To: Gunnar Johannsson, Jessica Sullivan, Sarah McCabe, Brian Lee

From: Avalere

Date: May 31, 2024

Re: Skin Substitutes Evidence Review Memorandum

Memorandum Overview

On April 25, 2024, Medicare Administrative Contractors ("MACs") proposed eight (8) Local Coverage Determinations (LCDs) regarding coverage for skin grafts, cellular and tissue-based products used by Medicare beneficiaries with diabetic foot ulcers (DFU) and venous leg ulcers (VLU), with an open public comment period ending on June 8, 2024. If the proposed LCDs are finalized for coverage by MACs, they will establish evidentiary requirements and guidance to determine coverage for cellular and tissue-based skin graft products for DFU and VLU, which have been shown to have failed established methods to affect healing. If finalized as proposed, only 15 products currently listed within the proposed LCD would retain Medicare coverage, impacting Medicare beneficiary patient access to more than 200 alternatives that would now be considered investigational and experimental under the final LCD.

In this memorandum, Avalere summarizes:

- An analysis of the explicit (i.e., denoted within the proposed LCD) and implicit (i.e., discerned from Avalere review of products recommended for coverage within the proposed LCD) evidentiary requirements based on the LCDs and 15 covered products,
- An assessment of the scientific rigor of studies demonstrating the quality and efficacy of fish skin graft in treating DFU and VLU,
- Implications for the proposed LCD, which would impact 200+ skin substitute products.

Kerecis MariGen (Omega3) and Kerices Marigen Shield are intact fish skin grafts used in hospital outpatient settings to treat patients with chronic wounds, including DFU. Recognizing the MAC's initial feedback on evidence published through 2022, the Avalere analysis concludes that inclusion of Lantis et al. 2023 would address concerns about missing outcome data, small sample size, and short-term follow-up period. The Avalere analysis showcases the robust evidence from published studies to support Kerecis' case for favorable coverage determinations under the proposed LCDs for DFU and VLU treatments.

Methodology

Avalere reviewed the guidance, critiques, and general comments made by MACs in establishing evidentiary requirements for RCTs supporting skin substitute technologies in DFU and VLU. The most common requirements and themes for RCTs outlined by MACs in LCDs include, but are not limited to:

- Recency of Publication
- Publication in a Peer-Reviewed Journal
- Appropriate Sample Size
- Appropriate Comparators
- Longitudinal Outcomes
- Risk of Bias
- Randomization
- Blinding of Results

For efficiency, Avalere assessed relevant LCDs to identify any material differences aside from administrative information (e.g. contractor information, coverage areas, contact details). Avalere then performed a spot check of the remaining LCDs to confirm the list of 15 covered products and to identify the evidence cited by the MACs (refer to **Appendix B. Selected Evidence for Covered DFU Products based on LCDs**). Avalere then assessed the extent to which:

- Covered Product RCT have met the requirements listed in the LCD
- Lantis et al. 2023 has met the requirements listed in the LCD.

Next, Avalere populated an evidence table with the following information for the 15 covered products, as it pertains to DFU[1].

- Product
- Citation
- Comparator Information
- Sample Size
- Blinding
- LCD Relevant Endpoints
- Follow-up Beyond 12 weeks (Yes, No, N/A)
- Results
- Risk of Bias
- Publication Year
- MAC Comments

1 The MACs define the standard of care (SOC) for patients with a DFU as: assessment of Type 1 or Type 2 diabetes and management history with attention to certain comorbidities (e.g., vascular disease, neuropathy, osteomyelitis), review of current blood glucose levels/hemoglobin A1c (HbA1c), diet and nutritional status, activity level, physical exam that includes assessment of skin, ulcer, regional arterial perfusion (ABI), and assessment of off-loading device or use of appropriate footwear.

Finally, Avalere reviewed three fish skin graft publications to assess the extent to which Kerecis Marigen and Kerices MariGen Shield RCTs have satisfied the evidentiary standards. Refer to **Appendix A** for the references and abstracts.

