

WOUND LITERATURE COMPENDIUM

# MicroMatrix® and Cytal® Wound Matrix in Clinical Practice



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ACell's proprietary platform technology – MatriStem UBM™ (Urinary Bladder Matrix) technology – is an extracellular matrix (ECM) derived from porcine urinary bladder and differentiated from other ECM products by its intact acellular epithelial basement membrane. MatriStem UBM technology is the only commercially available form of Urinary Bladder Matrix (UBM), and is utilized in the manufacturing of Cytal Wound Matrix and MicroMatrix devices.

UBM has been found to facilitate a remodeling response by the body that leads to the formation of biomechanically functional, site-appropriate tissue. As a result, ACell's wound management devices, including MicroMatrix devices and Cytal Wound Matrix devices, are often used in complex, slow-healing wounds where traditional treatments have not been effective.

UBM has a considerable breadth of research supporting its unique biologic characteristics, as well as its value in clinical settings. The extensive body of research includes more than 100 pre-clinical and 50 clinical peer-reviewed articles. Several of the most clinically relevant publications in the area of wound management are summarized in this compendium.

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The publications presented in this compendium contain the opinions of and personal techniques practiced by the treating physician(s). The techniques presented herein are for informational purposes only. The decision of which techniques to use in a particular clinical application lies with the treating physician(s) based on patient profile, particular circumstances surrounding the procedure, and previous clinical experiences.

Cases presented involving Veterans Administration facilities or physicians do not reflect the opinion of the United States military or Veterans Affairs office.

Note: Cytal® Wound Matrix and MicroMatrix® were previously marketed under the brand name MatriStem.

The authors of certain publications presented in this compendium may make claims that are not made by ACell or its representatives. In these publications, the underlying use of the ACell wound devices to manage wounds falls within the current indications for use of these devices, and therefore these publications are summarized within this compendium.

§ Former ACell Employee | ¶ Consultant | ▲ ACell Sponsored Research Agreement | # ACell Employee



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# Regenerative medicine for soft tissue coverage of the hand and upper extremity.

Lanier ST, Ruter DI, Valerio IL. *Current Orthopaedic Practice*. 2018; 29(2): 120-126. doi:10.1097/BCO.0000000000000592.

Extensive tissue loss can add significant complications to the management of complex wounds. Authors of this review article focused on the role of extracellular matrices (ECMs) in providing reconstructive options to help mitigate the complexities inherent with current reconstruction options. The authors suggest that ECMs can provide an alternative to advanced procedures in the reconstructive ladder and present examples where various devices were used for complex wound management. In many cases, the complex wounds presented with exposed avascular structures. ECMs, including Integra® Dermal Regeneration Template (DRT), were used to provide a healthy vascularized wound bed that could further be managed with autologous skin grafting.

The article detailed a case of a traumatic forearm wound with devitalized tendon and exposed muscle, which was managed with MicroMatrix and Cytal Wound Matrix. In this case, skin grafting was not needed to achieve closure, and the wound remained closed six months following reconstruction procedures.



**A)** Traumatic forearm wound including the presence of devitalized tendon and exposed muscle. Wound was managed with MicroMatrix and Cytal Wound Matrix. **B)** Three weeks following salvage procedures. **C)** Six months following salvage procedures, wound demonstrates stable coverage without the use of skin grafting.

Images reprinted with permission from Walter Klowers Health, Inc.

# A value analysis of microsurgical lower extremity reconstruction vs. acellular urinary bladder matrix (UBM) for radiation wounds of the lower extremity.

Micallef CJ, Johnson JN, Johnson MR. *Journal of Surgical Case Reports*. 2019; 3,1-3. doi: 10.1093/jscr/rjz051.

