

Value Appraisal of NEOX® CORD 1K for Complex Diabetic Foot Ulcers

Eric Giza, MD¹

¹Department of Orthopaedics, University of California, Davis, Sacramento, CA, USA

INTRODUCTION

According to the US Centers for Disease Control and Prevention (CDC), 29.1 million Americans or 9.3% of the US population had diabetes in 2014. Unfortunately, people with diabetes have a ~25% risk of developing a foot ulcer in their lifetime,¹ with an estimated annual incidence rate of 0.5-3.0%.²⁻⁶ When the foot ulcer is non-healing, the dermal first line of defense is compromised for a prolonged period, and the patient is susceptible to tissue loss, infection, and eventual limb amputation.^{7, 8} In fact, foot ulceration is a precursor to approximately 85% of the lower extremity amputations within this population.^{1, 9-20}

Amputations are common in diabetic patients, with more than 73,000 non-traumatic lower extremity amputations performed in the US each year. After one major lower extremity amputation, the 5-year survival rate is estimated to be 50%^{14, 15} which is worse than most malignancies.^{14, 16} For amputation survivors, day-to-day function is greatly impaired; many cannot walk, with or without the use of a cane or walker. Moreover, the financial burden is cumbersome. One recent study demonstrated that excess health care costs of diabetic foot ulcers (DFU) are approximately twice that attributable to the treatment of diabetes alone, with annual incremental per-patient medical costs ranging from \$11,710 to \$16,883. This translates to an annual incremental payer burden ranging from \$9.1 to \$13.2 billion.²¹ Consequently, non-healing DFUs pose a substantial clinical and economic burden on healthcare systems, with significant reductions in quality of life for those affected.

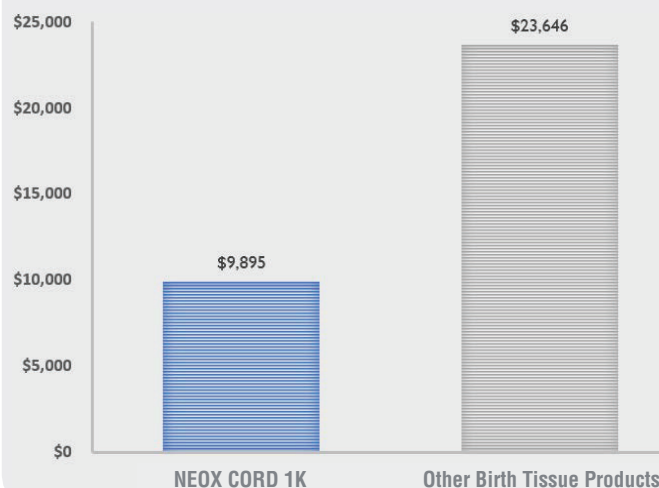
NEOX CORD 1K for DFU

To overcome the limitations with traditional treatment options, physicians have evaluated the potential of placental tissue products (amnion, chorion, umbilical cord) in its various processed forms to support the healing process in DFUs. One such product is NEOX CORD 1K, which is a cryopreserved umbilical cord and amniotic membrane product that is used as a wound covering for dermal ulcers or defects. Multiple studies have reported wound healing rates of >78% in DFU patients who received NEOX CORD 1K²²⁻²⁶ with an average time to wound closure of 13.8-16 weeks^{22, 27}. Most notably, these studies were performed in patients with severe DFUs (Wagner 3 & 4) that had exposed bone/tendon/ligaments, osteomyelitis, and in some cases gangrene that are commonly contraindicated for other products.^{22, 23, 25, 27} Traditionally, the healing rate in this patient population is 35% at 16 weeks using all other available therapies.²⁸ Hence, NEOX CORD 1K represents a potential alternative solution for the unmet medical need of complex DFUs.

