Tiger BioSciences • 555 E North Lane, Ste 5000, Bldg D • Conshohocken, PA 19428 • www.tigerbios.com

Submitted electronically to ***http://www.regulations.gov***

September 12, 2025

Dr. Mehmet Oz, Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
200 Independence Ave., S.W.
Washington, D.C. 20201

Re: Comments on CMS-1832-P, "Medicare and Medicaid Programs; CY 2026 Payment Policies Under the Physician Fee Schedule and Other Changes to Part B Payment and Coverage Policies; Medicare Shared Savings Program Requirements; and Medicare Prescription Drug Inflation Rebate Program" (CMS-1832-P, 90 Fed. Reg. 32352, July 16, 2025)

Re: Comments on CMS-1834-P, "Medicare and Medicaid Programs: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems; Quality Reporting Programs; Overall Hospital Quality Star Ratings; and Hospital Price Transparency" (CMS-1834-P, 90 Fed. Reg. 33476, July 17, 2025)

Dear Administrator Oz:

Tiger Medical Holdings, LLC, Tiger Wound Care Medical, LLC, Extremity Care, LLC, RegenTX Partners, LLC, and Birth Tissue Recovery, LLC (collectively "Tiger BioSciences") submit these comments to express their grave concerns with respect to certain proposals included in the Medicare Physician Fee Schedule (MPFS)[1] and Hospital Outpatient Prospective Payment System (OPPS)[2] proposed rules cited above (collectively and individually, the "Proposed Rule(s)"). Tiger BioSciences' comments below pertain to the proposed Medicare reimbursement framework for cellular, acellular, and matrix-like products (CAMPs or "skin substitutes") in Section II.K. of the MPFS Proposed Rule and Section V.B.9. of the OPPS Proposed Rule (the "Skin Substitutes Proposals"). **As the Skin Substitutes Proposals in both Proposed Rules are intertwined and identical in many respects, our comments pertain in equal measure to both the MPFS and OPPS Proposed Rules, except as expressly noted otherwise.**

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[1] CY 2026 MPFS Proposed Rule, 90 Fed. Reg. 32352, 32512-22 (Jul. 16, 2025) [CMS-1832-P] RIN 0938-AV50, *available at* https://www.govinfo.gov/content/pkg/FR-2025-07-16/pdf/2025-13271.pdf.

[2] CY 2026 OPPS Proposed Rule, 90 Fed. Reg. 33276, 33639-49 (Jul. 17, 2025) [CMS-1834-P] RIN 0938-AV51, *available at* https://www.govinfo.gov/content/pkg/FR-2025-07-17/pdf/2025-13360.pdf.

Understanding the various issues the Government is seeking to address by these rules,[3] as proposed, the rules will not cure those issues and will instead greatly limit Medicare beneficiary access to wound healing products, rendering these rules arbitrary and capricious on their face. Put simply, the fee schedule proposed is significantly out of line with the operational costs to bring these necessary products to market and thus will negatively impact the very patients we are all striving to assist. Based on the concerns set forth in detail below, we respectfully request the withdrawal of the Skin Substitutes Proposals in the Proposed Rules and that, instead, that a uniform fee schedule be implemented consistent with the figures set forth below.

Please note, our comments and the evidence included in this Comment Letter also have been distilled into an Executive Summary attached hereto as **Appendix A**.

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[3] *See* CMS Proposes Physician Payment Rule to Significantly Cut Spending Waste, Enhance Quality Measures, and Improve Chronic Disease Management for People with Medicare (July 14, 2025) (hereinafter "MPFS Proposed Rule Press Release"), *available at* https://www.cms.gov/newsroom/press-releases/cms-proposes-physician-payment-rule-significantly-cut-spending-waste-enhance-quality-measures-and.

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I. Who We Are and What We Do

a. Our Mission

Tiger BioSciences is a leader in wound care and soft tissue reconstruction, utilizing many products, including the inherent basic characteristics of placental tissue to create CAMPs, that provide the barrier or covering to allow the human body to heal itself through its own regenerative capabilities. Delivering a wide range of human cell and tissue products backed by science, Tiger BioSciences oversees every stage of its products, including donor screening and tissue collection, ensuring each of its human tissue-based skin substitute products meets the highest standards for safety, consistency, and sterility, and backed by clinical efficacy. Tiger BioSciences is a privately-owned, vertically-integrated, biotechnology enterprise headquartered in Conshohocken, Pennsylvania, focusing on human cell and tissue technologies. We have more than 750 employees spread across the United States, including in, among other locations, Pennsylvania, Texas, Illinois, Wisconsin, and North Carolina. Our products have been used in the treatment of hundreds of thousands of wounds, and have helped clinicians save patients from complications, amputations, and death. We are deeply concerned that these rules as proposed are going to reverse the great progress we have made in helping these patients.

b. Our Products

Tiger BioSciences produces and/or distributes multiple, placental human tissue products that are used for the treatment of non-healing wounds including, among others, ACApatch, caregraFT, alloPLY™, completeFT™, Resolve Matrix™, Procenta®, barrera™, and carePATCH™. Each of our products is either regulated by the U.S. Food and Drug Administration (FDA) as human cell, tissue, and cellular/tissue based products under Section 361 of the Public Health Service Act or cleared by the FDA through the 510(k) process.

Our placental-based products are grounded on years of extensive research proving that placental tissue is the material of choice for the treatment of non-healing wounds. Engineered placental tissue frequently differ depending on how many layers of the placental membrane were incorporated into the placental cover design. Retaining the full placental membrane (at least 3 layers) retains a broader profile of proteins and covers the wound so as to avoid the introduction of contaminants or bioburden, which has been shown to support wound closure and have a direct correlation with (1) reduced wound infections and (2) overall limb removal reductions. And, as evidenced below, preliminary data from our ongoing randomized clinical trials proves that our products work and is consistent with other studies on other similar products.

c. Our Patients

Many of our products address the advanced care needs of homebound patients and those residing long term in residential care settings (e.g., nursing facilities). In today's non-healing wound reality, many patients treated with CAMPs are unable physically to go to seek treatment. They rely on the provider's ability to come and treat the wound wherever the patient resides. Many times, especially in the treatment of pressure inflicted wounds for this non-mobile population,

mobile wound care providers are the last resort for critically ill patients, many of whom have underlying co-morbidities. In addition to basic access restrictions, patients who receive our products suffer from chronic pain, the inability to complete activities of daily living, amputations, loss or limb or even life.

Additionally, many of our products provide critical care for vulnerable and at-risk patients. Diabetes, for example, disproportionately affects vulnerable patient populations including aging Americans eligible for Medicare, minority populations, and those living in rural and underserved communities. According to the American Diabetes Association (ADA), nearly thirty percent (29.2%) of Americans aged sixty-five (65) and older suffer from diabetes, with diagnosis rates disproportionately higher for adult American Indian and Alaskan Native, Black, Hispanic, and Asian American populations.[4] Prevalence is also higher among adults in rural (nonmetropolitan) areas.[5]

Diabetic foot ulcers and venous leg ulcers are also associated with significant preventable morbidity, including lower-extremity amputation, decline in functional status, hospitalization, and death.[6] Up to thirty-four percent (34%) of older diabetic patients will eventually develop a diabetic foot ulcer; sixty-five percent (65%) of patients who develop one DFU will develop another within three to five years; twenty percent (20%) of DFU patients will eventually require a lower-extremity amputation; and fifty to seventy percent (50-70%) of DFU patients will likely die within five years of their first DFU.[7]

More than seventeen percent (17.6%) of Medicare beneficiaries hospitalized with diabetic foot ulcers ultimately underwent major leg amputation or died.[8] This number increases to nearly twenty-two percent (21.9%) for patients identifying as Black and more than twenty-eight percent (28.1%) for *rural* patients identifying as Black.[9] Medicare beneficiaries with venous leg ulcers had nearly two times as many hospital days and fifty-percent (50%) more emergency room visits compared to those without ulcers.[10]

Diabetes and related conditions place a staggering burden on our healthcare system—especially on these vulnerable populations.[11] With patient access to our products through

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[4] https://diabetes.org/about-diabetes/statistics/about-diabetes.

[5] https://www.cdc.gov/diabetes/php/data-research/.

[6] *See*, *e.g.*, Katherine McDermott et al., *Etiology, Epidemiology, and Disparities in the Burden of Diabetic Foot Ulcers*, 46 Diabetes Care 209-21 (2023), https://doi.org/10.2337/dci22-0043.

[7] Id.

[8] Brennan MB et al., Association of Race, Ethnicity, and Rurality With Major Leg Amputation or Death Among Medicare Beneficiaries Hospitalized With Diabetic Foot Ulcers, *JAMA Netw Open*. 2022;5(4):e228399; https://doi.org/10.1001/jamanetworkopen.2022.8399.

[9] Id.

[10] Rice JB et al., Burden of venous leg ulcers in the United States, *J. Med. Econ.* 2014 May; 17(5):347-356; https://pubmed.ncbi.nlm.nih.gov/24625244/.

[11] According to a study published in the January 2024 edition of ADA's *Diabetes Care* journal, the estimated average additional healthcare expenditures *per-person* aged sixty-five (65) or older with diabetes was $17,180 per year in

Medicare, however, this burden is reduced, and these vulnerable patient populations are healthier and better equipped to prevent further morbidity.

II. How We Got Here

Although a common belief is that the exploding Medicare spend on CAMPs is due to fraud, abuse, and overutilization, the fact is that the marketplace has changed.[12]

Without denying the reality that some fraud and abuse may occur, the increase in Medicare spend relating to skin substitutes is primarily a result of the fact that more individuals with larger wounds in rural locations are now finally able to access treatment and survive the ailment.[13] And, with proven efficacy, more physicians, providers, and patients choose these products because of their high success rates.

Care locations, including mobile wound care providers, have increased to fill the gap needed for homebound patients and those residing in other residential care settings (including nursing facilities). This has brought significant health care treatment opportunities to patients in rural, socioeconomically challenged, and underserved communities. This has also led to increased treatment not only for diabetic foot ulcers and venous leg ulcers, but pressure wounds and other wound care needs.[14]

When used appropriately and at fair market value, CAMPs actually reduce overall health costs by closing high risk chronic non-healing wounds and preventing complications such as infections that can lead to amputations, increased hospital visits, and death.[15]

It is important to note that cost and reimbursement frameworks for mobile wound care providers—who serve a vulnerable patient population—are significantly different than for hospitals, making these providers less able to weather losses caused by sustained inadequate reimbursement rates for skin substitute application procedures and products and increased (and

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2022. Emily D. Parker et al., Economic Costs of Diabetes in the U.S. in 2022. *Diabetes Care* 2 January 2024; 47 (1): 26–43; https://doi.org/10.2337/dci23-0085. It follows that the Medicare program's costs to manage diabetes-related complications for a diabetic population of approximately 29.2 percent of approximately sixty-eight (68) million Medicare fee-for-service and managed care enrollees in 2025 likely exceeds $340 billion annually.

[12] CMS acknowledges this: "We continue to believe that our existing payment policies are unsatisfactory, unsustainable over the long term, and rooted in historical practice established two decades ago prior to significant evolutions in medical technology and practice." 90 Fed. Reg. at 33639. (OPPS Proposed Rule)

[13] William Tettelbach et al., *Safeguarding access, fiscal responsibility and innovation: a comprehensive reimbursement framework for CAMPs to preserve the Medicare Trust Fund*, 34:10 J. of Wound Care (Oct. 2025), https://doi.org/10.12968/jowc.2025.0396.

[14] Id.

[15] *See generally* William Tettelbach et al., *The Hidden Costs of Limiting Access: Clinical and Economic Risks of Medicare's Future Effective Cellular, Acellular and Matrix-Like Products (CAMPs) Local Coverage Determination*, 34:5 J. of Wound Care (May 2025), https://pubmed.ncbi.nlm.nih.gov/40358505/.

illegal) claw-backs, masquerading as if the repeatedly postponed, proposed Local Coverage Determination (LCD), discussed further below, were already in effect.

While it is clear from available Medicare claims data and patient demographic information that Medicare spending on wound care, including skin substitutes, has increased significantly due to expanded patient access to treatment, as discussed above, it is also clear that Medicare's historic Average Sales Price (ASP)-based reimbursement framework has propelled increases in Medicare spending over the last several years.

The existing ASP-based reimbursement model has led to price increases and Medicare cost explosion. Forcing ASP on industry participants drove significant price increases. We wholeheartedly support, and have for years advocated for, the transition to a site-neutral, fixed-rate fee schedule reimbursement framework over the historical ASP-based system. This approach would yield substantial and material savings to the Medicare program, as further discussed below.

Although we acknowledge the need to curb the increase in Medicare spending for skin substitutes over the past several years, and we support the transition to a site-neutral, fixed-rate fee schedule reimbursement framework for CAMPs, the proposed payment rate of $125.38/cm^2 is far too low and is completely indefensible on the facts and law.

The rate proposal included in the Proposed Rules ignores marketplace realities, as well as critical changes and challenges in patient care and care delivery settings, rendering the proposals arbitrary and capricious. The rate proposal has no viable substantiation in any calculation methodology. The proposed rate in combination with the deeply problematic proposed LCD—currently slated to go into effect January 1, 2026[16]—will together lead to substantial avoidable adverse effects for the Medicare population.

III. Our Products Work

There is no doubt that placental-based products work. As discussed below, empirical evidence has proven that the products save limbs and lives, improve patient quality of life, and reduce overall costs of care. Indeed, national media outlets, including the likes of the New York Times, have often highlighted and applauded the efficacy of placental-based products, like our

[16] *See, e.g.*, Novitas, Skin Substitute Grafts/Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers (L35041) (eff. 1/1/2026) (collectively, with all the MACs' respective LCDs on this topic , the "Proposed LCD"), *available at* https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35041&ver=140.

products.[17] It is also clear that more technologically advanced, multi-layer products like ours work better than single- or dual-layer products.[18,19]

Wound healing is the process by which the body repairs and regenerates damaged tissue after an injury. This is a complex process that involves a variety of cellular and molecular events, including homeostasis, inflammation, cell migration, proliferation, and tissue remodeling.[20,21] Chronic wounds can develop due to a patient's poor circulation, nerve damage, immobility, weakened immune system, or other factors, impairing a wound's ability to heal using standard of care. Chronic wounds increase a patient's risk of complications, like infection, scarring, and even amputation.[22]

Placental-derived skin substitutes are composed of extracellular matrix (ECM) that stand in place of native tissue, which scientific studies have stated create a reparative environment to reduce inflammatory response and promote cell migration and tissue regeneration.[23] As the studies recognize, placental tissues exhibit remarkable similarities to skin in terms of their regenerative capacity, structural composition, and abundance of growth factors.[24,25] And, further, these studies explain that these properties enable them to promote tissue repair and wound closure in ulcers.[26] When compared with standard wound care, the application of placental-derived products significantly improves the proportion of ulcer closures, time to closure and rates of closure, and ulcer size.[27]

There is a long history of the success of these products. The first report of skin transplantation with the use of the fetal membrane was in 1910 by Davis, J. W., and in 1940, De

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[17] *See*, *e.g.*, Kate Morgan, Her Face Was Unrecognizable After an Explosion. A Placenta Restored It, N.Y. Times (Oct. 8, 2024), https://www.nytimes.com/2024/10/08/well/placenta-donations-burns-wounds.html.