Findings

Analysis of Evidentiary Requirements

In the LCDs, the MACs state that products must have quality supportive evidence to demonstrate **product safety**, **effectiveness**, and **positive clinical outcomes** to qualify as a covered skin substitute graft or cellular tissue-based product (CTP) under the LCD. High quality evidence plays an important role in determining what is considered reasonable and necessary in healthcare can vary, influenced by evolving medical knowledge, technological advancements, and shifts in healthcare delivery models. Of the eligible products, MACs considered the following conditions for evidence:

- Well-designed randomized control trial (RCT) with sufficient sample size, appropriate follow-up period, meaningful primary & secondary endpoints, and other design features (e.g., blinding, multi-site vs. single-site, randomization, funding source)
- Low risk of bias
- Recent publication in a peer-reviewed journal.

Avalere extracted information from the LCD for 35 RCTs and/or studies related to DFUs for the 15 products recommended for coverage. Table 1 below summarizes Avalere's main findings and observations as they relate to Kerecis Marigen and Kerecis MariGen Shield RCTs.

Table 1. LCD Analysis & Evidence Review

Criterion	Findings	Observations
Recency of Publication	Oldest: 1996 Newest: 2022 <u>Distribution</u> 1995-2000: 1 2001-2005: 4 2006-2010: 5 2011-2015: 10 2016-2020: 13 2021-2025: 2	<u>Summary of Covered Product RCTs</u> Most of the evidence in support of the 15 covered products was published after 2011 (25 of 35). However, it appears that the "cut-off" for this LCD was 2022, which overlooks more recent publications such as Lantis, 2023 and Zehnder, 2022. <u>Summary of Lantis et al. 2023</u> Published April 2023 in *Wounds.*

Criterion	Findings	Observations
Publication in a Peer-Reviewed Journal	100%	Summary of Covered Product RCTs All covered products had at least 1 publication in a peer-reviewed journal. Summary of Lantis et al. 2023 Lantis et al. 2023 was published in *Wounds Journal*, an indexed, peer-reviewed journal. focused on clinical research and practice in the study and management of chronic and acute wounds.
Appropriate Sample Size	Min: 23 Max: 314 Median: 72	Summary of Covered Product RCTs Excluding retrospective matched-cohort studies, there was a wide range in sample sizes for the covered products. Summary of Lantis et al. 2023 The sample size for Lantis et al. 2023 **exceeds** the median for covered products (*n*=102 vs. *n*=72).
Appropriate Comparators	MAC Standard of Care Definition The standard of care (SOC) defined by MACs for DFU consists of: • Debridement (as appropriate) • Offloading and sustained compression dressings • Infection control • Management of exudate with maintenance of a moist environment • Documentation of smoking history and efforts for smoking cessation	Summary of Covered Product RCTs Most RCTs appropriately assessed skin substitute grafts/CTPs as an adjunctive treatment to SOC alone. However, RCTs were heterogeneous in establishing and defining SOC, due in part to a lack of clear, uniform evidence-based guidelines for DFU. Summary of Lantis et al. 2023 SOC defined by Lantis et al. 2023 consisted of: • Debridement • Moist wound care (application of collagen alginate therapy and dressing) • Offloading with a walking boot Outcomes for fish skin graft compared to SOC included wound closure rate, healing rate and percentage wound area reduction. Avalere believes Lantis et al. 2023 has met the requirements in establishing an appropriate comparator in the absence of a uniformly recognized standard of care for DFU.

Criterion	Findings	Observations
Longitudinal Outcomes	RCTs were variable with study periods and follow-up spanning 6, 12, 16 and 20 weeks generally. MACs were able to assess key outcomes (i.e., wound closure) at 12 weeks for comparison against products.	Summary of Covered Products RCTs The vast majority of RCTs (32 of 35) demonstrated outcomes with a minimum of 12 weeks. Summary of Lantis et al. 2023 Outcomes for Lantis et al. 2023 were assessed at 12 weeks for wound closure, healing rate, and percentage wound area reduction. Further, wound recurrence was assessed between at 6-12 months for study participants. Avalere believes Lantis et al. 2023 has met the requirements for demonstrating longitudinal outcomes.
Risk of Bias[2]	Distribution High: 18 Med: 4 Low: 7 N/A: 6 Intent to Treat vs. Per Protocol Analysis RCTs were not uniformly consistent in reporting results for both Intent to Treat (ITT) and Per Protocol (PP) patient populations. Where possible, the LCDs have identified potential biases in RCTs where PP analysis was reported without ITT analysis.	Summary of Covered Products RCTs A majority of the evidence used to support coverage for 15 DFU products (18 of 35) were determined to have a **high** risk of bias, undermining the value of this criterion. A meta-analysis comparing GraftJacket to SOC was cited for publication and reporting biases, study selection biases, and incomplete data selection.[3] The most common reason cited by MACs were related to missing outcome data or unvalidated outcome measurements (19 of 22 studies with comments). Summary of Lantis et al. 2023 The Risk of Bias 2 Tool can be used to assess Lantis et al. 2023 on the following domains: randomization; deviations from the intended interventions; missing outcome data; measurement of the outcome; selection of the reported result; overall risk of bias. *Note that these measures are explored elsewhere in Tables 1 & 2.* Further, Lantis et al. 2023 has reported outcomes for study participants for ITT and PP sample sizes (102 and 77 patients, respectively). Results for both populations and rationale/explanation for participant dropouts (which are provided in the RCT) should alleviate MAC concerns for bias in reporting incomplete outcomes.