Aside from the clinical outcomes, another benefit of using NEOX CORD 1K is the reduced number of applications required. Clinical evidence suggests only 1.2 to 1.7 product applications have been needed to promote wound closure despite a relatively large average wound size of 10.6-15.6 cm².^{22, 27} This is far less than the number of applications needed for other advanced tissue products, which averages between 2.5 and 6 product applications for smaller and less severe wounds.²⁹⁻³³ In terms of financial benefit, this translates to a lower overall cost (\$13,751 less costly) to achieve healing with NEOX CORD 1K over a 16-week period compared to another cryopreserved human placental membrane tissue (\$9,895 vs. \$23,646; Figure 1).³⁴ The main reason for the difference in costs was the amount of tissue product (in cm²) used, driven by less frequent applications. Of note, these costs did not account for the higher proportion of more severe wounds in the NEOX CORD 1K patient population (Wagner 3 & 4) compared to competitor product

patient population (Wagner 2), even though severe wounds are associated with higher costs (Wagner 2: \$8,260 per episode, Wagner 3: \$23,298 per episode, and Wagner 4/5: \$52,701 per episode adjusted for inflation), and 29.4% of wounds have been shown to worsen in severity overtime.³⁵ Moreover, only ~4% of wounds necessitated the need for major amputation (above the ankle) after 1-year of NEOX CORD 1K exposure,²² which thereby improves patient outlook and reduces healthcare costs. As such, when compared to other human placental tissue, NEOX CORD 1K is shown to be a more-cost effective option to improve outcomes in DFU patients.

Figure 1. Costs to Achieve Wound Healing Over 16 Weeks Using Different Birth Tissue Products