[18] William V. Padula et al., *Comparative Effectiveness of Placental Allografts in the Treatment of Diabetic Lower Extremity Ulcers and Venous Leg Ulcers in U.S. Medicare Beneficiaries: A Retrospective Observational Cohort Study Using Real-World Evidence*, 13 Advances in Wound Care 350–362 (2024). https://doi.org/10.1089/wound.2023.0143.

[19] Pragya Singh et al., *Comparative Study of Placental Allografts with Distinct Layer Composition*, 26 Int'l. J. Molecular Sci. (2025), https://pmc.ncbi.nlm.nih.gov/articles/PMC11989501/.

[20] Nicole M. Protzman et al., *Placental-Derived Biomaterials and Their Application to Wound Healing: A Review*, 10 Bioengineering (2023), https://pubmed.ncbi.nlm.nih.gov/37508856/.

[21] Marion Rouzaire et al., *Application of Fetal Membranes and Natural Materials for Wound and Tissue Repair*, 25 Int'l J. Mol. Sci. (2024), https://www.researchgate.net/publication/385572903_Application_of_Fetal_Membranes_and_Natural_Materials_for_Wound_and_Tissue_Repair.

[22] Id.

[23] Id.

[24] Daniela J. Arezina & Dan Li, *The exploration of the use of placenta in Diabetic Ulcer Disease: A Systematic Review*, 12 Med. Rsch. Archives (2024), https://doi.org/10.18103/mra.v12i12.5978.

[25] John P. McQuilling et al., *Characterisation of dehydrated amnion chorion membranes and evaluation of fibroblast and keratinocyte responses in vitro*, 16 Int'l Wound J. 827-40 (2019), https://doi.org/10.1111/iwj.13103.

[26] Arezina & Li, *supra* note 24.

[27] Protzman, *supra* note 20.

Roth first reported the use of fetal membranes in the ocular surface.[28,29,30] Since then, placental tissues have gained significant popularity as coverings or barriers for wounds to allow for the body to regenerate tissue.[31] The amniotic membrane was used for numerous applications as a surgical dressing for burns and as an adjunctive tissue in surgical reconstruction of the oral cavity, bladder, and also for tympanoplasty, arthroplasty, repair of omphaloceles, and prevention of adhesions in pelvic and abdominal surgery.[32] The use of CAMPs has expanded to broader clinical applications in wound management, including treatment of both acute and chronic wounds.[33]

Over time, placental allografts have arisen as promising options due to their rich composition of extracellular matrix components and growth factors, as such they have emerged as valuable adjuncts for use alongside traditional wound-related standard of care.[34,35] For example, a review of placental tissue therapies applied to diabetic foot ulcers (DFUs) revealed that within the initial 11 weeks of treatment, patients undergoing placental tissue therapies experience major improvements in wound closure rates and symptom relief.[36] The time to heal with placental tissue interventions is notably shorter compared to the standard of care using conventional methods including debridement, wound dressing, offloading, and antibiotics, with patients experiencing faster closure rates and reduced healing times, including a mean healing time of 37 days versus 67 days.[37] These comparisons highlight the effectiveness of placental therapies in promoting faster and more comprehensive wound healing.

That said, not all skin substitutes are created equally. The placental membrane consists of three distinct layers.[38] Some products contain only one of these naturally occurring layers, while

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[28] Iveta Schmiedova et al., *Using of Amniotic Membrane Derivatives for the Treatment of Chronic Wounds*, 11(12):941 Membranes (2021), https://pmc.ncbi.nlm.nih.gov/articles/PMC8706466/.

[29] Mathilde Fénelon et al., *Applications of Human Amniotic Membrane for Tissue Engineering,* 11(6):387 Membranes (2021), https://pmc.ncbi.nlm.nih.gov/articles/PMC8227127/.

[30] Antonietta R. Silini et al., *The long path of human placenta, and its derivatives, in regenerative medicine*, 3 Front. Bioengineering & Biotechnology (2015), https://doi.org/10.3389/fbioe.2015.00162.

[31] Id.

[32] Id.

[33] Seana Rutherford et al., *A retrospective, observational case series of lower-extremity wound management using CompleteFT*, 1 The Int'l J. of Tissue Repair (2025), https://www.internationaljournaloftissuerepair.com/index.php/ijtr/article/view/2.

[34] Olena Pogozhykh et al., *Placenta and Placental Derivatives in Regenerative Therapies: Experimental Studies, History, and Prospects*, 2018 Stem Cells Int'l (2018), https://doi.org/10.1155/2018/4837930.

[35] Taja Železnik Ramuta et al., *Antimicrobial Activity of Human Fetal Membranes: From Biological Function to Clinical Use* 9 Front. Bioengineering & Biotechnology (2021), https://doi.org/10.3389/fbioe.2021.691522.

[36] Arezina & Li, *supra* note 24.

[37] Id.

[38] Arezina & Li, *supra* note 24.

others contain two or three.[39] More advanced, multi-layer placental-based products—such as our products—ultimately provide a thicker covering for a wound that would lead to more rapid wound closure rates and reduced amputation, recurrence, and mortality as compared to less advanced products.[40]

One recent study compared the inherent basic characteristics of placental tissue in allografts with distinct layer composition. As noted in that study, the placenta is naturally composed of three distinct layers including the amnion, intermediate (or spongy) layer, and chorion, each contributing unique biological components to support wound protection:

- The **amnion**, the innermost layer, is composed of an epithelium, a basement membrane, a compact layer, and a fibroblast layer. Its ECM is particularly rich in collagens I and III as well as other matrix-associated proteins.

- The **intermediate layer**, located between the amnion and chorion, contains proteoglycans, glycoproteins, hyaluronic acid (HA), and collagen type III, and serves as a reservoir for additional ECM components. It also contains naturally occurring growth factors such as ANG-2 (angiopoietin-2), EGF (epidermal growth factor), PDGF-AA (platelet-derived growth factor), and VEGF (vascular endothelial growth factor). These growth factors, intrinsic to the intermediate layer, play essential roles in fetal development, participating in cellular processes such as vascularization, proliferation, and tissue remodeling.[41]

- The **chorion**, the outermost layer, contains the reticular layer, basement membrane, and trophoblast layer, with a dense ECM composed of collagens I, III, IV, V, and VI, along with other structural components.

This study found that, of the three products tested, the two more advanced allografts, which retain all three layers, contain significantly higher protein content than the amnion-only allograft. Because ECM proteins are central to forming a cohesive barrier at injury sites, these findings suggest that retaining more placental layers yields an allograft with greater biochemical complexity.[42]

As a result of findings like these, recent allograft advancements have led to the development of "full-thickness" grafts which retain all three placental membrane layers.[43] One such Tiger BioSciences product is our completeFT™, which preserves the placenta's rich ECM and retains naturally occurring growth factors. In a recent case series of completeFT™, the product

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[39] Thomas J. Koob et al., *Cytokines in single layer amnion allografts compared to multilayer amnion/chorion allografts for wound healing,* 103(5):1133-40 J. Biomed. Materials Rsch. Part B (2014), https://pubmed.ncbi.nlm.nih.gov/25176107/.

[40] Padula, *supra* note 18.

[41] Singh, *supra* note 19.

[42] Id.

[43] Rutherford, *supra* note 33.

demonstratedly succeeded in wound closure. The study examined seven wounds (including pressure injuries, traumatic wounds, and vascular ulcers) with wound sizes varying from 2 cm to 440 cm^2. Each of these wounds were managed with standard of care prior to the application of completeFT™ with minimal progress in wound closure observed during that period. Of seven wounds evaluated, the study reflected that four saw complete closure and the largest wound (measuring 440 cm^2) showed 87.3% wound closure at the 12-week mark.[44]

In contrast, many commercially available placental-derived allografts do not retain all three layers in their final forms due to the intermediate layer's susceptibility to separation during processing.[45] Instead, some allografts consist of only amnion, others include both the amnion and chorion layers, and some feature additional amnion layers that form tri- or quad-layer allografts. These construct variations can lead to differential retention of the inherent basic characteristics of placental tissue, such as collagen and other ECM components, which can consequently affect the allograft's utility as a wound covering that also serves as a physical barrier to protect the wound. For example, collagen is essential for forming a protective barrier, providing mechanical strength and durability to placental allografts, while elastin enhances flexibility and resilience. Within placental tissue, proteoglycans and HA contribute to matrix organization and hydration, and growth factors work to sustain the biological environment. Despite compositional differences, many of these allografts report the presence of vital placental components after processing and dehydration, which may contribute to their wound-protective properties.[46]

Our approach in the development of different products preserves all three natural layers of the placenta, amnion, intermediate layer, and chorion. Retaining the placenta's natural structure brings important advantages for wound closure. Specifically,

- The intermediate layer contains natural growth factors, absent from the amnion layer. This contributes to a more robust wound environment and supports the body's own healing processes.

- The chorion layer is the thickest part of the placenta and is rich in unique ECM proteins. This adds durability and structural support to the allograft, helping to protect the wound and maintain stable coverage that is less likely to be disturbed.

- The preservation of each unique placental tissue layer, such as the intermediate and chorion layer, allows for the retention of higher levels of key extracellular matrix components and native growth factors including ANG-2, EGF, PDGF-AA, and VEGF.

Thus, by preserving the natural layers of the placenta, our products retain the tissue's native biological components. This supports both tissue repair and provides the inherent basic

[44] Id.

[45] Singh, *supra* note 19.

[46] Id.

characteristics of placental tissue, resulting in versatile products that provide reliable wound protection.[47,48]

Numerous randomized control trials (RCTs) have demonstrated that skin substitutes work to reduce wound size and to increase healing rates. By way of example only:

- In one RCT, the study group treated with a dehydrated human amnion and chorion allograft experienced notably faster rates of healing as compared to the group receiving standard of care alone. At 12 weeks, 85% (34/40) of the allograft-treated DFUs healed, compared with 33% (13/40) treated with standard of care alone. Mean time to heal within 12 weeks was significantly faster for the allograft- treated group (37 days) as compared with the standard of care group (67 days) (P = .000006).[49]

- In another RCT, at 4 weeks, 62% in the allograft group and 32% in the control group showed a greater than 40% wound closure ($p = 0.005$), thus showing a significant difference between the allograft-treated groups and the multilayer compression therapy alone group at the 4-week surrogate endpoint; after 4 weeks, wounds treated with allograft had reduced in size a mean of 48.1% compared with 19.0% for controls.[50]

Although the success of our products is supported by all of the existing clinical studies in addition to our real life patient experiences, in an effort to further substantiate that our specific products work, Tiger BioSciences is in the process of running two of its own RCTs, both of which have been approved by the governing Institutional Review Board (IRB). Specifically:

- A Multicenter, Prospective, Randomized Controlled Modified Multi-Platform (Matriarch) Trial Evaluating Several Cellular, Acellular, and Matrix-like Products (CAMPs) and Standard of Care Versus Standard of Care Alone in the Management of Nonhealing Diabetic Foot and Venous Leg Ulcers (NCT06826339)[51]

- A Multicenter, Prospective, Randomized Controlled Modified Platform Trial Evaluating Several Cellular, Acellular, and Matrix-like Products (CAMPs) and Standard of Care

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[47] Annelise Roy & Sarah Griffiths, *Intermediate layer contribution in placental membrane allografts*, 14:8 J. Tiss. Engineering & Regen. Med. 1126–35 (2020), https://doi.org/10.1002/term.3086.

[48] Singh, *supra* note 19.

[49] Lawrence A DiDomenico 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. 15(6):950–957 (2018), https://pmc.ncbi.nlm.nih.gov/articles/PMC7949511/.

[50] Thomas E. Serena et al., *A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers,* 22 Wound Repair & Regeneration 688–93 (2014), https://doi.org/10.1111/wrr.12227.

[51] *See* https://www.clinicaltrials.gov/study/NCT06826339.

Versus Matched Standard of Care Controls in the Management of Nonhealing Pressure Ulcers (NCT06999590)[52]

While these studies are ongoing, early preliminary results already show promising wound closure benefits for subjects in the study group as compared to the control group.

IV. Patients Need Our Products And Services

There can be no doubt that our products are reasonable and necessary for the treatment of Medicare beneficiaries' non-healing wounds. One administrative law judge recently confirmed the necessary aspects of placental tissue-based skin substitutes and the related application services. Overturning the decision of the Unified Program Integrity Contractor, in a 54-page decision, Administrative Law Judge Jaya Shurtliff analyzed the various empirical studies and independently concluded the products met "the requirements to be reasonable and necessary in the treatment of beneficiaries."[53] A parade of physicians and providers are available to attest also to this fact, and CMS should not ignore their voices nor the voices of patients—to do so clearly evidences arbitrary and capricious proposed rulemaking.

Large portions of the population are impacted. Approximately 6 of 100 individuals within the US Medicare population are diagnosed with a DFU annually, and, as diabetes rates are projected to increase worldwide with estimates of up to 592 million individuals by 2035.[54] Venous leg ulcers greatly impact daily life[55] and are a significant problem in those aged 65 years and older. The annual prevalence of venous leg ulcer among the elderly was 1.69 (95% CI, 1.65, 1.74). The overall incidence rate was 0.76 (95% CI, 0.71, 0.83) for men and 1.42 (1.35, 1.48) per 100 person-years for women.[56]

And, the situation is dire. Morbidity following incident ulceration is high, with recurrence rates of 65% at 3–5 years, lifetime lower-extremity amputation incidence of 20%, and 5-year mortality of 50–70%. New data suggest overall amputation incidence has increased by as much as 50% in some regions over the past several years after a long period of decline, especially in young and racial and ethnic minority populations. The International Diabetes Foundation estimates that 40 million to 60 million people globally are affected by DFU, a marked increase from 2015 estimates that ranged from 9 million to 26 million. Among people who develop a diabetic foot infection, the majority will require operative intervention for debridement and 15% to 20% will

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[52] *See* https://www.clinicaltrials.gov/study/NCT06999590.

[53] **Exhibit 2**, Decision in OMHA Appeal No. 3-15100221910 ("OMHA Decision").

[54] McQuilling, *supra* note 25.

[55] Anke Persoon et al., *Leg ulcers: a review of their impact on daily life*, 13 J. of Clinical Nursing 341-54 (2004) https://pubmed.ncbi.nlm.nih.gov/15009337/.