2 All RCTs were evaluated with the Risk of Bias 2 Tool (RoB2) to identify areas of potential concern in study designs. Risk of bias was impacted by randomization and stratification of subjects, pooled data, funding source, and missing outcome data. Risk of bias tools - RoB 2 tool.

3 Reyzelman A, Bazarov I. Human acellular dermal wound matrix for treatment of DFU: literature review and analysis. Journal of Wound Care. 2015;24(3):128-134.

Criterion	Findings	Observations
Randomization	At least 4 of the studies for covered products were not RCTs (e.g., retrospective matched-cohort studies[4,5], prospective study without control[6,7]).	Summary of Covered Products RCTs Majority of studies were randomized control trials; however, randomization strategies varied in terms of rigor or sufficient detail (i.e., unreported methodology). Summary of Lantis et al. 2023 The patient sample (n=102) was randomized with 51 patients in each study arm.
Blinding of Results	Adjudicator Blinding A significant number of RCTs did not report adjudicator blinding, and/or third party adjudicators in assessing wound outcomes at the conclusion of the study period. Clinician/Patient Blinding A majority of RCTs assessed skin substitutes against SOC, where use of a placebo skin substitute in the comparator arm would be illogical or illadvised.	Summary of Covered Products RCTs Different handling requirements, and visual heterogeneity of skin substitute products may also pose significant challenges in blinding patients and clinicians. Many authors acknowledged feasibility challenges . Different dressing regimens and treatment differences reveals the group assignment.[8] Summary of Lantis et al. 2023 As is the case for other skin substitutes, Lantis et al. were limited in their ability to fully blind the study and instead applied a single-masked assessment for wound healing following a methodology approved by WIRB-Copernicus Group. In a previous technical brief, AHRQ has previously acknowledged challenges with full blinding.

Avalere considered the methodological rigor (including sample size, randomization process, control groups) and the clarity of primary and secondary endpoints of the industry-sponsored evidence for Kerecis MariGen and Kerecis MariGen Shield. We reviewed the results statistical significance, particularly the efficacy in wound closure rates and healing times and the safety profile indicated by the documented adverse events.

4 Gurtner GC, Garcia AD, Bakewell K, Alarcon JB. A retrospective matched-cohort study of 3994 lower extremity wounds of multiple etiologies across 644 institutions comparing a bioactive human skin allograft, TheraSkin, plus standard of care, to standard of care alone. International Wound Journal. 2020;17(1):55-64.

5 Barbul A GG, Gordon H, Bakewell K, Carter MJ. Matched-cohort study comparing bioactive human splitthickness skin allograft plus standard of care to standard of care alone in the treatment of diabetic ulcers: A retrospective analysis across 470 institutions. Wound Repair Regen. 2020 28(1):81-89.

6 DiDomenico L, Landsman AR, Emch KJ, Landsman A. A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. Wounds. 2011;23(7):184-189.

7 Cazzell S, Moyer PM, Samsell B, Dorsch K, McLean J, Moore MA. A prospective, multicenter, single-arm clinical trial for treatment of complex diabetic foot ulcers with deep exposure using acellular dermal matrix. Advances in Skin & Wound Care. 2019;32(9):409.

8 (AHRQ). AfHRaQ. Evidence-based Practice Center Technical Brief Protocol. Project Title: Skin substitute graft for Treating Chronic Wounds. https://effectivehealthcare.ahrq.gov/products/skin-substitutes/protocol. Published 2018 (rev 2019). Accessed3/15/2023.