In this retrospective case study, authors reviewed the management protocol and outcome of a 77-year-old male patient with a radiation wound treated with Cytal Wound Matrix and MicroMatrix. The patient was a smoker with bilateral squamous cell carcinoma of the lower extremities treated with external beam radiation. Radiation therapy often provides successful outcomes, but can result in recalcitrant chronic radiation wounds that can be difficult to manage. In this case, radiation therapy resulted in non-healing ulcers on both legs. The right leg had an exposed tibia and tibialis anterior tendon which was managed with a free latissimus dorsi muscle flap. The left leg had a chronic indolent medial mid-calf wound, which was unsuccessfully treated for two years with conservative wound treatment options including wet to dry dressings, alginate silver, and Integra Bilayer. The patient was then treated with weekly applications of Cytal Wound Matrix and MicroMatrix until the wound completely closed and re-epithelialized. Authors of the study found that using Cytal Wound Matrix and MicroMatrix provided a successful alternative to previously failed treatment options and negated the need for additional flap procedures. Furthermore, they noted that the use of Cytal Wound Matrix and MicroMatrix in this patient eliminated the comorbidities and costs associated with undergoing an additional free flap procedure.



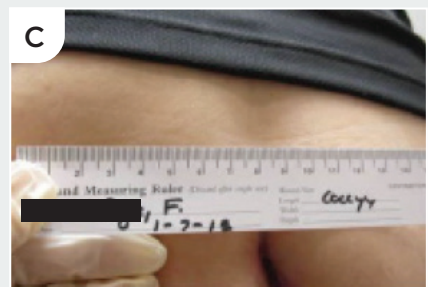
A 77-year old male patient with bilateral wounds resulting from external beam radiation. **A)** Right leg wound managed using free latissimus dorsi flap. **B)** Recalcitrant left leg wound following various wound treatment modalities including Integra Bilayer and hyperbaric treatment. **C)** Fully healed wound six months following wound management with Cytal Wound Matrix and MicroMatrix.

Images reprinted with permission from Oxford University Press.

### Complex wounds treated with MatriStem xenograft material: case series and cost analysis.

Sasse KC<sup>1</sup>, Ackerman EM, Brandt JR. *OA Surgery*. 2013 Dec 01;1(1):3.

This clinical, retrospective case series reviewed 10 cases of complex open wounds managed with MicroMatrix and/or Cytal Wound Matrix 1-Layer devices. Treatment costs with the UBM devices were compared to alternative wound treatment modalities at the same institution, including negative pressure wound therapy (NPWT). The cases were complex wounds ranging from recurrent, non-healing wounds to wounds in patients with compound comorbidities. Utilizing weekly applications of the UBM devices, authors achieved wound closure in all 10 cases without infection or complication by a median of 11 weeks. The authors concluded that ACell's wound management devices allowed for healing of complex wounds at lower costs due to requiring less material and employee hours than NPWT with comparable healing times.



**A)** A 61-year-old male patient with stage IV sacral pressure ulcer. Patient treated with topical wound care treatments and seven weeks of NPWT without healing. **B)** Sacral wound after three, weekly treatments of MicroMatrix and Cytal Wound Matrix. **C)** Sacral wound closed at six weeks.



**A)** Colostomy closure wound. **B)** Colostomy closure wound healed four weeks following application of MicroMatrix and Cytal Wound Matrix.

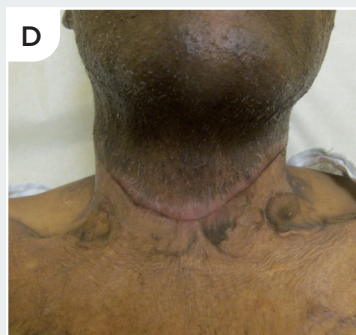
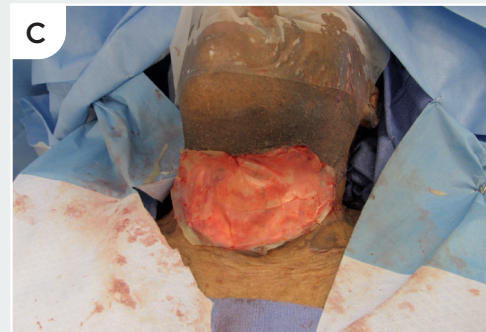
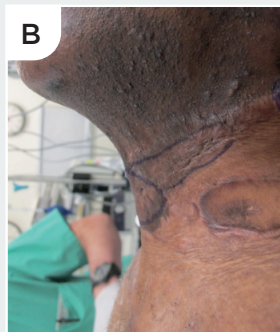
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# Porcine bladder extracellular matrix for closure of a large defect in a burn contracture release.