[56] David J. Margolis et al., *Venous leg ulcer: Incidence and prevalence in the elderly*, 46 J. Am. Acad. Dermatology 381-86 (2002), https://doi.org/10.1067/mjd.2002.121739.

require amputation for adequate source control or healing. In people with severe infection or osteomyelitis, the amputation rate rises to almost 90%.[57]

Our patient population predominantly resides in long term residential care settings (e.g., nursing facilities) and rural communities lacking ready access to hospital care. It has been documented that, historically, in the United States, 5.7% of adults report a lack of reliable transportation and approximately 5.8 million people postponed medical treatment because of transportation obstacles.[58] In addition, low-income and minority populations are more reliant on public transportation to access healthcare, and certain regions of the country have significantly higher amputation rates.[59] One study has confirmed that: "Transportation is clearly a significant barrier to care for chronic diseases, including DFU, particularly for low-income populations. Potential solutions to this problem include NEMT, telemedicine, and mobile care."[60]

V. The Proposed Rules and Fee Schedule

The Proposed Rules would dramatically and adversely impact this situation by effectively denying many patients access to products that "meet the requirements to be reasonable and necessary in the treatment of beneficiaries." [61]

In the Proposed Rules, CMS proposes to: (a) separate payment for skin substitute products by reimbursing skin substitutes used in the non-facility setting as incident-to supplies under Social Security Act (SSA) § 1861(s)(2)(A) and excluding skin substitutes used in the facility setting from the OPPS packaging policy at 42 C.F.R. § 419.2(b)(16), (b) create a consistent, site-neutral reimbursement rate for skin substitutes irrespective of care settings, and (c) establish uniform reimbursement rates. As discussed in greater detail below, we concur with (a) and (b) but the reimbursement rates are artificially and indefensibly low without a factual basis and will greatly impede the continuation of care that our patient population requires. *See infra* Section VII.

The Medicare reimbursement scheme will have real-world implications for patient care. A too-low reimbursement rate will lead to:

- Economic disincentives for both hospitals and physicians, including mobile wound care providers (who routinely furnish care to patients in post-acute and long-term residential care facilities), to treat both large and small wounds;
- Reduced patient access to high-performing multilayer placental CAMPs, which will have a detrimental impact on patient care in places of service where CAMPs have shown the

[57] McDermott, *supra* note 6.

[58] Lauren T. Vanasse et al., *Spatial associations between measures of public transportation and diabetic foot ulcer outcomes in the state of Georgia: 2016-2019*, 12 BMJ Open Diabetes Rsch. & Care (2024), https://pubmed.ncbi.nlm.nih.gov/39719390/.

[59] Id.

[60] Id.

[61] OMHA Decision, *supra* note 53.

most significant impact on wound healing and limb salvation and will ultimately result in increased Medicare spending and unnecessary deaths; and

- Anemic future investment in product research and development and associated clinical trials, stifling technological advancement and associated improvements in patient outcomes.

It is crucial that Medicare establish a payment rate capable of covering providers' and suppliers' costs for advanced, multi-layer skin substitute products, so patients can receive the tailored, evidence-based wound care solutions they need, as directed by their providers based on their wound type and severity. The payment and coverage landscapes for CAMPs must be addressed synergistically. The CY 2026 payment rate proposals will constrain provider and supplier reimbursement, preventing them from reaching patients and providing much needed medical care. The looming proposed LCD (due to be implemented January 1, 2026), as currently drafted, will constrict product coverage and prevent patient access to some of the most technologically advanced and clinically effective CAMPs, contrary to the Make America Healthy Again (MAHA) Commission's directive to facilitate the use of regenerative medicine products and innovation by modernizing policies to reflect clinical data.[62] The combined impact of these conjoined policies will be to materially and significantly harm vulnerable Medicare patients.

VI. Access Restriction Will Harm Patients and Increase Medicare Costs

In the United States, chronic nonhealing wounds impact 8.2 million Medicare beneficiaries with associated costs ranging from USD 28.1 to USD 96.8 billion.[63] The alarming number of patients affected by chronic nonhealing wounds is expected to rise because of the combined effects of an aging population and the rising rates of diabetes and obesity.[64] As such, chronic wounds represent a significant economic burden to the healthcare system. Patients who do not find relief from their chronic wounds and ulcers experience increased hospitalization, infections, limited mobility and inability to complete ADLs, extended medical treatments, and loss of limb. Many patients experiencing deep non-healing foot ulcers, for example, require multiple surgeries and/or amputations over the years—perhaps one toe amputation at first, a partial bone extraction next, a secondary toe amputation years later, and potentially a foot or below the knee amputation over time. This is not uncommon and—in some cases—is a preventable reality (and cost) for patients with extreme ulcer complications.

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[62] *See* MAHA Commission, *Make Our Children Healthy Again Strategy Report* (Sept. 9, 2025) ("MAHA Strategy Report"), *available at* https://www.whitehouse.gov/wp-content/uploads/2025/09/The-MAHA-Strategy-WH.pdf.

[63] Protzman, *supra* note 20.

[64] Id.

DFUs place a great economic burden on society, both to our healthcare system and due to lost productivity.[65,66,67] In 2017, diabetes directly cost $237 billion in the United States, a 26% increase from 2012.[68] Around one-third of these direct costs were attributable to care for diabetic foot disease.[69] In remarkable contrast, the 2015 direct costs for cancer in the United States were $80.2 billion–nearly equal to the attributable cost of diabetic foot disease.[70] Patients with chronic wounds have poor health-related quality of life in general and wound-related costs are substantial.[71] Restricting access to high-performing CAMPs will disproportionately impact rural and underserved populations who already face significant access-to-care barriers and elevated risk of suboptimal health outcomes.[72] Studies show that racial and socioeconomic disparities in wound care outcomes are closely linked to access to advanced biologics.[73] Additionally, the mortality rate for those who undergo lower extremity amputation due to a DFU is alarming: more than half of people with a major amputation will be deceased within five years.[74] We can and should do better—not worse as is being proposed by CMS and its Medicare Administrative Contractors (MACs).

Despite the widespread occurrence of DFUs, a gap exists for effective treatment strategies, with amputation often presented as the best "solution."[75] The current approach lacks a concrete method for addressing DFUs, because DFU can recur after treatment in approximately 40% of patients treated within 1 year and 65% in 5 years.[76] The presence of recurring wounds and high risk of infection shows the need for an alternative treatment.[77] Studies have shown that timely

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[65] David G. Armstrong et al., *Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer* 13 J. of Foot & Ankle Rsch. (2020), https://onlinelibrary.wiley.com/doi/10.1186/s13047-020-00383-2.

[66] Charles M. Zelen et al., *Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: A long-term follow-up study*, 4:1-4 Wound Medicine (2014), https://www.sciencedirect.com/science/article/pii/S2213909513000402.

[67] Alexandra M. Haugh et al., *Amnion Membrane in Diabetic Food Wounds: A Meta-analysis,* PRS Global Open (2017), https://journals.lww.com/prsgo/fulltext/2017/04000/amnion_membrane_in_diabetic_foot_wounds__a.15.aspx.

[68] Id.

[69] Id.

[70] Id.

[71] Maja Olsson et al., *The humanistic and economic burden of chronic wounds: A systematic review*, 27 Wound Repair & Regeneration 114-15 (2019), https://onlinelibrary.wiley.com/doi/10.1111/wrr.12683.

[72] Jacqueline Cavalcante-Silva et al., *Racial/ethnic disparities in chronic wounds: Perspectives on linking upstream factors to health outcomes*, 32:5 Wound Rep. & Regeneration 770–79 (2024), https://doi.org/10.1111/wrr.13200.

[73] Tettelbach, *Safeguarding access*, *supra* note 13.

[74] Armstrong, *supra* note 65.

[75] Arezina & Li, *supra* note 24.

[76] Id.

[77] William Tettelbach et al., *Treatment patterns and outcomes of Medicare enrolees who developed venous leg ulcers*, 32:11 J. Wound Care 704-18 (2023), https://www.magonlinelibrary.com/doi/pdf/10.12968/jowc.2023.32.11.704.

access to advanced wound care reduces emergency department visits, 30-day hospitalization rates, and long-term care costs.[78] CMS's Skin Substitutes Proposals are shortsighted insofar as they risk harming beneficiaries while increasing net Medicare spending to manage more costly adverse outcomes.

Based on projected 2025 Medicare spending on skin substitutes in the private office and post-acute care settings of $15.38 billion, implementing a fixed reimbursement rate of $704/cm², for example, would result in:

- An immediate **69%** reduction in Medicare reimbursements for skin substitute products,
- An estimated cost savings of up to **$10.57 billion** in the private office and post-acute care settings in the first year of implementation alone, and
- A projected 10-year savings of up to **$105.7 billion**.[79]

It is clear that use of high-quality wound care products can reduce overall spending by shortening treatment, lowering rates of complications, reducing hospitalizations, and reducing rates of amputation.[80]

VII. Our Proposal

a. Summary

We support CMS's proposal to make separate payment for skin substitute products by reimbursing skin substitutes used in the non-facility setting as incident-to supplies under Social Security Act (SSA) § 1861(s)(2)(A) and excluding skin substitutes used in the facility setting from the OPPS packaging policy at 42 C.F.R. § 419.2(b)(16).

We further support CMS's objective of creating a consistent, site-neutral reimbursement rate for skin substitutes irrespective of care settings. However, the separate payment rates established for skin substitute products and skin substitute application procedures must appropriately reimburse providers and suppliers for both their product cost and their work and overhead expenses associated with the application procedures themselves. And, most importantly, the reimbursement rates proposed by CMS in the Proposed Rules are unsustainable, as they will not cover providers' and suppliers' product, labor, and overhead expenses associated with wound care treatments utilizing the most effective, technologically advanced skin substitutes.

On the product side, we support the establishment of a uniform base reimbursement rate of $700 per cm² for all skin substitute products, irrespective of product type or FDA regulatory pathway. This proposed rate is consistent with the clearly supported range of $704 to $975 per cm², which range is supported by publicly available Medicare data and aligns with several

[78] Id.; *see also* Tettelbach, *Safeguarding access*, *supra* note 13. Note that any projections run on current or earlier static data would create false results, failing to consider the *projected* savings.

[79] *See generally* Tettelbach, *Safeguarding access*, *supra* note 13.

[80] Schmiedova, *supra* note 28.

other data-supported reimbursement benchmarks endorsed by various key stakeholders. Moreover, this payment level will:

- Provide significant Medicare savings for skin substitute products;
- Provide significant secondary savings to Medicare through reductions in infections, limb amputations, and hospital and care costs associated with non-healing wounds; and
- Maintain and enhance patient access to these proven limb and life-saving technologies throughout the United States for minorities, veterans, underserved communities, rural communities, and others.

Adopting our proposed reimbursement rate of $700 per cm^2 will result in an immediate reduction in Medicare CAMP expenditures of more than 69%, while providing patients with access to the care they so desperately need.[81] In doing so, CMS will achieve its stated goal of "significantly reducing unnecessary spending."[82]

On the procedural side, the Skin Substitutes Proposals do not adequately reimburse institutional providers for their facility overhead expense nor mobile wound care suppliers for their practice expense associated with skin substitute application procedures. As further discussed below, hospitals have no opportunity to realize increased reimbursement for treating larger wounds, and mobile clinicians are unable to cover their high labor and travel costs. These treatment disincentives will negatively impact beneficiary access to care.

We caution, though, that, even if CMS adopts higher, more supportive reimbursements for skin substitute products and procedures, as we recommend, this still would not be enough to assure continued product and treatment availability if Medicare coverage is constricted under the proposed LCD slated to go into effect on January 1, 2026.[83] Accordingly, we support the development of a National Coverage Determination (NCD) with appropriate product coverage reflective of the most current available clinical data and includes all major non-healing wound types, including not only diabetic foot ulcers and venous leg ulcers, but also pressure injury ulcers.

Above all else, it is critical that the Skin Substitutes Proposals in the Proposed Rules be revised to establish Medicare reimbursement and coverage at levels that assure the future availability of these limb and life-saving treatments and sustainability of existing care delivery models. Our specific concerns and proposals are more fully addressed below.

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[81] Tettelbach, *Safeguarding access*, *supra* note 13 (citing a 69% reduction in Medicare spending on skin substitutes based on projected CY 2025 utilization levels at a reimbursement rate of $704 per cm^2).

[82] *See* MPFS Proposed Rule Press Release.

[83] Proposed LCD, *supra* note 16.

b. Reimbursement for Skin Substitute Products Must Be Right-Sized Based on Available Data

1. Site-Neutral Product Payment Rate Should Be Based on Data from All Care Settings

a) CMS's Rate Setting Methodology Is Inadequately Explained

As an initial matter, contrary to its obligation to provide adequate notice to the public, CMS provided incomplete information regarding its data sources and calculation methodology used to establish the initial proposed reimbursement rate for skin substitute products in CY 2026 as $125.38/cm^2—rendering it arbitrary and capricious on its face. The information provided in the Proposed Rules is insufficient to enable commenters to understand and recreate the calculations CMS performed, and certain inconsistencies in the data and descriptions of the calculation methodology impede meaningful engagement with industry stakeholders on this important issue.

What information is provided in the Proposed Rules, however, makes clear that CMS's calculations were skewed to the hospital setting. The Proposed Rules indicate that CMS attempted to calculate the volume-weighted average per-unit cost of skin substitute products based exclusively on Q4 2024 ASP pricing files and hospital outpatient claims data, then retrofitting its calculations onto professional claims data for this same period to assign practice expense (PE) and malpractice (MP) relative value units (RVUs) for purposes of MPFS payment. The Proposed Rules describe the relevant data sources and processes as follows:

- Per-unit pricing and/or cost data by product HCPCS code appears to have been pulled from reported ASP pricing data for Q4 2024, or if none, the mean unit cost (MUC), which CMS calculates from hospital OPPS claims data.
- Utilization data (for volume-weighting purposes) was pulled solely from hospital OPPS claims data.[84]

Reference is made in both Proposed Rules to pulling volume data from professional claims (CMS-1500) with dates of service in Q4 2024 that included line-level allowed amounts for skin substitute products by HCPCS code,[85] but it is not at all clear for what purpose, if any, this data was used to set the proposed reimbursement rate for skin substitutes products, as both Proposed Rules clearly stated that for purposes of CY 2026, rates were established based on reported ASP and OPPS claims data only.[86]

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[84] *See* 90 Fed. Reg. at 32519-21 [MPFS Proposed Rule]; 90 Fed. Reg. at 33646-47 [OPPS Proposed Rule].

[85] 90 Fed. Reg. at 32521 [MPFS Proposed Rule] ("For professional claims, we excluded claims without a positive line-level allowed amount, so that we did not inadvertently include volume without presumed costs in the calculation."); 90 Fed. Reg. at 33647 [OPPS Proposed Rule] (same).

[86] Id.

Then, for purposes of the MPFS Proposed Rule, CMS assigned each skin substitute product 3.70 non-facility PE RVUs and 0.01 MP RVUs for total non-facility RVUs of 3.71.[87] Assuming a conversion factor, as proposed, of $33.59 for qualifying alternative payment model participants, this equates to only $124.62/cm^2 (i.e., 3.71 multiplied by $33.59), which represents a shortfall of $0.76/cm^2 below the advertised proposed rate of $125.38/cm^2.