Implications

Avalere believes studies for Kerecis products demonstrate non-inferiority by meeting or exceeding the evidentiary standards of covered products for DFUs. Avalere recommends that MACs reconsider coverage for Kerecis MariGen and Kerecis MariGen Shield in light of the available and compelling evidence. Excluding alternatives with demonstrated safety, effectiveness, and positive outcomes would be a disservice to patients, providers, payers, and policymakers. Fish skin, in particular, is a unique solution with additional patient-centric benefits:

- Alleviates ethical or religious concerns,
- No risk of viral transmission from cold-water fish to humans,
- Does not require a harsh chemical process, and
- Longer shelf life compared to mammalian products.

A key RCT omitted from the proposed LCDs (Lantis et al. 2023) demonstrated statistically significant results of a 12-week wound closure rate for Kerecis fish skin graft technology compared to the standard of care for DFU. Based on an independent Avalere analysis, the study design and outcomes (e.g., 12-week wound closure for DFU) presented by Lantis et al. is of comparable quality to the evidence base for products recommended for approval in this LCD, and therefore it warrants consideration by MACs in assessing the Kerecis fish skin graft technology for potential coverage.

Table 2: Lantis, 2023 compared to DFU RCTs Assessed as Low Risk through RoB2

RCT	Sample Size	ITT Wound Closure at 12 Weeks		p-Value	ITT vs. PP
		Graft/CTP	SOC		
Lantis et al. 2023	102	57% (Kerecis Marigen)	31%	.01630	102 77
Armstrong et al. 2022[9]	100	76% (Theraskin)	36%	.00056	100 77
Serena et al. 2019[10]	76	55% (Affinity)	29%	.02000	76 (not reported)
Tettelbach et al. 2018[11]	155	70% (EpiCord)	48%	.00890	155 134
Tettelbach et al. 2019[12]	110	70% (EpiFix)	50%	.03380	110 98

9 Armstrong DG, Galiano RD, Orgill DP, et al. Multi-centre prospective randomised controlled clinical trial to evaluate a bioactive split thickness skin allograft vs standard of care in the treatment of diabetic foot ulcers. International Wound Journal. 2022;19(4):932-944.

10 Serena TE, Yaakov R, Moore S, et al. A randomized controlled clinical trial of a hypothermically stored amniotic membrane for use in diabetic foot ulcers. Journal of Comparative Effectiveness Research. 2020;9(1):23-34.

11 Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. International wound journal. 2018;16(1):122-130.

12 Tettelbach W, Cazzell S, Reyzelman AM, Sigal F, Caporusso JM, Agnew PS. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. Int Wound J. 2019;16(1):19-29.

Further, AHRQ identified wound recurrence after initial healing, return of function, and pain relief as key evidence gaps in a Technical Brief conducted in 2020.[13] Unlike many RCTs supporting products proposed for coverage, Lantis et al. 2023, assessed long term outcomes beyond a 12 week treatment period. The current body of published RCTs in 2024 still has not produced long-term outcomes beyond typical study periods of 12, 16 and 20 weeks, and this is an area that continues to warrant future evidence generation by manufacturers. Lantis et al. 2023 provides sufficient long term outcomes data to offer a relevant basis from which other skin graft technologies can be assessed by CMS / MACs, as more evidence becomes available for long term outcomes.

Given the oversight of Lantis et al. 2023, Avalere encourages CMS / MACs to update its cut-off date for publications to be inclusive of the most recent innovations in skin substitutes and CTPs. Avalere believes the same standards and requirements used by MACs in assessing RCTs for proposed covered products have been met by Lantis et al. 2023.

Avalere's conclusions are based on quantitative comparisons of study designs and outcomes and on qualitative assessments. To mitigate the subjective nature of qualitative research, Avalere relied on subject matter experts familiar with clinical research methods, LCDs/NCDs, and diabetes technology.

13 Snyder D, Sullivan N, Margolis D, Schoelles K. Skin substitutes for treating chronic wounds. Technology Assessment Program Project ID No. WNDT0818. (Prepared by the ECRI Institute-Penn Medicine Evidence-based Practice Center under Contract No. HHSA 290-2015-00005-I) Pub Med® Web site. Accessed May 28, 2024.

