-

tion of a larger-than-necessary sheet of graft material for the wound size will produce both product and dollar wastage, as product is dispensed on a per-patient, per-application basis and any unused product must be discarded. This wastage must be factored in when determining the true cost-effectiveness of a wound-healing product. Indeed, when a graft of 44 cm² or 37.5 cm² must be used to treat wounds averaging less than 3 cm² over 90% of material is discarded. The availability of various-sized EpiFix grafts resulted in less waste of graft material when compared with Apligraf and Dermagraft. Although actual cost of materials may vary greatly due to contractual prices, we estimated differences in costs of treatment based on allowable charges for each product from the CMS product reimbursement schedule. The per-square centimeter price allowed for EpiFix is higher than for Apligraf and Dermagraft, but the ultimate product expense per patient was reduced by 55.2% (EpiFix versus Apligraf) and 73.6% (EpiFix versus Dermagraft) due to the reduction of product wastage with the EpiFix various sized grafts and more rapid healing times.

There are limitations to our analysis. Data were identified from source documents in the public domain and we did not have patient-level data from the Apligraf and Dermagraft studies, so we were limited in the amount of statistical analysis that could be conducted, including comparison of demographic factors that may or may not influence healing. As raw data were unavailable for the Apligraf and Dermagraft studies, we were unable to control for differences in study design and degree of off-loading. As both studies (Veves 2001, Marston 2003) were published more than 10 years ago, changes in clinical practice may have influenced outcomes compared with data collected more recently (Zelen 2013a,

Zelen 2013b, Zelen 2014a). Our cost comparisons were estimated from data collected in separate studies and based on mean number of grafts used per study patient and may not reflect product costs outside a study setting. Product cost data were obtained from a recent CMS reimbursement schedule and do not reflect the cost of material when studies were performed. Although inclusion and exclusion criteria among all protocols were similar, the Veves and Marston studies were larger and multicenter, whereas the Zelen studies were smaller and conducted at one site. Although the differences we observed in this analysis show the superiority of EpiFix in achieving complete wound closure when compared with Apligraf and Dermagraft, prospective comparative effectiveness trials are needed to elucidate these results. This analysis was conducted to assist in sample size calculations for proposed trials.

Advanced wound care products have been shown to increase healing rates of diabetic foot ulcers compared to standard wound care. Although prospective comparative studies are needed to confirm our findings, this retrospective analysis of published data appears to favor the use of EpiFix as a clinically effective and a cost-effective treatment for diabetic foot ulcers over Apligraf and Dermagraft, with high rates of rapid wound healing, low number of grafts per healed wound, availability of multiple sized grafts, and simplicity of application.

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