Further complicating matters, on August 11, 2025—three and a half weeks into the comment period—CMS posted a supplemental document on the MPFS Proposed Rule Homepage, "Additional Description of Calculation of Proposed Payment Rates for Skin Substitutes," purporting to clarify the methodology used by CMS to calculate the proposed payment rates.[88] Unfortunately, the described methodology confuses rather than clarifies the situation, as it describes steps that the Proposed Rules indicate were not actually performed for purposes of the CY 2026 rate proposals[89] and conflicts with different information included in the Proposed Rules.[90] All of this establishes clearly that the proposals are arbitrary and capricious.

To address this lack of clarity, we submitted a Freedom of Information Act (FOIA) request on August 14, 2025, seeking the relevant information and data sources underlying CMS's rate calculations for skin substitute products and associated application procedures. As of the date of submission of these comments, we have yet to receive the Agency's response.

Given questions regarding CMS's methodology, stakeholders have not received appropriate information on which to base meaningful comments. The proposed changes in payment are arbitrary and capricious as they stand and should not be finalized until accurate and detailed information is shared with appropriate time for stakeholder comment.

b) CMS's Rate Setting Methodology Relies on Incomplete Data

To the extent that CMS indeed based its proposed reimbursement rate for CY 2026 solely on reported ASP pricing data for Q4 2024 and hospital OPPS claims data—omitting consideration of professional claims data—the calculations are not reflective of the marketplace and are therefore

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[87] MPFS Proposed Rule, Addendum B, *available at* CMS-1832-P, https://www.cms.gov/medicare/payment/fee-schedules/physician/federal-regulation-notices/cms-1832-p ("MPFS Proposed Rule Homepage"), Downloads, CY 2026 PFS Proposed Rule Addenda - Updated 07/29/2025.

[88] *See* MPFS Proposed Rule Homepage, Downloads, CY 2026 PFS Proposed Rule Skin Substitute Products - Updated 08/11/2025.

[89] *Compare id.* (noting at Steps 2c and 2d that for products lacking a reported ASP or MUC in the fourth quarter of 2024, CMS developed the CY 2026 proposed rats using the product's WAC, or if none, then 89.6 percent of AWP) *with* 90 Fed. Reg. at 32519 [MPFS Proposed Rule] and 90 Fed. Reg. at 33647 [OPPS Proposed Rule] (indicating that the CY 2026 proposed rates were developed using product pricing inputs pulled solely from ASP and MUC data).

[90] *Compare id.* (noting at Step 4 that, "[d]epending on the rate specification," professional claims volume was sometimes used for volume-weighting purposes in addition to OPPS facility claims data) *with* 90 Fed. Reg. at 32520 [MPFS Proposed Rule] and 90 Fed. Reg. at 33647 [OPPS Proposed Rule] (indicating that the CY 2026 proposed weights were calculated using only the OPPS volume data).

fatally skewed, and indeed, arbitrary and capricious. And, as discussed further below, Medicare data does not even support CMS's position.

First, ASP pricing data for Q4 2024 omits fully 156 (more than 61%) of the 254 skin substitute products on the market in CY 2024.

Second, the product mix used in the outpatient setting varies significantly and materially from that in the physician clinic setting. Of the 87 products used in the hospital outpatient setting and 81 products used in the physician clinic setting in CY 2024, only 35 products (roughly 40%) had utilization in both settings. On the whole, the products used in the hospital outpatient setting tend to be significantly lower-cost than those used in the physician clinic setting. This is unsurprising in light of existing constraints in hospital reimbursement for skin substitute products and application procedures (discussed further below), which prevent hospitals from realizing adequate reimbursement to cover acquisition costs of more technologically advanced—and therefore higher cost—skin substitute products. Acknowledging the appreciable challenges with the historic ASP + 6% reimbursement methodology for skin substitute products paid under the MPFS, the fact remains that physician clinics have been freer than hospitals to select more sophisticated products tailored to their patients' treatment needs despite the products' higher price point.

Further exacerbating the discrepancies between the hospital outpatient versus physician clinic utilization data, we note that hospital outpatient wound care treatments using skin substitute products account for only 22% of all utilization for treatments furnished to Medicare beneficiaries in the fourth quarter of CY 2024. Thus, when the OPPS claims data is extrapolated to the entire relevant population of Medicare beneficiaries being treated with skin substitutes in both hospital and physician clinic settings, the impact of the discrepancies is magnified. All in all, the hospital outpatient utilization data is deeply biased in favor of lower-cost, less advanced skin substitute products and is not reflective of the standard of care in the broader patient population.

c) <u>A Site-Neutral Reimbursement Rate for Skin Substitute Products Must Be Based on Fulsome Data From All Relevant Sites of Service</u>

As noted at the outset, we support the establishment of a consistent, site-neutral base reimbursement rate for skin substitute products, but we emphasize that the rate must be based on data that accurately reflects the skin substitute marketplace and existing utilization patterns across care settings.

On the cost side of the equation, the Q4 2023 ASP Pricing File is superior to the Q4 2024 ASP data utilized by CMS, per the Proposed Rules, because this was significantly after manufacturers were obligated to report quarterly ASP, but before dramatic ASP price increases were observed in the data.

Further, crucially important for volume-weighting purposes, a *site-neutral* reimbursement rate for skin substitute products must be based on utilization as reflected in both hospital outpatient

and professional claims data. Only by considering both data sources can CMS generate an accurate snapshot of the relevant Medicare treatment population irrespective of care setting.

Consistent with the principles outlined above, a corrected calculation aligns with a right-sized reimbursement range of $704 to $975 per cm^2. As previously noted and consistent with these calculations, Tiger BioSciences supports a reimbursement rate of $700 per cm^2. Although an increase over CMS's rate proposal in the Proposed Rules, this more appropriate and sustainable reimbursement range will nevertheless achieve an immediate spending reduction of 69% and $10.57 billion in Medicare savings on skin substitute products in CY 2026.[91]

d) Federal Lawmakers Have Endorsed This Approach

We support the reimbursement methodology outlined in Senate Bill 2561, introduced by Senator Bill Cassidy on July 31, 2025. Senate Bill 2561 reflects a thoughtful and objective, *truly site neutral* approach to developing a rational Medicare payment rate based on historic ASP reimbursement data, while also controlling for significant ASP increases observed after CY 2023. As provided in the draft legislative language, the reimbursement rate for skin substitute products would be established based on Q4 2023 ASP data and volume-weighted according to actual utilization in Medicare Part B claims data.[92]

According to an analysis by an independent third-party consultant engaged by Tiger BioSciences to analyze available Medicare data (as described more fully in the next subsection immediately below), the approach outlined in Senator Cassidy's legislation would establish a Medicare rate of roughly $712 per cm^2 if ASPs are volume-weighted based on both professional and OPPS utilization (or roughly $862 per cm^2 if ASPs are volume-weighted based on professional utilization only).[93] This thoughtful rate-setting approach would help ensure ongoing beneficiary access to these life and limb-saving products, while achieving billions of dollars in Medicare savings annually.

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[91] *See* Tettelbach, *Safeguarding access*, *supra* note 13 (performing cost-saving calculations based on a suggested reimbursement rate of $704/$cm^2$ at projected CY 2025 utilization levels).

[92] *See* Skin Substitute Access and Payment Reform Act of 2025 (S.2561) (introduced July 31, 2025), *available at* https://www.congress.gov/bill/119th-congress/senate-bill/2561. S.2561 proposes to reimburse skin substitute products at the "volume-weighted average of the payment allowance limit," determined as follows—

(i) calculating the sum of the products of—

(I) the published payment allowance limit for each billing and payment code listed in the ASP Pricing File published by the Secretary for the fourth calendar quarter of 2023 for each skin substitute product; and

(II) the total number of units . . . for each billing and payment code described in subclause (I), billed with dates of service from October 1, 2023, to December 31, 2023, and listed in the Integrated Data Repository for Part B claims data; and

(ii) dividing the sum calculated under clause (i) by the total number of units under subclause (II).

[93] *See* FTI Analysis, *infra* note 94, at slides 5-8.

e) An Independent Consultant Agrees With Our Approach

Tiger BioSciences engaged FTI Consulting (FTI), a nationally respected independent third-party consulting firm, to analyze CMS's Skin Substitutes Proposals in the Proposed Rules based on available Medicare data. FTI's analysis concludes that:

> "CMS's published rate appears **arbitrary and non-replicable** under its own stated framework."
>
> "CMS's $125.38 rate cannot be replicated using any transparent weighted calculation; defensible estimates range from $712–$975 per cm², depending on methodology and claim inclusion." [94]

Despite best efforts, FTI was unable to reproduce CMS's reimbursement calculation based on information provided by CMS in the Proposed Rules. Indeed, it appears that using a *truly site neutral* volume-weighting approach based on skin substitute product utilization in both the professional and OPPS settings, Medicare data supports a reimbursement rate of **$975.31 per cm²**, which is ***nearly eight times higher*** **than CMS has proposed**. FTI concludes, in relevant part:, as follows:

- **Weighted average results**: The published $125.38 rate cannot be reconciled with CMS's stated parameters. Calculating simple volume-weighted averages produces dramatically different results depending on which claims are included:
  - **All claims (OPPS + Professional)**: $975.31 per cm²
  - **OPPS-only**: $67.80 per cm² (*this illustrates that professional claims are included in CMS's calculation, but at an undisclosed weighting*)[95]

Further, as mentioned in the preceding subsection, the FTI analysis also analyzed the pricing methodology proposed in Senate Bill 2561, introduced by Senator Cassidy, and concluded that even using lower, Q4 2023 ASP data (instead of Q4 2024 data, as proposed by CMS), the data supports a reimbursement rate in the range of $712–$862 per cm^2.[96]

In sum, CMS's proposed reimbursement rate of $125.38 per cm^2 is impossible to reconcile with either the described calculation methodology in the Proposed Rules or available Medicare claims data and is arbitrary and capricious for this reason alone.

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[94] **Exhibit 1**, FTI Consulting, Summary of Observations from FTI Analysis of 90 Fed. Reg. 32352 and 33276 (Sept. 12, 2025) ("FTI Analysis"), at slide 2.

[95] Id.

[96] Id.

f) An Examination of Manufacturer Costs Supports This Rate

An informed estimate of manufacturers' fully loaded cost burden to develop technologically advanced skin substitute products and bring them to market supports our proposed reimbursement rate of $700 per cm^2, as illustrated in the following graphic from a recent article published in the Journal of Wound Care:[97]

Table 3. Full cost burden ($ USD), justifying CAMP reimbursement range of $478–704 USD/cm²

Cost category	Entry-scale estimate (per cm²)	Late-stage estimate (per cm²)	Description
Clinical trials and R&D	$115	$185	Amortised cost of $11.5–15 million USD in past and future R&D over 3 years at early-stage volume (240,000–500,000cm²)
Procurement, manufacturing and processing	$38	$59	Includes GMP production, quality assurance/quality control, raw materials, tissue preparation, production batch loss and sterile packaging
SG&A expenses (including inflation)	$132	$151	Overhead for ~100 employees at $150,000 USD average salary, adjusted for inflation
Regulatory, legal and compliance	$37	$50	US FDA engagement, IP, safety monitoring, tissue bank compliance, audit readiness
Marketing, education and access	$95	$143	Sales force, provider education, payer contracting and outreach
Insurance, risk and fixed costs	$30	$70	Product liability insurance, risk mitigation, professional service fees
Subtotal (fully burdened cost)	$447	$658	Total cost to sustain product in market prior to margin
+ Margin (industry standard)	$31 (7%)	$46 (7%)	Operating margin to support reinvestment, future R&D, capital stability and pipeline continuity
Total justified reimbursement	$478 per cm²	$704 per cm²	Full reimbursement range needed to maintain innovation and ensure access for Medicare patients

FDA—Food and Frug Administration; GMP—good manufacturing practice; IP—intellectual property; R&D—research and development; SG&A—selling, general and administrative

As explained in the article, the cost estimates in the table above are "informed by industry benchmarks and representative, publicly available data . . . factoring in a sustainable operating margin to support future innovation or development and ensure long-term viability."[98] It is arbitrary and capricious for CMS to blindly establish a reimbursement rate for skin substitute products in total disregard of applicable product development, manufacturing, and market-based expenses.

g) A Crosswalk to Analogous CPT Codes Achieves a Similar Result

Existing analogous Medicare payment rates for amniotic membrane products used in certain eye procedures also supports our proposed reimbursement rate. Specifically, CPT 65778 (Placement of amniotic membrane on the ocular surface; without sutures) utilizes the human amniotic membrane allograft mounted on a non-absorbable self-retaining ring (SD248) supply,

[97] Tettlebach, *Safeguarding access*, *supra* note 13, at Table 3.

[98] Id.

which was reimbursed at $1,149 in CY 2025. Similarly, CPT 65779 (Placement of amniotic membrane on the ocular surface; single layer, sutured) utilizes the human amniotic membrane allograft (SD247) supply, which was reimbursed at $835 in CY 2025. Amniotic membranes used for ocular purposes are typically 14mm diameter discs, comprising a surface area of approximately 1.5 cm^2 ($A=\pi r^2$). On a square centimeter basis, these CY 2025 reimbursement rates for these substantially identical products align closely to our proposed reimbursement rate for skin substitute products of $700 per cm^2.

2. All Skin Substitute Products Should Be Subject to Uniform Base Reimbursement, with Payment Incentives for Products with Demonstrated Efficacy and Innovative Products

As noted above, we support the establishment of a uniform, site-neutral Medicare reimbursement rate for skin substitute products across all care settings and irrespective of product type (i.e., human tissue-based allograft, animal-sourced xenograft, or synthetic) and/or FDA regulatory pathway. That said, given the number of skin substitute manufacturers collectively offering a huge range of both older and newer products, establishment of a uniform Medicare payment rate introduces a risk of triggering "race to the bottom," whereby manufacturers of legacy products who are better able to drop their prices precipitously conceivably could capture a disproportionate market share that is not reflective of their product's efficacy or suitability for any particular patient. To combat this risk and avoid a reimbursement disincentive for providers and suppliers to select the most efficacious products for their patients, we believe CMS should establish payment codes or modifiers to increase payment rates for certain products whose efficacy is supported by product-specific randomized clinical trial (RCT) study data. Similarly, CMS should create a payment modifier or other mechanism under the MPFS to support innovative skin substitutes products, as already exists under the OPPS in the form of pass-through payments and as new technology add-on payments (NTAP) under the inpatient prospective payment system (IPPS).

a) Keeping Biologics on ASP Pricing Creates Perverse Incentives

CMS proposes that biologics licensed under section 351 of the Public Health Service Act (PHS Act) would continue to be paid as biologicals under the ASP + 6% methodology per SSA § 1847A.[99] Continuing to pay this comparative handful of skin substitute products under the historic ASP + 6% methodology creates a perverse incentive for manufacturers of these products to continue to increase prices and drive higher Medicare spending for stale technology and clinically indistinguishable products. For instance, and while relating to a non-biologic, in the most recently released ASP file, one company, which in early 2025 had removed a product from the market that it historically had sold in the $140 per cm^2 range, appears to have added that same product back into the ASP file at a price of $2,850—i.e., roughly 20 times higher.