Mitchell KB, Gallagher JJ. Journal of Wound Care. 2012 Sep;21(9):454-6. doi:10.12968/jowc.2012.21.9.454. Retrieved from <http://www.oapublishinglondon.com>.

This manuscript is a retrospective review of a complex case involving excision of a contracting scar from the patient's anterior neck. Patient initially presented with a third-degree burn to the anterior neck and face. A skin graft was placed over the debrided neck burn; however, 17 months after surgery, the patient developed significant contracture and experienced sinus and fistulae formation. Upon excision and independent management of the fistula, the resulting wound edges retracted and an 8 cm x 14 cm wound remained. Patient was managed with MicroMatrix and Cytal Wound Matrix technology\*, with bi-weekly dressing changes and additional applications of ACell wound management devices as necessary. At 16 weeks post-initial application, the wound was fully closed and the patient expressed great satisfaction with the functional and cosmetic outcome. The patient's Vancouver Scar Scale score was reduced from a seven pre-operatively to a four before being discharged from physical therapy. There was no observed recurrence of the fistula or sinus formation at the time of submission of this manuscript.



Patient with sinus tract and fistulae formation from a mature, hypertrophic scar across the neck. **A,B)** Initial presentation at the junction of the healed area of the anterior neck and the hypertrophic upper edge of the mature skin graft. **C)** Large tissue defect resulting from operative excision of the burn wound. **D,E)** Definitive closure achieved 16 weeks post-application of MicroMatrix and Cytal Wound Matrix.