Appendix A. Relevant Fish Skin Graft Studies

1. **Lantis II JC, Lullove EJ, Liden B, et al. Final efficacy and cost analysis of a fish skin graft vs standard of care in the management of chronic diabetic foot ulcers: a prospective, multicenter, randomized controlled clinical trial. Wounds. 2023;35(4):71-79. doi:**10.25270/wnds/22094.

   Introduction. DFUs remain a cause of significant morbidity. Objective. This is the third of 3 planned articles reporting on a prospective, multicenter, randomized controlled trial evaluating the use of omega-3–rich acellular FSG (fish skin graft) compared with CAT (collagen alginate therapy) in the management of DFUs.

   Materials and Methods. A total of 102 patients with a DFU (n = 51 FSG, n = 51 CAT) participated in the trial as ITT candidates, with 77 of those patients included in the PP analysis (n = 43 FSG, n = 34 CAT). Six months after treatment, patients with healed ulcers were followed up for ulcer recurrence. A cost analysis model was applied in both treatment groups.

   Results. The proportion of closed wounds at 12 weeks was compared, as were the secondary outcomes of healing rate and mean PAR. Diabetic foot wounds treated with FSG were significantly more likely to achieve closure than those managed with CAT (ITT: 56.9% vs 31.4%; P =.0163). The mean PAR at 12 weeks was 86.3% for FSG vs 64.0% for CAT (P =.0282).

   Conclusions. Treatment of DFUs with FSG resulted in significantly more wounds healed and an annualized cost savings of $2818 compared with CAT.

2. **Lullove EJ, Liden B, McEneaney P, et al. Evaluating the effect of omega-3–rich fish skin in the treatment of chronic, nonresponsive diabetic foot ulcers: penultimate analysis of a multicenter, prospective, randomized controlled trial. Wounds. 2022;34(4):e34-e36. doi:**10.25270/wnds/2022.e34e36.

   Objective: This is the second of 3 planned articles reporting on a prospective, multicenter, randomized controlled trial assessing the efficacy of fish skin graft in the management of diabetic foot ulcers in comparison with the standard of care (collagen alginate dressing).

   Materials and Methods: The primary end point of this prospective randomized trial is the number of closed wounds at 12 weeks.

   Results: As of the time of this writing, 94 patients had completed the protocol. At 12-week follow-up, healing was achieved in 63.0% of index ulcers (29 of 46 patients) in the acellular fish skin graft group compared with 31.3% in the control group (15 of 48 patients) (P =.0036). In both groups, the mean time to healing was 7 weeks. The median number of applications of the fish skin graft to achieve healing was 6.

Conclusion: A clinically and statistically significant difference in healing was observed between patients treated with acellular fish skin graft and those treated with a collagen alginate dressing. The data support the completion of this prospective randomized trial.

3. **Zehnder T, Blatti M. Faster Than Projected Healing in Chronic Venous and Diabetic Foot Ulcers When Treated with Intact Fish Skin Grafts Compared to Expected Healing Times for Standard of Care: An Outcome-Based Model from a Swiss Hospital. The International Journal of Lower Extremity Wounds. 2022;0(0). doi:10.1177/15347346221096205.**

Purpose: Inadequate response to wound management is defined as a reduction in the wound area of <40-50% following four weeks of standard of care (SOC) and should be managed with a skin substitute product. We set out to evaluate a novel outcome-based model focusing on the management of hard-to-heal venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs) using SOC treatment or intact fish skin grafts (FSGs) in a regional hospital.

Methods: We built an outcome-based model applying surrogate markers and endpoints of wound healing for VLU and DFU to determine the healing trajectory with SOC treatment. We could predict if VLU and DFU would heal by weeks 20 and 24, respectively, after four weeks of evaluating the initial wound area reduction. 51 patients were recruited (26 VLUs and 25 DFUs) and 42 wounds were randomized. 17 wounds deemed unlikely to heal by week 8 received management with FSG as per the Swiss Society for Dermatology and Venereology (SGDV) and the Swiss Association for Woundcare (SAfW) guidelines for the use of skin replacement products, and 26 wounds continued SOC for weeks 5-8.