Instead, we urge CMS to consider updating the payment rates finalized for CY 2026 on an annual basis using the CPI-U, rather than recalculating rates annually based on ASP as proposed.

[99] 90 Fed. Reg. at 32517 [MPFS Proposed Rule]; 90 Fed. Reg. at 33644 [OPPS Proposed Rule].

Updating rates based on the CPI-U will increase predictability and stability and address the concern regarding the potential for gaming that CMS raised in the proposed rule. Furthermore, basing updates on the CPI-U would reduce regulatory burden for manufacturers and for CMS, because although reporting would still be required under law, the accuracy and completeness of ASP reporting for these products would no longer impact payment rates.

b) PMA Products Do Not Warrant Higher Reimbursement

CMS has solicited comments regarding whether to create separate payment rate for skin substitute products in the PMA category, i.e., those subject to rigorous premarket approval requirements under section 515 of the FD&C Act.[100]

We do not support higher reimbursement for PMA products simply because they obtained PMA approval. PMAs do not inherently mean that the product is more safe or effective at treating the same wounds. Rather, a PMA is a different pathway that specifically requires clinical data to get to the market initially due to some attribute of the device that the FDA deems to require more data to ensure that the product is safe and effective. It does not mean the product is any more safe or effective and is in no way an indicator of better or improved clinical outcomes compared to a product approved under a different regulatory pathway. There is no evidence that placental-based PMA products perform as well as or better than tissued-based placental products regulated under section 361 of the PHS Act (so-called "361 HCT/P" products).

CMS also suggests that differentiating payment based on FDA pathway because the FDA cleared indications for PMAs may include wound healing. However, we note that none of the skin substitute products approved via the PMA pathway have indications for wound healing in their Instructions for Use (IFU) or FDA intended use/indications.

As noted by CMS in the Proposed Rules, there has not been a substantial increase in the number of skin substitute products with approved PMAs in recent years.[101] This is because owing to the FDA regulatory regime, recent advancements in skin substitutes technologies have not been required to follow the PMA pathway. Thus, many existing products on the market today that hold a PMA are older, less advanced, and, as a result, lower-cost products that are no longer considered innovative and whose product development costs have long since been fully amortized.

Finally, we believe that there are more appropriate methods for rewarding clinical innovation in the skin substitute category. As noted in the proposed rule, existing pathways such as New Technology Add-on Payments (NTAP) are already in place specifically for this purpose as further discussed below.

[100] 90 Fed. Reg. at 32520 [MPFS Proposed Rule]; 90 Fed. Reg. at 33647 [OPPS Proposed Rule].

[101] Id.

c) CMS Should Create Payment Adjusters for Products with Demonstrated Efficacy

As noted above, the substantial benefits of administrative simplification and predictability stemming from a uniform reimbursement rate for skin substitute products is offset by the risk of triggering a "race to the bottom," which could incentivize providers and suppliers to select lower-cost, less effective products less well suited to Medicare beneficiaries' individual clinical circumstances. To combat these incentives, CMS should exercise its "Ancillary Policies" authority under SSA § 1848(c)(4) to establish dedicated HCPCS codes and/or modifiers to boost reimbursement for products with demonstrated wound healing efficacy and documented performance data as supported by one or more published, peer reviewed RCT studies. For example, CMS could establish a framework for affording higher payments to qualifying skin substitute products using longitudinal outcomes and quality metrics to benchmark their relative performance against a threshold. We would welcome the opportunity to collaborate with CMS to develop appropriate measurable metrics and threshold performance levels.

d) **MPFS Proposed Rule Only** CMS Should Create Payment Incentives for New Technology

To appropriately reimburse new skin substitute products with technological advancements, CMS should establish additional payments under the MPFS for new technology modeled after OPPS pass-through status and NTAP under the IPPS.[102] Technological advancement in this space, as with other medical devices, drugs, and biological products, requires significant investment of research and development resources—expenses that often are not recoverable. To properly compensate developers and manufacturers of truly new products that substantially improve patient outcomes, additional payments should be available under the MPFS as under other Medicare payment systems that reimburse for costs of skin substitute products. However, without explicit consideration for such pathways, the proposed rule may unintentionally penalize cutting-edge therapies and favor lower-cost, established alternatives, undermining incentives for manufacturers to develop innovative treatments. Manufacturers with FDA-intensive products may also experience payment compression when grouped with clinically less innovative substitutes receiving equivalent reimbursement.

3. **MPFS Proposed Rule Only** *Bona Fide Service Fees*

a) Problems with CMS's Approach

Under the Proposed Rules, ASP would continue to be relevant for prospective rate setting purposes for skin substitute products. Specifically, CMS has proposed that biologics would continue to be paid at ASP + 6%, and applicable manufacturers would continue to be required to report ASP data. For non-biologic skin substitutes, although no longer required to be reported by manufacturers, ASP would somehow continue to be used for annual rate adjustment purposes—of

[102] *See* 42 C.F.R. § 419.66 [OPPS medical device pass-through status criteria]; 42 C.F.R. § 412.87 [IPPS NTAP criteria].

course, to the extent it is reported, which would no longer be a requirement under the Proposed Rules. CMS's proposal to modify the ASP reporting rules pertaining to price concessions and bona fide service fees (BFSFs)[103] is unclear in its application, introduces new variables and uncertainty into long-settled ASP reporting methodologies, and will impair the accuracy and consistency of available ASP data. Without necessary clarity, this proposal is arbitrary and capricious.

b) Our Proposed Solution

We oppose the changes proposed by CMS in connection with price concessions and BFSFs pending clearer guidance to the industry sufficient to put the regulated community on notice of evolving CMS interpretations.

c. Reimbursement Rates for Application Procedures Must Be Sufficient to Support Care Delivery in Applicable Care Settings

As currently structured, the Skin Substitutes Proposals are inadequate to support care delivery in either the hospital or mobile clinic setting. The insufficient and indefensible proposed product reimbursement rate of $125.38/cm^2 exacerbates care delivery challenges stemming from already inadequate procedural reimbursements for skin substitute application procedures to render these treatments money-losers for both hospitals and mobile wound care suppliers alike. This reimbursement dynamic will leave the most under-resourced Medicare beneficiaries vulnerable to limb and life-threatening care shortages.

1. **OPPS Proposed Rule Only** ***Proposed APC Payment Rates for Skin Substitute Application Procedures Should Be Increased***

a) CMS Provided No Rationale for Demoting Skin Substitute Application Procedures to Lower-Paying APCs, Exacerbating Existing Treatment Incentives in Outpatient Hospital Settings

Hospitals have long labored under a reimbursement model that disincentivizes large wound treatments with skin substitute products and, as previously discussed, disincentivizes selection of more advanced (higher-cost) products altogether. This is because, as currently structured, hospitals receive a single APC reimbursement for skin substitute application procedures irrespective of wound size or product. Thus, hospitals are not compensated more for larger wound treatments coded using applicable HCPCS add-on administration codes denoting additional surface area (CPTs 15272, 15274, 15276, and 15278). Current OPPS reimbursement for CY 2025 is as follows:

[103] *See* 90 Fed. Reg. at 32540-45, 32849 (proposing changes to 42 C.F.R. §§ 414.802 and .804).

APC	APC Name	Skin Substitute HCPCS Codes (CY 2025)	CY 2025 Payment
5053	**Level 3 Skin Procedures**	Low-cost skin substitute applications: **C5271** (trunk/arm/leg, first 25 cm^2) **C5275** (face/neck/hands/feet/genitalia, first 25 cm^2) **C5277** (face/neck/hands/feet/genitalia, first 100 cm^2)	**$612.13**
5054	**Level 4 Skin Procedures**	**C5273** (low-cost skin substitute application to trunk/arm/leg, first 100 cm^2) **15271** (Skin sub graft trnk/arm/leg, first 25 cm^2) **15275** (Skin sub graft face/nk/hf/g, first 25 cm^2) **15277** (Skn sub grft f/n/hf/g child, first 100 cm^2)	**$1,829.23**
5055	**Level 5 Skin Procedures**	**15273** (Skin sub grft t/arm/lg child, first 100 cm^2)	**$3,660.97**

The current proposal will magnify existing treatment disincentives for hospitals. Although the Skin Substitutes Proposals decouple the product reimbursement from the procedural reimbursement, they fail to correct hospitals' treatment disincentive for larger wounds by (i) failing to incorporate the additional surface area add-on codes into the APC reimbursement amounts, and (ii) failing to adequately reimburse product costs (as previously discussed). Moreover, the current proposals create an *additional* treatment disincentive for *small* wounds owing to the demotion of skin substitute graft base codes (CPTs 15271, 15273, and 15275) to lower-paying APCs, reducing their payment amount by $1,082.62 (for CPTs 15271 and 15275) and $1,523.52 (for CPT 15273) from CY 2025 to CY 2026, as shown in the following chart:

APC	APC Name	Skin Substitute HCPCS Codes (CY 2026 Proposed)	CY 2026 Payment
5053	**Level 3 Skin Procedures**	**15271** (Skin sub graft trnk/arm/leg, first 25 cm^2) **15275** (Skin sub graft face/nk/hf/g, first 25 cm^2)	**$746.61**
5054	**Level 4 Skin Procedures**	**15273** (Skin sub grft t/arm/lg child, first 100 cm^2) **15277** (Skn sub grft f/n/hf/g child, first 100 cm^2)	**$2,137.45**
5055	**Level 5 Skin Procedures**	[none]	**$3,659.96**

This unexplained reduction is not adequately offset by the proposed reimbursement rate for skin substitute products (which, as already discussed, is insufficient on its face to cover product costs of any of the newer, multi-layer products on the market). By way of example, a hospital that treats a small wound (CPT 15271) that requires 4 cm^2 of a moderately priced skin substitute product (currently categorized as "high cost" under OPPS) would receive $1,829.23 in CY 2025

under APC 5054 and only $1,248.13 in CY 2026 (i.e., $746.61 + (4 × $125.38)) under APC 5053, a difference of nearly $600.

b) CMS Should Revert to Existing APC Classifications for Skin Substitute Application Procedures

For the reasons above, we oppose CMS's proposal to demote three skin substitute graft base codes (CPTs 15271, 15273, and 15275) to lower-paying APCs. We request that CMS retain these codes' CY 2025 APC payment classifications with the payment rate updates proposed for these APCs in CY 2026.

c) CMS Should Create a New APC (or APCs) for Large Skin Application Procedures to Reflect Applicable Add-On Codes

For the reasons above, we request that CMS create one or more new APCs to appropriately compensate hospitals for increased direct and indirect facility expenses associated with larger skin substitute application procedures coded with applicable add-on codes denoting additional surface area (CPTs 15272, 15274, 15276, and 15278).

2. **MPFS Proposed Rule Only** *Additional Procedural Payment Should Be Provided for Services of Mobile Wound Care Providers*

Mobile wound care providers serve a critical unmet need, offering flexible delivery models for patients in rural and medically underserved communities. Mobile providers are able to reach and treat homebound patients and others in remote areas or residential treatment settings, often in underserved communities, without the means to travel for this essential care. Mobile wound care providers have an inherently higher cost structure as compared to brick-and-mortar physician clinics owing to the significant personnel time and expense associated with traveling to see patients in their homes and locale.

It bears emphasis that owing to the travel intensive care delivery model, many mobile wound care clinicians are non-physician practitioners, who are reimbursed at 85% of standard MPFS rates applicable to physician services. This means that notwithstanding their high costs of care and the critical gap they fill in taking care of vulnerable Medicare patients, mobile providers often would receive only $106.57/cm^2 (0.85 × $125.38) for skin substitutes products under CMS's Skin Substitutes Proposal in the MPFS Proposed Rule. This level of reimbursement is absolutely unsustainable.

Under the existing reimbursement regime, mobile wound care providers have been able to sustain this care model under the ASP + 6% methodology. Now, however, with the shift to fixed-fee reimbursement for skin substitutes products, the reimbursement model for mobile wound care providers will become unsustainable. We are gravely concerned that absent appropriate fee schedule reimbursement for wound care services furnished by mobile providers, this entire category of care provider will no longer be available to furnish this much needed care to an

especially vulnerable segment of the Medicare community, leaving millions of patients without care and left to suffer and die.

It is imperative that mobile wound care providers be appropriately reimbursed for their care and services furnished to Medicare beneficiaries with non-healing wounds. We urge CMS to consider establishing a dedicated G-code or payment modifier to more appropriately reimburse the higher overhead practice costs for mobile wound care providers applying skin substitute products.

d. Payment Reform Must Be Addressed Concurrently with Coverage Reform

Even if CMS adopts all of our proposed reimbursement recommendations discussed herein, we remain concerned about looming product coverage restrictions slated for implementation on January 1, 2026, should the proposed LCD—virtually identical versions of which have been promulgated by all seven MACs nationwide—go into effect as currently constructed.[104] If permitted to take effect without modification, the LCD will constrain coverage of skin substitute products to only seventeen of the more than 200 products currently available on the market in the U.S. This would have a significant adverse impact on the availability of skin substitute products, causing immediate and irreparable harm to vulnerable patients who rely on advanced wound care products to manage their chronic conditions.

It bears emphasis that the LCD is currently on hold and under review. CMS has requested that supplemental clinical study results be furnished to the CMS Coverage and Analysis Group by November 1, 2025, and has committed to "ensure all evidence received will be sent to the MACs to review to determine if revisions to the LCD are appropriate."[105] In its new Strategy Report, the MAHA Commission directs FDA and to CMS to "Facilitate the use of regenerative medicine innovation by modernizing policies as clinical data is established."[106] We support and appreciate the Agency's responsiveness to industry concerns regarding the LCD and its commitment to reviewing and incorporating additional clinical evidence of product efficacy.

We fully support determinations of Medicare coverage that are based on products' demonstrated clinical efficacy. We remain concerned that, absent appropriate clinical criteria for product coverage, lower-quality, less expensive and unstudied products will glut the market to the detriment of Medicare beneficiaries. That said, we counsel strongly against implementation of a narrow LCD that will have significant detrimental effects for patients and the marketplace. Thus, to the extent necessary, we urge CMS to further delay implementation of the looming LCD to allow adequate time for MACs to review all newly submitted study findings and supplement the LCD accordingly. We further urge CMS to direct the MACs to provide a pathway to LCD coverage of additional products on a rolling basis as RCTs are completed and efficacy data becomes available. In sum, it is critically important that comprehensive, evidence-based product

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[104] Proposed LCD, *supra* note 16.

[105] *See* CMS Statement on Local Coverage Determination for Certain Skin Substitute Grafts (April 11, 2025), *available at* https://www.cms.gov/newsroom/press-releases/cms-statement-local-coverage-determination-certain-skin-substitute-grafts.

[106] MAHA Strategy Report, *supra* note 62.

coverage criteria be adopted that fully incorporate available scientific data and insights, while imposing reasonable limitations on as-yet-unproven products without sacrificing flexibility in this fast-moving area.