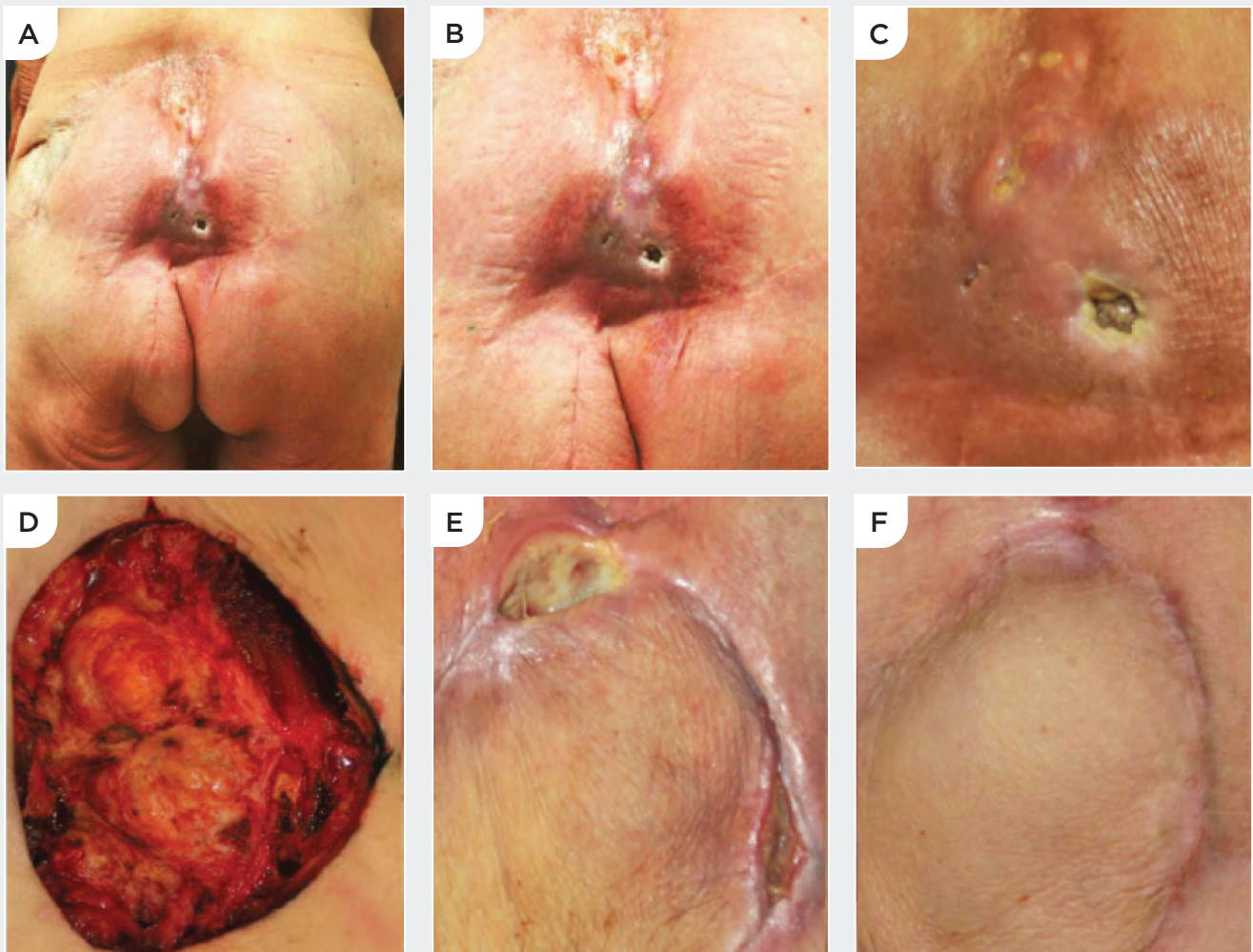
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\* Actual device utilized in the case was a Gentrix® Surgical Matrix device. The base technology and process employed during the manufacturing of Gentrix Surgical Matrix devices is equivalent to the base technology and process employed during the manufacturing of Cytal Wound Matrix 3- and 6-layer devices. Cytal Wound Matrix devices are fenestrated while Gentrix Surgical Matrix devices are unfenestrated.

# Urinary bladder matrix for the treatment of recalcitrant nonhealing radiation wounds.

Rommer EA, Peric M, Wong A<sup>\*</sup>. *Advances in Skin & Wound Care*. 2013 Oct;26(10):450-5. doi: 10.1097/01.ASW.0000434617.57451.e6.

In this retrospective case series, the authors reviewed the management protocols and the results of three patients presenting with complex wounds years after receiving radiation therapy. Authors used MicroMatrix and Cytal Wound Matrix when skin grafting of tissue flaps were considered high risk due to the irradiated and aged tissue. The average patient age was  $67.7 \pm 3.5$  years with the average time between radiation therapy and wound evaluation by the authors of  $36.3 \pm 17.8$  years. Before the use of ACell wound management devices, patients had undergone hyperbaric oxygen treatment, Negative Pressure Wound Therapy (NPWT), or Regranex<sup>™</sup> interventions without wound closure. All wounds closed after repeat applications of MicroMatrix and Cytal Wound Matrix.



**A)** A 71-year-old woman with previously irradiated scar tissue. **B)** Initial defect. **C)** Initial defect shown closely. **D)** Defect following debridement prior to coverage with posterior thigh fasciocutaneous flap. **E)** 2.5 cm x 1.5 cm wound breakdown, eight weeks following flap coverage. MicroMatrix applied biweekly, until wound closure at eight weeks. **F)** Wound remained closed 19 months after initial MicroMatrix application.