REFERENCES

1. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012; 54: e132-73.
2. Lavery LA, Peters EJ, Williams JB, et al. Reevaluating the way we classify the diabetic foot: restructuring the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. *Diabetes Care*. 2008; 31:154-6.
3. Moss SE, Klein R and Klein BE. The prevalence and incidence of lower extremity amputation in a diabetic population. *Arch Intern Med*. 1992; 152:610-6.
4. Ramsey SD, Newton K, Alrough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care*. 1999; 22: 382-7.
5. Kumar S, Ahe HA, Parnell LV, et al. The prevalence of foot ulceration and its correlates in type 2 diabetic patients: a population-based study. *Diabet Med*. 1994; 11: 480-4.
6. Moss SE, Klein R and Klein BE. The 14-year incidence of lower-extremity amputations in a diabetic population. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care*. 1999; 22: 951-9.
7. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G and Apelqvist J. The global burden of diabetic foot disease. *Lancet (London, England)*. 2005; 366: 1719-24.
8. Margolis DJ, Allen-Taylor L, Hoffstad O and Berlin JA. Diabetic neuropathic foot ulcers and amputation. *Wound Repair Regen*. 2005; 13: 230-6.
9. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders. A clinical practice guideline (2006 revision). *J Foot Ankle Surg*. 2006; 45: 51-66.
10. Hingorani A, LaMuraglia GM, Henke P, et al. The management of diabetic foot: A clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. *J Vasc Surg*. 2016; 63: 29-215.
11. Danaei G, Fruicane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet*. 2011; 378: 31-40.
12. Aydin S, Basaran AA and Basaran N. The effects of thyme volatiles on the induction of DNA damage by the heterocyclic amine IQ and miltomycin C. *Mutagenesis*. 2005; 581: 43-53.
13. Calhoun JH, Murray CK and Manning MM. Multidrug-resistant organisms in military wounds from Iraq and Afghanistan. *ClinOrthopRelat Res*. 2008; 466: 1356-62.
14. Richardson GD, Bobson CN, Lang SH, Neal DE, Maitland NJ and Collins AT. CD133, a novel marker for human prostatic epithelial stem cells. *J Cell Sci*. 2007; 117: 3539-45.
15. Sem CK, Gordillo GM, Roy S, et al. Human skin wounds: a major and snowballing threat to public health and the economy. *Wound repair and regeneration: official publication of the Wound Healing Society [and] the European Tissue Repair Society*. 2009; 17: 763-71.
16. Singh N, Armstrong DG and Lipsky BA. Preventing foot ulcers in patients with diabetes. *Jama*. 2005; 293: 217-28.
17. Mills JL, Sr., Conte MS, Armstrong DG, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). *J Vasc Surg*. 2014; 59: 220-34 e1-2.
18. Game FL. Osteomyelitis in the diabetic foot: diagnosis and management. *Med Clin North Am*. 2013; 97: 947-56.
19. Lima AL, Oliveira PR, Carvalho VC, Cimerman S, Savio E and Dietztes Panamericanas para el Tratamiento de las Osteomielitis e Infecciones de Tejidos Blandos G. Recommendations for the treatment of osteomyelitis. *Braz J Infect Dis*. 2014; 18: 526-34.
20. Chua SM, O'Connell J, Kang S, et al. An Open Label Prospective Pilot Study to Evaluate the Efficacy of Cryopreserved Amniotic Tissue Grafts for Chronic Non-Healing Ulcers. *Wounds*. 2014; 26(5):E30-E38.
21. Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M and Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. *Diabetes Care*. 2014; 37: 653-8.
22. Caputo WJ, Vasquez C, Monterosa JA, et al. A retrospective study of cryopreserved umbilical cord as an adjunctive therapy to promote the healing of chronic, complex foot ulcers with underlying osteomyelitis. *Wound repair and regeneration: official publication of the Wound Healing Society [and] the European Tissue Repair Society*. 2016; 24: 885-93.
23. Raphael A and Gonzales J. Use of cryopreserved umbilical cord with negative pressure wound therapy for complex diabetic ulcers with osteomyelitis. *Journal of wound care*. 2017; 26: S38-S44.
24. Raphael A. A single-center, retrospective study of cryopreserved umbilical cord/amniotic membrane tissue for the treatment of diabetic foot ulcers. *Journal of wound care*. 2016; 25: S10-S17.
25. Raphael A and Grimes L. Implantation of cryopreserved umbilical cord allograft in hard-to-heal foot wounds: a retrospective study. *Journal of wound care*. 2020; 29: S12-S7.
26. Couture M. A Single-center, Retrospective Study of Cryopreserved Umbilical Cord for Wound Healing in Patients Suffering From Chronic Wounds of the Foot and Ankle. *Wounds: a compendium of clinical research and practice*. 2016; 28: 217-25.
27. Raphael A. A single-center, retrospective study of cryopreserved umbilical cord/amniotic membrane tissue for the treatment of diabetic foot ulcers. *Journal of wound care*. 2016; 25(Suppl 7):S10-S7.
28. Marston ea. An open-label trial of cryopreserved human umbilical cord in the treatment of complex diabetic foot ulcers complicated by osteomyelitis. *Wound Repair Regen*. 2019.
29. Landsman AS, Cook J, Cook E, et al. A retrospective clinical study of 188 consecutive patients to examine the effectiveness of a biologically active cryopreserved human skin allograft (TheraSkin®) on the treatment of diabetic foot ulcers and venous leg ulcers. *Foot & ankle specialist*. 2011; 4: 29-41.
30. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Graft(R) for the treatment of chronic diabetic foot ulcers: results of a multi-center, controlled, randomized, blinded, clinical trial. *International wound journal*. 2014; 11: 554-60.
31. Marston WA, Hanft J, Norwood P and Pollak R. 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: 1701-5.
32. Neves A, Falanga V, Armstrong DG and Sabolinski ML. 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: 290-5.
33. Snyder RJ, Shimozaki K, Tallis A, et al. A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of Dehydrated Antimicrobial Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcer. *Wounds: a compendium of clinical research and practice*. 2016; 28: 70-7.
34. Voigt land Isner S. P0855: cost analysis comparing two human allografts in healing diabetic foot ulcers over a 16 week period. *Wound Health*. 2019; 29: S148-59.
35. Stodd K, Vanderplas A, Tafesse S and Chang E. Costs of lower-extremity ulcers among patients with diabetes. *Diabetes Care*. 2004; 27: 2129-34.