Results/Discussion: 12 wounds managed with FSG beat the modeled SOC healing predictions, with the majority healed >50% sooner and as early as <10% of the time than was predicted. Of these 17, five wounds failed to achieve the required size reduction in Week 4-8 (over 25% improvement in wound area vs. SOC). The FSG were assigned to treatment-resistant VLU and DFUs and were still able to heal these wounds most of the time and even changed the wound's healing trajectory that increased in size in the initial four weeks.

Conclusion: This pilot study showed that management with FSG results in faster healing wounds than SOC predicted, while SOC-treated wounds mostly followed model predictions.

Appendix B. Selected Evidence for Covered DFU Products based on LCDs

Product	Citation
Affinity® Hypothermically Stored Amniotic Membrane (HSAM)	Serena TE, Yaakov R, Moore S, et al. A randomized controlled clinical trial of a hypothermically stored amniotic membrane for use in diabetic foot ulcers. Journal of Comparative Effectiveness Research. 2020;9(1):23-34.
AmnioBand® Dehydrated Human Amnion and Chorion allograft (dHACA)	Glat P, Orgill DP, Galiano R, et al. Placental Membrane Provides Improved Healing Efficacy and Lower Cost Versus a Tissue-Engineered Human Skin in the Treatment of Diabetic Foot Ulcerations. Plast Reconstr Surg Glob Open. 2019;7(8):e2371.
AmnioBand® Dehydrated Human Amnion and Chorion allograft (dHACA)	DiDomenico LA, Orgill DP, Galiano RD, et al. Aseptically Processed Placental Membrane Improves Healing of Diabetic Foot Ulcerations: Prospective, Randomized Clinical Trial. Plast Reconstr Surg Glob Open. 2016;4(10):e1095.
AmnioBand® Dehydrated Human Amnion and Chorion allograft (dHACA)	DiDomenico LA, Orgill DP, Galiano RD, et al. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients. Int Wound J. 2018;15(6):950-957.
Apligraf®	Veves A, Falanga V, Armstrong DG, Sabolinski ML, Apligraf Diabetic Foot Ulcer S. 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(2):290-295.
Apligraf®	Steinberg JS, Edmonds M, Hurley DP, Jr., King WN. Confirmatory data from EU study supports Apligraf for the treatment of neuropathic diabetic foot ulcers. J Am Podiatr Med Assoc. 2010;100(1):73-77.
Apligraf®	Edmonds M, European, Australian Apligraf Diabetic Foot Ulcer Study G. Apligraf in the treatment of neuropathic diabetic foot ulcers. Int J Low Extrem Wounds. 2009;8(1):11-18.
Apligraf®	Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. Int Wound J. 2015;12(6):724-732.
DermACELL®, awm, porous	Walters J, Cazzell S, Pham H, Vayser D, Reyzelman A. Healing rates in a multicenter assessment of a sterile, room temperature, acellular dermal matrix versus conventional care wound management and an active comparator in the treatment of full-thickness diabetic foot ulcers. Eplasty. 2016;16.

Product	Citation
DermACELL®, awm, porous	Cazzell S, Moyer PM, Samsell B, Dorsch K, McLean J, Moore MA. A prospective, multicenter, single-arm clinical trial for treatment of complex diabetic foot ulcers with deep exposure using acellular dermal matrix. Advances in Skin & Wound Care. 2019;32(9):409.
Dermagraft®	Marston WA, Hanft J, Norwood P, Pollak R, Dermagraft Diabetic Foot Ulcer Study G. 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(6):1701-1705.
Dermagraft®	Sanders L, Landsman AS, Landsman A, et al. A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. Ostomy/wound management. 2014;60(9):26-38.
Dermagraft®	Gentzkow GD, Iwasaki SD, Hershon KS, et al. Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. Diabetes care. 1996;19(4):350-354.
Epicord®	Tettelbach W, Cazzell S, Sigal F, et al. A multicentre prospective randomised controlled comparative parallel study of dehydrated human umbilical cord (EpiCord) allograft for the treatment of diabetic foot ulcers. International wound journal. 2018;16(1):122-130.
EpiFix®	Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. Int Wound J. 2013;10(5):502-507.
Epifix®	Zelen CM, Serena TE, Gould L, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. International wound journal. 2016;13(2):272-282.
Epifix®	Tettelbach W, Cazzell S, Reyzelman AM, Sigal F, Caporusso JM, Agnew PS. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. Int Wound J. 2019;16(1):19-29.
Epifix®	Zelen CM, Gould L, Serena TE, Carter MJ, Keller J, Li WW. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. Int Wound J. 2015;12(6):724-732.
FlexHD/AllopathHD/ Allopatch pliable/ Matrix HD®	Zelen C, Orgill D, Serena T, et al. A prospective, randomised, controlled, multicentre clinical trial examining healing rates, safety and cost to closure of an acellular reticular allogenic human dermis versus standard of care in the treatment of chronic diabetic foot ulcers. Int Wound J. 2017;14(2):307-315.
Grafix stravix prime pl®	Lavery L, Fulmer J, Shebetka K, et al. The efficacy and safety of Grafix®) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. Int Wound J. 2014 5:554-66.