# Evaluation of tissue engineering products for the management of neuropathic diabetic foot ulcers: An interim analysis.

Frykberg RG, Cazzell SM, Arroyo-Rivera J, Tallis A, Reyzelman AM, Saba F, Warren L, Stouch BC<sup>†</sup>, Gilbert TW<sup>§</sup>. Journal of Wound Care. 2016 July;25 Suppl 7:S18-25. doi:10.12968/jowc.2016.25.7.S18.▲

In this prospective, randomized, multi-center, clinical trial interim analysis, the concomitant use of MicroMatrix and Cytal Wound Matrix 1-Layer ("MicroMatrix and Cytal Wound Matrix group") was compared to Dermagraft® ("Dermagraft group") in the management of neuropathic DFUs. The study evaluated the incidence of complete ulcer closure, rate of ulcer healing, wound characteristics, patient quality of life (QoL), cost effectiveness, and reoccurrence. Ninety-five patients at 13 sites entered the study, from which the evaluable data of 56 patients at eight study facilities were analyzed. Patients were randomized between the MicroMatrix and Cytal Wound Matrix and Dermagraft groups. Twenty-seven MicroMatrix and Cytal Wound Matrix and 29 Dermagraft subjects had complete evaluable data at this interim analysis. These subjects were managed with weekly applications for up to eight weeks or until complete wound closure, whichever occurred first. A two-week period of Standard of Care (SOC) followed the treatment phase, and wound closure was assessed at the end of that period. Any wounds that completely healed were evaluated at six months after initial treatment for evaluation of reoccurrence. There were no statistically significant differences between the patient populations including gender, age, race, ethnicity, size of ulcer, ulcer location, diabetes type, and University of Texas Wound Classification System grade.

At the planned interim analysis, there was no statistical difference in incidence of complete wound closure or the rate of wound closure between the two groups; however, due to the small data set, direct clinical comparisons of safety and efficacy between the two groups could not be established. The MicroMatrix and Cytal Wound Matrix group showed statistically significant improvements in QoL measurements, although there was no correlation to any specific clinical variable, when compared to the Dermagraft group. Finally, the MicroMatrix and Cytal Wound Matrix group showed a statistically lower device cost per subject as compared to the Dermagraft group.

## Average Diabetic Foot Ulcer Scale (DFS) Scores

	MicroMatrix/Cytal	Dermagraft	P-Value
<b>Time of Consent</b>	181.56 (±53.04)	184.46 (±61.03)	0.851
<b>Randomization</b>	196.22 (±64.91)	193.897 (±64.85)	0.894
<b>End of Treatment (8 weeks)</b>	151.11 (±72.86)	195.73 (±81.59)	0.074
<b>End of Post-treatment SOC (10 weeks)</b>	134.15 (±74.35)	201.13 (±72.13)	0.023

The DFS is a validated QoL instrument that consists of 58 items grouped into eleven lifestyle domains. The scoring algorithm provides a health-related QoL response score, where a lower score correlates with a more positive subject assessment. DFS scores fall on a range of 58-290.\*

\* Abetz L, Sutton M, Brady L, McNulty P, Gagnon DD. The Diabetic Foot Ulcer Scale (DFS): a quality of life instrument for use in clinical trials. Practical Diabetes Int. 2002; 19(6): 167-175.