Longer term, we urge CMS to adopt a National Coverage Determination (NCD) to supersede and replace the LCD. An NCD would afford an opportunity for the CMS Coverage and Analysis Group to review new and rapidly expanding data on the utility and versatility of skin substitute products for patients with all types of non-healing wounds, balance complex beneficiary access-to-care considerations, and establish a uniform national coverage policy to provide predictability and stability to patients and providers. Implementation of an evidence-based, clinically sensible NCD would standardize best practices and reduce administrative burden for all industry stakeholders.

We urge the Agency to open the NCD development process as soon as possible on or after the November 1, 2025 deadline (discussed above) and to set its sights beyond diabetic foot ulcers and venous leg ulcers to address the gamut of chronic, non-healing wounds, including pressure injury ulcers, arterial ulcers, and stalled surgical wounds. Indeed, any wound that is documented as having failed to respond after thirty days or longer of standard wound care should fall within the NCD. We would welcome the opportunity to engage with the Agency in the NCD development process for these critically important medical therapies.

VIII. Adopting The Proposed Rules Would Be Arbitrary and Capricious

Although we understand and support CMS's efforts to develop a sustainable, site-neutral reimbursement methodology for skin substitute products and procedures, adopting the proposed rules as they stand would be arbitrary and capricious for the reasons discussed herein.[107] As a threshold matter, the Skin Substitutes Proposals lack essential clarity, depriving stakeholders of adequate notice and meaningful opportunity for comment.[108] The Proposals do not disclose the relevant information and data sources underlying CMS's rate calculations for skin substitute products and associated application procedures, and thus do not "provide sufficient factual detail and rationale for the rule to permit interested parties to comment meaningfully."[109] Further, the CMS Proposals are based on failed methodologies and inaccurate and incomplete datasets.

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[107] *See Motor Vehicle Mfers. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (explaining agency action is arbitrary and capricious if the agency "has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise").

[108] *See Allina Health Servs. v. Sebelius*, 746 F.3d 1102, 1110 (D.C. Cir. 2014) ("[A]n agency's failure to disclose *critical* material, on which it relies, deprives commenters of a right under § 553 "to participate in rulemaking"); *Shell Oil Co. v. EPA*, 950 F.2d 741, 751 (D.C. Cir. 1991) (holding agency notice insufficient because "[i]nterested parties cannot be expected to divine the [agency's] unspoken thoughts").

[109] *Nat'l Lifeline Ass'n v. FCC*, 921 F.3d 1102, 1115 (D.C. Cir. 2019) (quoting *Fla. Power & Light Co. v. United States*, 846 F.2d 765, 771 (D.C. Cir. 1988)); *see also Am. Radio Relay League, Inc. v. FCC*, 524 F.3d 227, 236 (D.C.

Moreover, the Skin Substitutes Proposals reflect a significant departure from settled policy, yet the agency has failed to "articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'"[110] Principally, CMS's Skin Substitutes Proposals "fail to consider important aspects of the problem"[111] and treat "similarly situated parties differently" without explanation.[112] The methodological error committed in calculating a reimbursement rate based solely on OPPS claims data is a material oversight that has resulted in an artificially deflated proposed reimbursement rate for skin substitute products that threatens dire consequences for providers, suppliers, and patients alike.[113] CMS has also failed to correct for chronic under-reimbursement for skin substitute application procedures in both the hospital outpatient setting and physician clinic settings that will impair vulnerable homebound and rural patients' ability to access medically necessary care and treatment. Accordingly, the Agency's myopic and misguided approach focuses on a small subset of data while ignoring the rest, fails to account for the significant consequences facing providers and patients, and is therefore arbitrary and capricious action.[114]

CMS's explanation for the Skin Substitutes Proposals also "runs counter to the evidence before the [A]gency" in violation of the Administrative Procedures Act.[115] Notably, much of CMS's and the MACs' rhetoric in connection with the Skin Substitutes Proposals and during the LCD development process indicates that the Agency believes the rapid increase in Medicare spending on skin substitute products and procedure is due solely to fraud, waste, and abuse.[116] Although we concede that there undoubtedly may be some bad actors, as is true in connection with any Medicare benefit category, CMS's and the MACs' view misapprehends actual CMS data and

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Cir. 2008) ("Among the information that must be revealed for public evaluation are the technical studies and data upon which the agency relies in its rulemaking.").

[110] *State Farm*, 463 U.S. at 43 (quoting *Burlington Truck Lines v. United States*, 371 U.S. 156, 168 (1962)); *see FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009) (commanding that an agency may not "depart from a prior policy *sub silentio* or simply disregard rules that are still on the books," and "must show that there are good reasons for the new policy").

[111] *State Farm*, 463 U.S. at 43; *Michigan v. EPA*, 576 U.S. 743, 753 (2015) ("[R]easonable regulation ordinarily requires paying attention to the advantages *and* the disadvantages of agency decisions."); *Marsh v. Or. Nat. Res. Council*, 490 U.S. 360, 378 (1989) (stating courts must set aside agency action that fails to account for "relevant factors" or evinces "a clear error of judgment").

[112] *Burlington N. & Santa Fe. Ry. Co. v. Surf. Transp. Bd.*, 403 F.3d 771, 776–77 (D.C. Cir. 2005) ("Where an agency applies different standards to similarly situated entities and fails to support this disparate treatment with a reasoned explanation and substantial evidence in the record, its action is arbitrary and capricious and cannot be upheld."); *Nat'l Cable & Telecomms. Ass'n v. Brand X Internet Servs.*, 545 U.S. 967, 981 (2005) ("Unexplained inconsistency is . . . a reason for holding [agency action] to be . . . arbitrary and capricious . . . .").

[113] *See PAM Squared At Texarkana, LLC v. Azar*, 436 F. Supp. 3d 52, 59 (D.D.C. 2020) ("[W]hen a mistake infects the agency's analysis or the outcome of the adjudication, it crosses the line into arbitrary and capricious territory.").

[114] *Genuine Parts Co. v. EPA*, 890 F.3d 304, 313 (D.C. Cir. 2018) (vacating rule as arbitrary and capricious that "rel[ied] on portions of studies in the record that support its position, while ignoring cross sections in those studies that do not").

[115] *State Farm*, 463 U.S. at 43.

[116] *See*, *e.g.*, MPFS Proposed Rule Press Release (citing "abusive pricing practices," remarking upon products' "limited evidence of clinical value," and citing a notable recovery by the CMS Fraud Defense Operations Center).

itself evidences the arbitrary and capricious nature of the proposals. The overwhelming evidence discussed above supports that the increase in Medicare spending primarily derives from expanded availability of these limb and life-saving products and the increased awareness surrounding product efficacy, driving treatments to more patients in more places over the past several years. Thus, because CMS justifies the proposed rules with general concerns of purported fraud and ignores the wealth of compelling evidence to the contrary, the Skin Substitutes Proposals are "counter to the evidence before the [A]gency" and, thus, arbitrary and capricious.[117]

Further, the Skin Substitutes Proposals are arbitrary and capricious because they do not reflect a "rational connection between the facts found and the choice made."[118] To the extent that CMS is chiefly worried about fraud, waste, and abuse, the Agency should tailor its coverage and reimbursement policies appropriately to detect and prevent such illicit activity, and to use the tools already available to CMS.[119] To do otherwise—by attempting to curb a perceived fraud, waste, and abuse by actually limiting product availability and imposing artificial payment restraints—is arbitrary and capricious.[120] In contrast to the contrived and arbitrary reimbursement policies proposed in the Proposed Rules, CMS should embark on a thoughtful strategy to provide greater provider oversight, potentially including, for example, (i) stricter controls on product wastage, (ii) clear coverage criteria with streamlined prior authorization requirements, and (iii) prepayment review and/or systematic spot-audits of high-volume billers, among other mechanisms. CMS should not be permitted to ignore its own underlying data sets and to do real and irreparable harm to Medicare beneficiaries. In sum, the Skin Substitutes Proposals are not "the product of reasoned decisionmaking."[121]

IX. Conclusion

For the reasons presented above, we urge CMS to revise the Skin Substitutes Proposals in accordance with these comments to ensure the continued availability of critical wound care treatments for Medicare beneficiaries.

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[117] *State Farm*, 463 U.S. at 43; *see, e.g.*, *Sorenson Commc'ns Inc. v. FCC*, 755 F.3d 702, 707–10 (D.C. Cir. 2014) (vacating FCC rule as arbitrary capricious where even though FCC claimed rule would deter fraud, there was no evidence of fraud or a relationship between floor price and fraud deterrence, and FCC ignored contrary evidence).

[118] *State Farm*, 463 U.S. at 43.

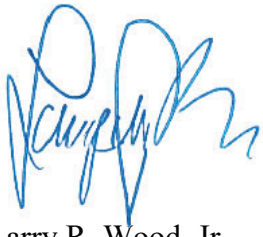
[119] *Env't Def. Fund v. EPA*, 922 F.3d 446, 454 (D.C. Cir. 2019) ("An agency acts arbitrarily and capriciously when it offers inaccurate or unreasoned justifications for a decision.").

[120] *Owner-Operator Indep. Drivers Ass'n, Inc. v. FMCSA*, 494 F.3d 188, 203–06 (D.C. Cir. 2007) (vacating agency rule that failed to provide reasoned explanation for overbroad driving fatigue model, where agency misinterpreted and ignored evidence); *Sorenson Commc'ns Inc.*, 755 F.3d at 707–10.

[121] *State Farm*, 463 U.S. at 52.

We welcome the opportunity to submit these comments and thank CMS for its review and consideration. Should the Agency have any questions or wish to further discuss any of the points addressed herein, please do not hesitate to contact Larry R. Wood, Jr. at larryw@tigerbios.com, Susan Banks, Holland & Knight LLP, at susan.banks@hklaw.com, or Lynn E. Calkins, Holland & Knight LLP, at lynn.calkins@hklaw.com.

Respectfully Submitted,



Larry R. Wood, Jr.
Chief Legal Officer
Tiger BioSciences

CC: John Brooks, Deputy Administrator & Chief Policy and Regulatory Officer, CMS ***(via email)***

EXHIBIT 1

FTI Consulting

Summary of Observations from FTI Analysis of 90 Fed. Reg. 32352 and 33276

(Sept. 12, 2025)

FTI Healthcare Risk Management & Advisory

Summary of Observations from FTI Analysis of 90 Fed. Reg. 32352 and 33276

FTI CONSULTING

9/12/2025

Overall Observations from 90 Fed. Reg. 32352 and 33276
Skin Substitute Payment Rate Analysis

- **Key Takeaways:**
  - **CMS's stated parameters:** CMS established clear parameters for its payment methodology, including a pricing hierarchy (ASP → MUC → AWP/WAC), the identification of 254 HCPCS codes, and the use of both OPPS and Professional claim data.
  - **Effect of high-volume ASP codes:** Several high-volume ASP-priced codes (such as Q4205) alone should drive the average far above CMS's stated amount of $125.38. Yet CMS's calculation yields the opposite result, suggesting that its methodology disproportionately suppressed the influence of these codes.
  - **Weighted average results:** The published $125.38 rate cannot be reconciled with CMS's stated parameters. Calculating simple volume-weighted averages produces dramatically different results depending on which claims are included:
    - **All claims (OPPS + Professional)**: $975.31 per cm^2
    - **OPPS-only**: $67.80 per cm^2 (*this illustrates that professional claims are included in CMS's calculation, but at an undisclosed weighting*)
  - **Comparison to Senate Bill 2561:** The true weighted average aligns closely with amounts calculated under Senate Bill 2561, a 2024 proposal to reform skin substitute payment by applying a volume-weighted average of published payment allowance limits for each applicable HCPCS code.
- **Overall implication:** CMS's published rate appears **arbitrary and non-replicable** under its own stated framework. The lack of transparency around weighting raises significant concerns that reimbursement was materially depressed through undisclosed adjustments.

Overall Observations from 90 Fed. Reg. 32352 and 33276
CMS's Stated Framework for Calculating $125.38

- **CMS Parameters (as published):**
  - **Pricing hierarchy**: CMS applied a hierarchy of payment rates: ASP → OPPS MUC → AWP/WAC.
  - **Scope of codes**: 254 HCPCS codes were identified as the relevant skin substitute products.
  - **Data sources**: CMS states that it included both OPPS outpatient and Professional Part B claims in the calculation.
  - **Weighting statement**: CMS indicated that weights could be based on combined OPPS + Professional volume or OPPS-only, but the precise application was not specified.

- **Our Replication Attempt:**
  - Assigned available payment rates to all 254 HCPCS using the ASP → MUC → AWP/WAC hierarchy.
  - Applied Q4 2024 claims data for both OPPS and Professional settings.
  - Calculated a straightforward volume-weighted average across all units: **$975.31/cm²** (nearly 8× CMS's published $125.38 rate).
  - Excluding Professional claims entirely yields **$67.80/cm²**, far below CMS's published rate.

- **Observation:**
  - The discrepancy indicates CMS did not apply a simple volume-weighted average across codes and data sources.
  - Instead, undisclosed adjustments to the weighting appear to have materially suppressed the calculated rate.

Overall Observations from 90 Fed. Reg. 32352 and 33276
Summary

- **Volume inclusion drives rate differences**
  - Including both OPPS and professional claims in CMS's stated methodology produces a standard weighted average of $975.31/cm².
  - Restricting the calculation to OPPS claims alone reduces the standard weighted average to $67.80/cm².

- **CMS methodology vs. Senate Bill**
  - Applying the S.2561 methodology yields pricing estimates that are internally consistent, whether including OPPS claims ($712/cm²) or professional claims only ($862/cm²).
  - These estimates align directionally with the CMS-based weighted average when OPPS and professional claims are fully included.

- **Policy implications:**
  - CMS's published $125.38 rate is artificially low due to OPPS inclusion and undisclosed weighting assumptions.
  - Analysis of 2024 Medicare OPPS and professional claims suggests ***a payment reduction of approximately $3.6 billion*** relative to a rate calculated using a transparent weighted-average methodology consistent with S.2561.

Overall Observations from 90 Fed. Reg. 32352 and 33276
Additional Observations with CMS's Rate-Setting Methodology

- Descriptive statistics regarding the 254:
  - 98 of the 254 have a 2024 Q4 ASP reflected. Of the remaining 156:
    - 45 had an OPPS MUC pricing available. "MUC" or geometric mean unit cost according to the NPRM Drug Blood and Brachy Cost Statistics File
    - 111 had neither an ASP nor an OPPS MUC. Per CMS, AWP or WAC pricing was used for these HCPCS.
  - In terms of FDA Regulatory Category (based on the category designated by CMS in the abovementioned list)
    - 7 of the 254 were reflected as "PMA" - (Premarket approval) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.
    - 53 of the 254 were 510(k) – i.e. a premarket submission made to FDA to demonstrate that the device to be marketed is as safe and effective.
    - 194 of the 254 were 361 HCT/P – i.e. are subject only to regulation under section 361 of the Public Health Service Act (PHS Act) and the regulations in 21 CFR part 1271. No premarket authorization is required.
- In terms of volume for the comparable population of claims CMS presumably analyzed to determine the $125.38 rate, we observed the following:
  - 121 HCPCS had no volume – OPPS or Professional
  - Among the remaining 133:
    - 52 are associated with OPPS claim volume only
    - 46 are associated with Professional claim volume only
    - 35 have both OPPS and Professional Claim data

Overall Observations from 90 Fed. Reg. 32352 and 33276
Additional Notes Regarding Senate Bill 2561

- **Scope:** Intended for professional claims; hospital outpatient claims are **generally excluded**, though the bill references the "Integrated Data Repository for Part B claims data," which some ambiguity exists around.