Product	Citation
Graftjacket®	Brigido SA, Boc SF, Lopez RC. Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. In. Vol 27: SLACK Incorporated Thorofare, NJ; 2004:S145-S149.
Graftjacket®	Brigido SA. The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. International wound journal. 2006;3(3):181-187.
Graftjacket®	Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. International wound journal. 2009;6(3):196-208.
Graftjacket®	Walters J, Cazzell S, Pham H, Vayser D, Reyzelman A. Healing rates in a multicenter assessment of a sterile, room temperature, acellular dermal matrix versus conventional care wound management and an active comparator in the treatment of full-thickness diabetic foot ulcers. Eplasty. 2016;16.
Integra® or Omniograft dermal regeneration template	Driver VR LL, Reyzelman AM, et al. A clinical trial of Integra Template for diabetic foot ulcer treatment. Wound Repair Regen 2015 23(6):891-900.
Oasis® tri-layer wound	Cazzell SM, Lange DL, Dickerson JE, Jr., Slade HB. The Management of Diabetic Foot Ulcers with Porcine Small Intestine Submucosa Tri-Layer Matrix: A Randomized Controlled Trial. Adv Wound Care (New Rochelle). 2015;4(12):711-718.
Oasis® wound matrix	Landsman A, Roukis TS, DeFronzo DJ, Agnew P, Petranto RD, Surprenant M. Living cells or collagen matrix: which is more beneficial in the treatment of diabetic foot ulcers? Wounds: a compendium of clinical research and practice. 2008;20(5):111-116.
Oasis® wound matrix	Niezgoda JA, Van Gils CC, Frykberg RG, Hodde JP. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. Adv Skin Wound Care. 2005;18(5 Pt 1):258-266.
PriMatrix®	Lantis JC, Snyder R, Reyzelman AM, et al. Fetal bovine acellular dermal matrix for the closure of diabetic foot ulcers: a prospective randomised controlled trial. J Wound Care. 2021;30(Sup7):S18-S27.
PriMatrix®	Kavros SJ, Dutra T, Gonzalez-Cruz R, et al. The use of PriMatrix, a fetal bovine acellular dermal matrix, in healing chronic diabetic foot ulcers: a prospective multicenter study. Advances in skin & wound care. 2014;27(8):356-362.
Theraskin®	Armstrong DG, Galiano RD, Orgill DP, et al. Multi-centre prospective randomised controlled clinical trial to evaluate a bioactive split thickness skin allograft vs standard of care in the treatment of diabetic foot ulcers. International Wound Journal. 2022;19(4):932-944.
Theraskin®	Sanders L, Landsman AS, Landsman A, et al. A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. Ostomy/wound management. 2014;60(9):26-38.

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Theraskin®	DiDomenico L, Landsman AR, Emch KJ, Landsman A. A prospective comparison of diabetic foot ulcers treated with either a cryopreserved skin allograft or a bioengineered skin substitute. Wounds. 2011;23(7):184-189.
Theraskin®	Gurtner GC, Garcia AD, Bakewell K, Alarcon JB. A retrospective matched-cohort study of 3994 lower extremity wounds of multiple etiologies across 644 institutions comparing a bioactive human skin allograft, TheraSkin, plus standard of care, to standard of care alone. International Wound Journal. 2020;17(1):55-64.
Theraskin®	Barbul A GG, Gordon H, Bakewell K, Carter MJ. Matched-cohort study comparing bioactive human splitthickness skin allograft plus standard of care to standard of care alone in the treatment of diabetic ulcers: A retrospective analysis across 470 institutions. Wound Repair Regen. 2020 28(1):81-89.