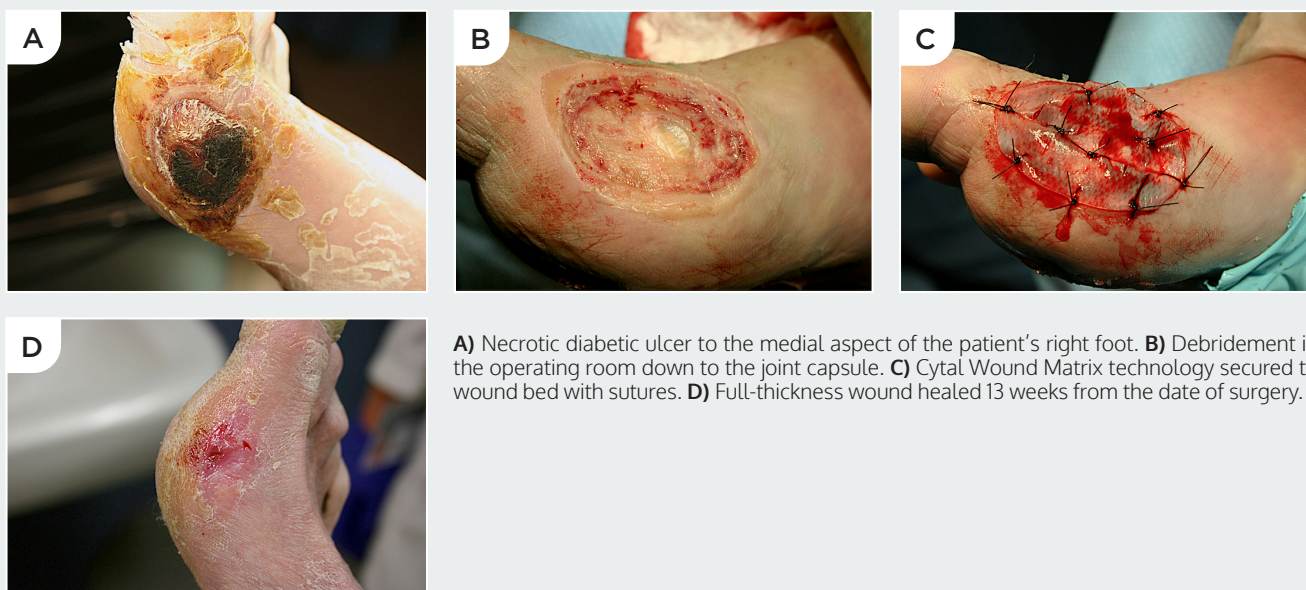
# The clinical effectiveness in wound healing with extracellular matrix derived from porcine urinary bladder matrix: a case series on severe chronic wounds.

Kimmel H, Rahn M, Gilbert TW<sup>§</sup>. *The Journal of the American College of Certified Wound Specialists*. 2010 Nov 30;2(3):55-9. doi: 10.1016/j.jcws.2010.11.002.

In this retrospective series of severe and complex wounds, the authors reviewed the cases of three patients managed with MicroMatrix and/or Cytal Wound Matrix technology\*. Wounds included a dehiscence of a superior lateral surgical wound to the foot, a necrotic DFU, and a full-thickness DFU probed to bone of the fifth metatarsal head. These wounds previously underwent standard and advanced wound care modalities and had stalled. Authors observed management with MicroMatrix and/or Cytal Wound Matrix technology led to epithelialization of recalcitrant, complex, chronic wounds involving tunneling or exposed joint capsules. Repeated applications of ACell wound management devices led to epithelialization in all patients, including those with multiple comorbidities. Authors observed limited formation of scar tissue by 13 weeks post-first application.



**A)** Dehiscence to the lateral surgical wound that was present for six weeks and was not responsive to standard wound care. **B)** Initial application of MicroMatrix. **C)** Wound closure after four weeks of treatment.



**A)** Necrotic diabetic ulcer to the medial aspect of the patient's right foot. **B)** Debridement in the operating room down to the joint capsule. **C)** Cytal Wound Matrix technology secured to wound bed with sutures. **D)** Full-thickness wound healed 13 weeks from the date of surgery.

Images reprinted with permission from Elsevier.

\* Actual device utilized in the case was a Gentrix Surgical Matrix device. The base technology and process employed during the manufacturing of Gentrix Surgical Matrix devices is equivalent to the base technology and process employed during the manufacturing of Cytal Wound Matrix 3- and 6-layer devices. Cytal Wound Matrix devices are fenestrated while Gentrix Surgical Matrix devices are unfenestrated.