- **Basis of Reimbursement:** Volume-weighted average of published payment allowance limits for each applicable HCPCS code.

- **Key Steps:**
  - Identify all HCPCS codes for skin substitutes used in professional (and OPPS) settings as well as the 2023Q4 ASP for each.
  - Multiply each HCPCS's price by its total units used to calculate weighted contributions.
  - Sum weighted contributions across all HCPCS and divide by total units to determine the per cm^2 reimbursement rate.

- **Data Vintage Difference: CMS vs. S.2561**
  - S.2561: Uses 2023Q4 ASPs, capturing reported prices after manufacturers' quarterly reporting obligations but before 2024 ASP spikes.
  - CMS Proposed Rule: Uses 2024Q4 ASP data, which reflects significant price increases in some skin substitute products.
  - Impact: Q4 2023 data produces a more representative weighted average for professional claims, supporting the $712/$cm^2$ reimbursement under S.2561, while CMS's approach contributes to the artificially low $125.38 rate when OPPS weighting is applied.

- **Outcome**: Replicating the S.2561 methodology for total 2023Q4 data (professional claims ± OPPS) yields a rate substantially higher than CMS's $125.38, roughly $712 per cm^2 when including OPPS and closer to $862 per cm^2 for professional claims only.

Overall Observations from 90 Fed. Reg. 32352 and 33276
Data Relied Upon

- Medicare Limited Data Set (LDS) – Carrier (Part B Professional Claims)
  - Line-level claims for services in physician offices, freestanding clinics, and other non-facility settings.
  - Includes HCPCS, units, allowed amounts, and place-of-service codes.
  - Captures professional utilization of skin substitute HCPCS.
- Medicare Limited Data Set (LDS) – OPPS (Hospital Outpatient Claims)
  - Line-level claims for services in hospital outpatient departments (facility-based). Includes HCPCS, units, revenue codes, and OPPS payment rates.
  - Captures facility utilization of skin substitute HCPCS.
- ASP Pricing Files (Quarterly, CMS)
  - Provides Average Sales Price (ASP) Medicare payment information per HCPCS.
- OPPS MUC Pricing (Medicare Utilization Crosswalk / Market-based Unit Cost)
  - CMS-developed reference pricing for HCPCS without ASPs.
  - Used to set relative values when ASP data are unavailable in the outpatient setting.
- Integration for This Analysis
  - OPPS and Carrier LDS claims were combined to replicate CMS's stated methodology.
  - ASP files and OPPS MUC data were layered in to assign payment allowance limits across all 254 HCPCS identified by CMS.
  - This framework enables a direct test of CMS's published $125.38 figure and comparison with alternative models (e.g., Senate Bill 2561).

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EXHIBIT 2

Decision in OMHA Appeal No. 3-15100221910

Department of Health and Human Services
OFFICE OF MEDICARE HEARINGS AND APPEALS
Arlington, VA

Appeal of:	[redacted]	OMHA Appeal No.:	**3-15100221910**
Beneficiary:	**Multiple (See Attachment A)**	Medicare Part:	B
Medicare No.:	**Multiple (See Attachment A)**	Before:	**Jaya Shurtliff** Administrative Law Judge

DECISION

After considering the evidence and arguments presented in the record, I enter a **FULLY FAVORABLE** decision. The amniotic and/ or placental tissue biologics and related application services provided to multiple Medicare beneficiaries from January 25, 2023, through January 12, 2024, by [redacted] (the "Appellant") meet the requirements to be reasonable and necessary in the treatment of the beneficiaries.

PROCEDURAL HISTORY

The Appellant seeks to overturn the finding of an overpayment against it for the following services, provided to three beneficiaries from January 25, 2023, through January 12, 2024[1]:

- 15002 - Surgical preparation or creation of recipient site by excision of open wounds, burn eschar, or scar (including subcutaneous tissues), or incisional release of scar contracture, trunk, arms, legs; first 100 square centimeter (sq cm) or one percent of body area of infants and children
- 15271 - Application of skin substitute graft[2] to trunk, arms, legs, total wound surface area up to 100 sq cm; first 25 sq cm or less wound surface area
- Q4180 – Revita, per sq cm
- Q4194 - Novachor, per sq cm
- Q4197 - PuraPly XT, per sq cm
- Q4217 - WoundFix, BioWound, WoundFix Plus, BioWound Plus, WoundFix Xplus or BioWound Xplus, per sq cm

[1] The following modifiers are on the claims: 59 – Distinct procedural service; JC – Skin substitute used as a graft; JW – Drug amount discarded; and JZ – Zero drug amount discarded.
[2] The Appellant physician and physician witnesses advise the updated term applicable to the codes at issue is Cellular, Acellular, and Matrix-like Products ("CAMPS").

The Appellant initially submitted the claims to First Coast Service Options, Inc., the Medicare Administrative Contractor (MAC), and was paid. However, on June 20, 2024, SafeGuard Services, LLC, the Unified Program Integrity Contractor (UPIC), initiated post-payment claim review pursuant to 20 C.F.R. § 404.980. The UPIC requested additional medical records, which the Appellant provided. The UPIC's review resulted in denial of all 34 claims and 98 lines of service, and accordingly, in an overpayment. The UPIC's Notice of Overpayment Findings states, "the documentation provided for review did not support the medical necessity for the services as billed per Medicare" and offered to provide a spreadsheet with a "detailed explanation of the denied claims" upon request. File 4, p. 61. The UPIC's Medical Review Summary dated February 29, 2024, identifies the denial reasons in greater detail as follows:

1) The documentation did not include comprehensive evaluations in order to determine if skin graft applications were necessary. The documentation did not support the underlying systemic conditions were stable or if conservative treatments were tried and failed. Examples:
    - AG, DOS 03/10/23
    - HP, DOS 04/19/23

2) The skin substitute graft was deemed not reasonable and necessary; therefore, the associated surgical preparation in conjunction with routine, simple and/or repeat application of skin substitute grafts is not reasonable and necessary. Examples:
    - HS, DOS 01/25/23
    - AG, DOS 03/10/23

Additional Denial Reasons were listed as:

3) The plan of care included the application of Puraply XT skin. substitute; however, Revita skin substitute was billed, making it unclear which type of skin substitute was used. Example:
    - AG, DOS 01/12/24

4) The documentation did not include sufficient information about the beneficiary's failure to respond to prior conservative wound care measures with documented compliance. Examples:
    - AG, DOS 01/12/24
    - HS, DOS 01/25/23

5) The Wound Care Consent form did not include a date or signature date. Example:
    - AG, DOS 03/10/23-01/12/24

File 4, p. 69.

Overall, the UPIC concluded, "the documentation failed to establish medical necessity for the services billed. Medical review revealed documentation lacked evidence of conservative wound therapy treatments attempted prior to applying skin substitute

advanced wound therapy techniques. Additionally, there was lack of evidence to support basic standards of wound care such as: medical evaluations of vascular status, metabolic/nutritional assessments, infection control measures, and management and stabilization of comorbid conditions." File 4, p. 73.

The MAC issued an overpayment notification letter / demand letter on October 7, 2024. File 4, p. 39.

On November 7, 2024, Erin M. Ferber, Esq. of Nicholson & Eastin, LLP, requested redetermination by the MAC. File 4. Ms. Ferber submitted additional medical records, [redacted] curriculum vitae, and detailed argument relating to the legal standards, the biologics used, and each beneficiary who received services at issue. Ms. Ferber notes that there is no applicable local coverage determination (LCD) or national coverage determination (NCD) and argues, in part:

> …no overpayment should be assessed as [redacted] is without fault with respect to any technical deficiency that might exist, particularly with respect to any billing or documentation requirement the carrier now seeks to impose which is not expressly applicable to the biologics at issue here and/or was not known to [redacted] at the time the services at issue were rendered and billed. The biologics applied were properly documented and billed in good faith. Pursuant to the Social Security Act, [redacted] should not be required to re-pay Medicare for the allografts at issue under the circumstances presented here. (See 42 U.S.C. 1395gg). File 4, p. 9.

The MAC upheld the UPIC's denial, finding that the documentation did not: include comprehensive evaluations; support that the beneficiary was under the care of a physician for these conditions; document that the systemic conditions were stable, and that the beneficiary failed to respond to prior conservative wound care measures with documented compliance. File 3, p. 95. As a result, the MAC found insufficient information to support that the services provided were reasonable and medically necessary. Id.

Ms. Ferber filed a Request for Reconsideration by the Qualified Independent Contractor. File 3. The QIC agreed that there is no LCD or NCD applicable to the claims, and that LCD L37166 for Wound Care was incorrectly cited for the previous denials. File 2, p. 10. The QIC identified the appropriate legal authority as the Centers for Medicare & Medicaid (CMS) Internet-Only Manual (IOM), Publication (Pub.) 100-08, and the Medicare Program Integrity Manual, Chapter 3, Section 3.6.2.2. File 2, p. 9. The QIC completed a "medical necessity review" wherein it concluded that the services at issue are experimental and investigational "as denoted by the Q code status nomenclature." File 2, p. 10. Under Medicare law, no payment can be made under Medicare for any expenses incurred for items or services that are considered investigational and are not considered reasonable and necessary. Id. The QIC determined that since the services (Q4180, Q4194, Q4197, and Q4217) are considered investigational and not payable as

per CMS, these services do not meet the medically reasonable and necessary requirements of the Section 1862(a)(1)(A) of the Social Security Act.

A Request for an Administrative Law Judge (ALJ) Hearing was received June 27, 2025, at the Office of Medicare Hearings and Appeals. File 1. After due Notice, a telephone hearing was held on August 12, 2025. Files 10, 15 (hearing recording). Ms. Ferber represented the Appellant. The following witnesses participated in the hearing and provided sworn testimony in support of the Appellant's claims[3]: Daniel L. Kapp, M.D., John [redacted], M.D., Ian [redacted], M.D., Jeffrey [redacted], M.D., Mervin [redacted], M.D., Michael [redacted], M.D., Thomas [redacted], M.D. and JP [redacted], Ph.D. File 11, p. 4; File 15 (hearing recording). The documents identified in the attached Exhibit List were entered into the Administrative Record without objection. The record is closed.

ISSUE(S)

Whether the amniotic and/ or placental tissue biologics and related application services provided by the Appellant to multiple Medicare beneficiaries from January 25, 2023, through January 12, 2024, meet the Medicare requirements to be reasonable and necessary in the treatment of the beneficiaries and, if not, who is responsible for the non-covered costs?

APPLICABLE LAW AND POLICY

Social Security Act § 1862(a)(1)(A) provides that Medicare will only cover items and services that are medically reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the function of a malformed body member. As the party seeking payment, the appellant has the burden to demonstrate the services for which it seeks coverage are reasonable and necessary for the purposes provided. 42 C.F.R. § 424.5(a)(6).

I. *LCD and NCD*

The Appellant asserts there is no national coverage determination (NCD), or local coverage determination (LCD) applicable to the claims at issue, and the QIC agrees. File 2, p. 10. The Appellant argues that the submitted medical documentation, hearing testimony, and medical literature is sufficient to demonstrate medical necessity of the services provided and billed. The Appellant argues that the "Q" code status nomenclature does not denote a product is experimental and investigational, as found by the QIC.

Absent an applicable NCD or LCD, as is the case here, contractors and adjudicators must make individual reasonable and necessary determinations by assessing whether the service is safe and effective, not experimental or investigational, and appropriate. MPIM, Ch. 3, §§ 3.3.3, 3.6.2.1-3.6.2.2. Medicare defines "appropriate" to require that the service is furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the beneficiary's condition or to improve the function of a malformed body member; that it is a service that meets, but does not exceed, the beneficiary's

[3] The witness Curriculum Vitae are of record at File 13, pp. 39-113.

medical need; and that it is at least as beneficial as an existing and available medically appropriate alternative. See id.; see also MPIM, Ch. 13, § 13.5.4.

Regarding the evidence that may be considered when making the above determination, manual guidance instructs that the Medicare contractors "shall use the available evidence of general acceptance by the medical community, such as published original research in peer-reviewed medical journals, systematic reviews and meta-analyses, evidence-based consensus statements and clinical guidelines." MPIM, Ch. 13, § 13.5.3. The MPIM clarifies that "[a]cceptance by individual health care providers, or even a limited group of health care providers, does not indicate general acceptance of the item or service by the medical community." Id. § 13.2.3.

II. *Medical Literature*

The Appellant supplemented the administrative record with a large number of Medical Literature (peer-reviewed journals and clinical trials) to show the services provided are generally accepted by the medical community and are not experimental or investigational. They were considered in making this decision and are summarized below.

A.) Fairbairn, et al. (2014), *The clinical applications of human amnion in plastic surgery.* Journal of Plastic, Reconstructive & Aesthetic Surgery 67, 662-675:

Since the early 1900s, human amnion has been applied to a wide variety of clinical scenarios including burns, chronic ulcers, dural defects, intra-abdominal adhesions, peritoneal reconstruction, genital reconstruction, hip arthroplasty, tendon repair, nerve repair, microvascular reconstruction, corneal repair, intra-oral reconstruction and reconstruction of the nasal lining and tympanic membrane. Amnion epithelial and mesenchymal cells have been shown to contain a variety of regulatory mediators that result in the promotion of cellular proliferation, differentiation and epithelialization and the inhibition of fibrosis, immune rejection, inflammation and bacterial invasion. The full repertoire of biological factors that these cells synthesize, store and release and the mechanisms by which these factors exert their beneficial effects are only now being fully appreciated. Although many commercially available biological and synthetic alternatives to amnion exist, ethical, religious, and financial constraints may limit the widespread utilization of these products. Amnion is widely available, economical and is easy to manipulate, process and store. Although many clinical applications are of historical interest only, amnion offers an alternative source of multi-potent or pluripotent stem cells and therefore may yet have a great deal to offer the plastic surgery and regenerative medicine
community.
File 13, p. 184.