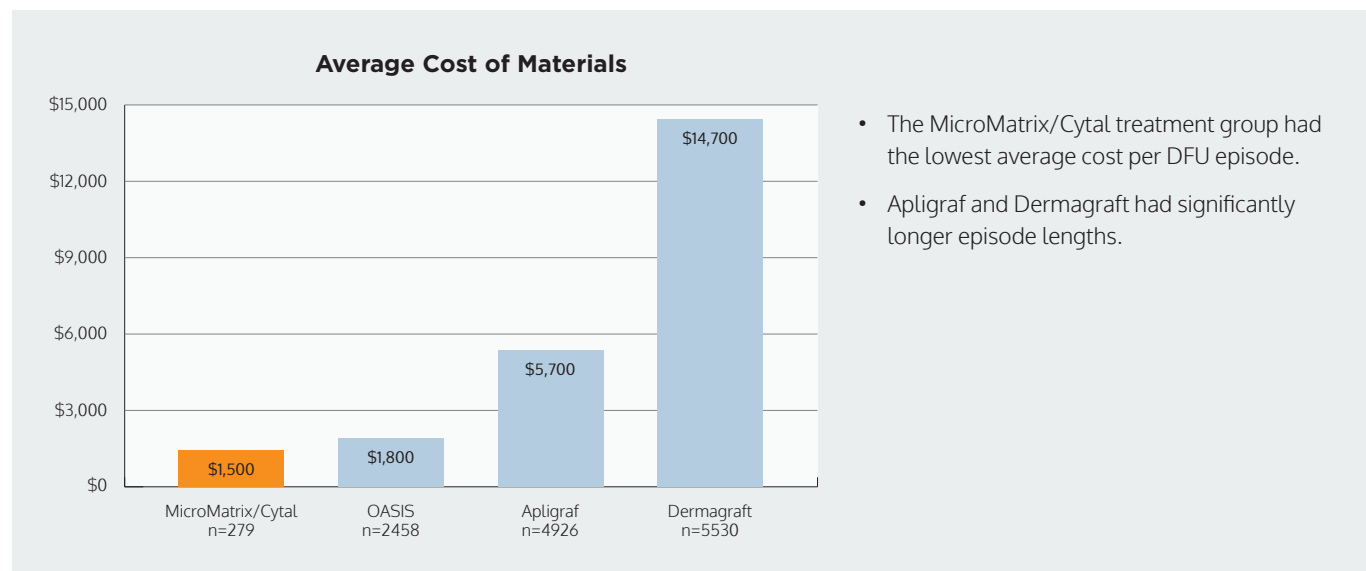
# A comparative analysis of skin substitutes used in the management of diabetic foot ulcers.

Martinson M, Martinson N. *Journal of Wound Care*. 2016 Oct 1;25(Sup 10):S8-S17. doi: 10.12968/jowc.2016.25.Sup10.S8.

Medicare claims data from 2011-2014 were used to compare relative product cost and clinical advanced wound therapy for management of DFU outcomes for four products: Cytal Wound Matrix, OASIS® Wound Matrix, Apligraf®, and Dermagraft.

Data from the Centers for Medicare & Medicaid Services (CMS) Standard Analytical Files (SAF) were used for analysis. Data was gathered from patients diagnosed with a foot ulcer, diabetes, and who had not had any foot ulcer claims for 60 days or more prior. Each episode had to last 30 days or more to eliminate any wounds that were easily healed. Costs, episode length, amputation rate, and product utilization were compared.

A total of 13,193 skin substitute treatment cases from 814 hospitals were investigated. The authors observed from their analysis the Apligraf and Dermagraft groups had a statistically significant longer episode length. Authors also observed in episodes where two skin substitutes were used, the incidence of Cytal as the second treatment increased, suggesting it was used after a previous advanced wound care modality had failed. It was also noted that there was an increased incidence of Cytal use in patients with osteomyelitis and gangrene indicating Cytal was chosen for more complicated cases. In addition, the Cytal group had the lowest average cost per DFU episode.



## Modulation of inflammation in wounds of diabetic patients treated with porcine urinary bladder matrix.

Paige JT, Kremer M, Landry J, Hatfield SA, Wathieu D, Brug A, Lightell DJ, Spiller KL, Woods TC. *Regenerative Medicine*. 2019 May;14(4):269-277. doi: 10.2217/rme-2019-0009. Epub 2019 Apr 25.

In this prospective case-control study, the authors intended to determine whether the macrophage phenotype-related gene expression after treatment with MatriStem UBM would differ in diabetic patients compared to nondiabetic patients. The study reviewed 18 patients (9 diabetic and 9 nondiabetic) with open

wounds that had not previously been treated with a biologic scaffold. More than 70% of the patients were smokers with a mean patient age of 51.8 and a mean BMI of 35.1. A sample of the initial debridement was saved for each patient prior to treatment with MicroMatrix and/or Cytal Wound Matrix 1-Layer wound management devices. Another wound debridement sample was taken 7-14 days post device-application. Using the pre- and post-treatment samples, the relative gene expression of M1 (pro-inflammatory) and M2 (pro-remodeling) macrophages was measure from both the diabetic and nondiabetic patients and the M1:M2 scores were calculated. Diabetic patients in this study exhibited a significantly higher M1:M2 score pre-treatment compared to post-treatment. The M1:M2 score was reduced to similar levels in both diabetic and nondiabetic patients following UBM wound management. Application of UBM was associated with statistically significant wound size reduction in both patient groups with a  $35\% \pm 14$  percent reduction in the diabetic and a  $43\% \pm 18$  percent reduction in the non-diabetic patients ( $p < 0.05$ ), with all but one diabetic patient exhibiting some magnitude of wound closure. The magnitude of the decrease in the M1:M2 score correlated with the rate of wound area reduction. Authors conclude that UBM has the potential to restore a normal inflammatory response in diabetic patients, suggesting that treatment with UBM in diabetic patients may result in healing rates similar to nondiabetic patients.

### Patient Population Characteristics

Characteristics	All Patients	Diabetic (n=9)	Nondiabetic (n=9)
Age (y)	51.8 ( $\pm 2.6$ )	55.8 ( $\pm 1.3$ )	46.8 ( $\pm 4.7$ )
BMI (lb/in <sup>2</sup> )	35.1 ( $\pm 1.8$ )	37.6 ( $\pm 2.6$ )	32.5 ( $\pm 2.4$ )
Initial wound area (cm <sup>2</sup> )	6.5 ( $\pm 1.7$ )	8.3 ( $\pm 2.9$ )	3.8 ( $\pm 1.2$ )
Smoker	13.0 (72%)	6 (33%)	7 (39%)

### M1:M2 scores pre and post treatment with MatriStem UBM devices for diabetic and nondiabetic patients.

	Pre-Treatment M1:M2 Score	Post-Treatment M1:M2 Score	Decrease in M1:M2 Score
Diabetic	4.42 ( $\pm 0.58$ )	2.075 ( $\pm 0.94$ )	2.89 ( $\pm 0.68$ )
Nondiabetic	2.06 ( $\pm 0.74$ )	1.67 ( $\pm 0.75$ )	0.66 ( $\pm 0.53$ )

**Note:** Per the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR Section 814.3, the FDA defines pediatric patients as persons aged 21 years or younger at the time of their diagnosis or treatment. The utilization of this article in promotional materials is not meant to infer or imply that ACell medical devices are cleared or approved for use in individuals younger than 22 years of age. This article contains scientific information relevant to the adult population ( $\geq 22$  years) where urinary bladder matrix (UBM) may assist in restoring a host tissue immune response seen in diabetic patients to one similar to that of nondiabetic patients.





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**Rx ONLY** Refer to IFU supplied with each device for indications, contraindications, and precautions.  
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