B.) Tettelbach, et al. (2024), Journal of Wound Care, North American Supplement, vol. 33, No. 3

Objective: To evaluate the cost-effectiveness of dehydrated human amnion/chorion membrane (DHACM) in Medicare enrollees who developed a venous leg ulcer (VLU).
Method: This economic evaluation used a four-state Markov model to simulate the disease progression of VLUs for patients receiving advanced treatment (AT) with DHACM or no advanced treatment (NAT) over a three-year time horizon from a US Medicare perspective.
DHACM treatments were assessed when following parameters for use (FPFU), whereby applications were initiated 30-45 days after the initial VLU diagnosis claim, and reapplications occurred on a weekly to biweekly basis until completion of the treatment episode. The cohort was modelled on the claims of 530,220 Medicare enrollees who developed a VLU between 2015-2019. Direct medical costs, quality-adjusted life years (QALYs), and the net monetary benefit (NMB) at a willingness-to-pay threshold of $100,000/QALY were applied. Univariate and probabilistic sensitivity analyses (PSA) were performed to test the uncertainty of model results. Results: DHACM applied FPFU dominated NAT, yielding a lower per-patient cost of $170 and an increase of 0.010 QALYs over three years. The resulting NMB was $1178 per patient in favor of DHACM FPFU over the same time horizon. The rate of VLU recurrence had a notable impact on model uncertainty. In the PSA, DHACM FPFU was cost-effective in 63.01 % of simulations at the $100,000/QALY threshold.
Conclusion: In this analysis, dehydrated human amnion/ chorion membrane following parameters for use was the dominant strategy compared to no advanced treatment, as it was cost-saving and generated a greater number of quality-adjusted life years over three years from the US Medicare perspective. A companion venous leg ulcer Medicare outcomes analysis revealed that patients who received advanced treatment with a cellular, acellular and matrix-like product (CAMP) compared to patients who received no advanced treatment had the best outcomes. Given the added clinical benefits to patients at lower cost, providers should recommend dehydrated human amnion/ chorion membrane following parameters for use to patients with venous leg ulcers who qualify. Decision-makers for public insurers (e.g., Medicare and Medicaid) and commercial payers should establish preferential formulary placement for reimbursement of dehydrated human amnion/ chorion membrane to reduce budget impact and improve the long-term health of their patient populations dealing with these chronic wounds.
File 13, p. 199

C.) Stern (1913), ***The Grafting of Preserved Amniotic Membrane to Burned and ulcerated Surfaces, Substituting Skin Grafts.***

Should the amniotic graft do as well or nearly as well as true skin, it must commend itself for general use, obviating, as it seems, the necessity of an anesthesia and the production of a secondary wound with no certainty of the outcome for its justification.
File 13, p. 212

D.) Rioridan (2015), ***Case report of non-healing surgical wound treated with dehydrated human amniotic membrane*****. Journal of Translational Medicine.**

Sterile, dehydrated amniotic tissue have proven effective in completely healing an otherwise non-healing wound in a 78-year-old male who failed six weeks of conservative wound care treatment.
File 13, p. 228.

The two dry amniotic patches applied on the patient's wound substantially accelerated the wound healing process. The dehisced surgical wound that showed no sign of healing even after 42 days post total knee replacement surgery, demonstrated a central scab formation in the middle of the wound dehiscence area only after 2 weeks of amniotic patch application. After eight more weeks, the wound was completely healed, and the patient was released from orthopaedic care to assume high levels of physical activity and activities of daily living. We suggest unreservedly that dehydrated tissue allograft patches derived from human amnion embody a viable and more effective alternative to current traditional means of wound care management.
File 13, p. 231.

E.) Christina Dai, Shawn Shih & Amor Khachemoune (2020) *Skin substitutes for acute and chronic wound healing: an updated review*, Journal of Dermatological Treatment, 31:6, 639-648, DOI 10.1080/09546634.2018.1530443

Wounds can be grouped into acute and chronic depending on the time they take to heal. When the adult skin experiences a wound, there is an activation of early inflammatory responses that results in an infiltration of immune cells and macrophages. They release cytokines such as fibroblast growth factor (FGF) and transforming growth factor beta (TFG-b), which play key roles in re-epithelization and skin remodeling. During wound healing, fibroblasts have an important role in the restoration of dermis. They produce collagen and extracellular matrix proteins that can result in fibrosis and scarring. Scar tissue formation prevents the complete recovery of skin function, resulting in skin that appears distinct from its original appearance. In wound care, skin substitutes have been widely used to minimize normal biological responses related to the activity of myofibroblasts, such as the development of wound contractures.
File 13, p. 234.

Skin substitutes are heterogenous biomaterials that were designed to accelerate wound healing by providing replacement of extracellular matrix. They are being increasingly used to treat both acute and chronic wounds. First developed in the 1880's by Joseph Gamgee …
File 13, p. 235.

F.) Malgorzata Litwiniuk and Tomasz Grzela (2014) *Amniotic membrane: New concepts for an old dressing.* Wound Repair and Regeneration 22, 451-456.

A strenuous literature search has provided data that suggest that amnion derivatives may offer new opportunities to make wound treatment easier and more effective. In addition to well-established applications in ocular surgery, some attempts have also made in the treatment of extensive skin bums with the use of sprayed amnion homogenates. Notably,

in the context of the previously discussed inter- and intra-donor variability of amniotic membrane samples, this method of amnion processing may enable the controlled combination of specimens originating from various donations. This approach would offer a higher stability and better quality of applied solution and, consequently, more predictable results during treatment. On the other hand, by selecting the appropriate zones for preparation, quite new opportunities may be provided for unlimited variations in the composition of prepared AM solution. In accordance with the idea of "personalized" treatment, this would allow the best adjustment of applied amniotic membrane homogenate suspension to the particular needs of the user.
File 13, p. 247.

G.) **Schmiedova et al., (2021)** ***Using of Amniotic Membrane Derivatives for the Treatment of Chronic Wounds*****. Membranes, 11, 941. https://doi.org/10.3390/membranes 11120941.**

Amniotic membrane grafts have some therapeutic potential for wound healing. Early application of amniotic membrane turned out as beneficial in healing ulcers, burns, and dermal injuries. Since the second half of the 20th century, the autotransplants of amniotic/ chorion tissue have been also used for the treatment of chronic neuropathic wounds, cornea surface injuries, pterygium and conjunctivochalasis, and dental and neurosurgical applications. The aim of this publication is to prepare a coherent overview of amniotic membrane derivatives use in the field of wound healing and also its efficacy. In total 60 publications and 39 posters from 2000-2020 were examined. In these examined publications of case studies with known study results was an assemblage of 1141 patients, and from this assemblage 977 were successfully cured. In case of posters, the assemblage is 570 patients and 513 successfully cured. From the investigated data it is clear that the treatment efficacy is very high---86% and 90%, respectively. Based on this information the use of the amniotic membrane for chronic wounds can be considered highly effective.
File 13, p 250.

In the last 50 years the autotransplants of the amniotic/ chorion tissue have been successfully used also for chronic neuropathic wounds, cornea surface injuries, pterygium, conjunctivochalasis, and dental and neurosurgical applications.

Regenerative qualities of amniotic membrane:

- Analgesic effect: Amniotic membrane covers loose nerve twigs in a wound and reduces the concentration of anti-inflammatory and algic cytokines and peptides which significantly reduces pain in the wound spot.
- Reducing scarring: One of the amniotic membrane's surfaces is non-adhesive, prevents [] from growing, and reduces occurring of undesired accretions and fibrotization. The hyaluronic acid present in the amniotic membrane also inhibits excessive fibrotization.
- Epithelization: Amniotic membrane contains tens of types of growth factors many of which directly and significantly supports epithelization. It especially contains epidermal growth factor (EGF), keratinocyte growth factor (KGF), and

hepatocyte growth factor (HGF) which support and activate migration, proliferation, and differentiation of epithelial cells.

• Angiogenic effect: Amniotic membrane releases a range of angiogenic factors into the wound, especially bFGB (Fibroblast Growth Factor-basic), TGF-B (Transforming Growth Factor-beta) which support vessel renewal in the area of the healing wound. Neoagiogenesis augmented by the amniotic membrane significantly shortens the time to regenerate.

• Anti-inflammatory effect: Amniotic membrane contains and releases Interleukin 10 (IL-10) which has the major anti-inflammatory effect, and thrombospondin-1, both are antagonists of the Interleukin 1 (IL-1) receptor and tissue inhibitors metalloproteinases (TIMPs).

• Mechanical effect: Amniotic membrane significantly reduces wound desiccation, and functions as a mechanical support and structure which allows epithelial and mesenchymal cells attachment, motility, and proliferation.

• Amniotic membrane is non-immunogenic: Amnion does not express transplantation antigens (HLA-A, B, C) and does not induce the recipient's organism's immune response.

File 13, p. 252.

Treatment with amniochorionic membrane derivatives can be used in a wide range of various injuries and illnesses. One of the most commonly treated conditions is wounds related to the advanced stage of diabetes and the occurrence of non-healing leg ulcers. Treatment of venous ulcers located in the lower limbs is typical for use of derivative applications and it is highly covered in the studies. Other derivative applications are post-surgery non-healing wounds and other injuries. It can also be used in the treatment of bums of all degrees.

File 13, p. 257.

H.)Ventia Lo and Elena Pope (2009) *Amniotic membrane use in dermatology,* The International Journal of Dermatology, 48, 935-940

There have been many successful reports of spontaneous re-epithelialization associated with amniotic membrane use. It promotes keratinocyte proliferation and differentiation by releasing various growth factors. Koizumi *et al.* performed reverse transcriptase-polymerase chain reaction to examine the expression of growth factors in the amniotic epithelium and stroma. Higher levels of growth factors, including epidermal growth factor, transforming growth factor (TGF), keratinocyte growth factor, hepatocyte growth factor, and basic fibroblast growth factor, were localized in the intact vs. denuded amniotic epithelium. In addition, the AM releases various growth factors for angiogenesis, which induces the formation of granulation tissue. 10'21 Yang *et al.* 22 reported that the presence of de-epithelialized AM in living skin-equivalent grafts outperformed grafts without AM in terms of keratinocyte proliferation and differentiation. The AM retains key basement membrane components that dynamically interact with the overlying epidermis, affecting migration, cell attachment, proliferation, and differentiation of keratinocytes and fibroblasts. It has been proven that amniotic epithelial cells express collagen types III and IV and other noncollagenous glycoproteins

(laminins, nidogen, and fibronectin). These components serve as adhesion ligands, which bind cell surface receptors, influencing signal transduction.
File 13, p. 264-265.

I.) Kirsner, et al. (2016) ***A Review of Cellular and Acellular Matrix Products: Indications, Techniques, and Outcomes,*** **Plast. Reconstr. Surg. 138: 138S.**

Background: Wound healing is a dynamic process whereby cells, growth factors (GFs), and the extracellular matrix (ECM) interact to restore the architecture of damaged tissue. Chronic wounds can be difficult to treat due to the increased presence of inflammatory cells that degrade the ECM, GF, and cells necessary for wound healing to occur. Cellular and acellular matrix products can be used in the management of a variety of chronic wounds including venous, diabetic, and pressure ulcers and other conditions such as burns, epidermolysis bullosa, pyoderma gangrenosum, and surgical wounds. These matrices provide cells, GF, and other key elements that act as a scaffold and promote re-epithelialization and revascularization of the wound bed.
Methods: This article focuses on cellular and acellular matrix products that have been well-studied clinically with positive results in randomized clinical trials and widely available matrices for chronic nonhealing wounds. We present trial results as well as their indications, techniques, and outcomes.
Results: There are a variety of matrix products available on the market. Some of these products are used to treat chronic wounds, for example, diabetic foot ulcers, venous leg ulcers, pyoderma gangrenosum, and pressure ulcers. In this review, we found that wounds of different etiologies have been treated with a variety of matrices, with successful outcomes compared with standard wound care.
Conclusions: Both cellular and acellular matrix products are useful in the management of a variety of chronic wounds. These matrices provide cells, GF, and other key elements that promote re-epithelialization and revascularization of the wound bed while preventing degradation of the ECM. The treatment of chronic wounds with matrix products in combination with standard wound care has been proven to aid in wound healing when added to standard of care.
File 13, p. 270.

J.) Armstrong, et al. (2021), ***Observed impact of skin substitutes in lower extremity diabetic ulcers: lessons from the Medicare Database 2015-2018,*** **Journal of wound Care North American Supplement, vol. 30, No. 7.**

Patients receiving advanced treatment with skin substitutes (AT) for lower extremity diabetic ulcers (LEDUs) versus no AT (NAT) for the management of LEDUs. AT for the management of LEDUs was associated with significant reductions in major and minor amputation, emergency department use, and hospital readmission compared with LEDUs managed with NAT. Clinics should implement AT in accordance with the highlighted parameters for use to improve outcomes and reduce costs.
File 13, p. 280.

K.)Felder (2012), ***A Systemic Review of Skin Substitutes for Foot Ulcers,*** **Plast. Reconstr. Surg. 130: 145**

A convincing body of evidence supports the effectiveness of living cell-based skin substitutes as an adjunctive therapy for increasing the rate of complete healing in chronic foot ulcers when basic tenets of wound care are also being implemented. Acellular skin substitutes also show some promise for treatment of foot wounds but require further study. File 13, p. 292.

L.) Su Y-N, Zhao D-Y, Li Y-H, et al. (2020) ***Human amniotic membrane allograft, a novel treatment for chronic diabetic foot ulcers: A systematic review and meta-analysis of randomized controlled trials*****. In Wound J. 2020; 17:753. https://doi.org/10.1111/iwj.13318**

Human Amniotic Membrane (HAM) plus standard of care (SOC) did accelerate the process of wound healing. HAM plus SOC achieved a much higher probability of wound recovery than SOC alone, about four times at 6 weeks and two times at 12 weeks. It also had a significantly shorter time to complete wound closure, about 30 days earlier. In addition, every two to three patients treated with HAM plus SOC would get one additional patient successfully cured within 6 weeks. Hence, HAM plus SOC might decrease the chance of amputation and improve the quality of life. The sensitivity analysis showed that our result was quite robust. The main reason for the excellent curative effect may be due to its special properties. It contains a large number of multiple growth factors and multiple proangiogenic factors, which can induce human dermal fibroblast proliferation and angiogenesis. Besides, it also has anti-inflammatory and antimicrobial properties and can be tolerated by the immune system. These properties make it an outstanding facilitator when serving as a scaffold for cell proliferation and differentiation in wound healing.
File 13, p. 312.

M.) Gordan, et al. (2019) ***Evidence for Healing Diabetic Foot Ulcers with Biologic Skin Substitutes: A Systematic Review and Meta-Analysis,*** **Annals of Plastic Surgery, Volume 83, supplement 1, October 2019**

Results: Twenty-five studies were identified that assessed the proportion of complete wound closure by 12 weeks. We found that wounds treated with biologic dressings were 1.67 times more likely to heal by 12 weeks than those treated with SOC dressings *(P* < 0.00001). Five studies assessed the proportion of complete wound closure by 6 weeks. Wounds treated with biologic dressings were 2.81 times more likely to heal by 6 weeks than those treated with SOC dressings *(P* = 0.000 I). Descriptively, 29 of 3l studies that assessed time to healing favored biologic dressings over SOC dressings.
Conclusions: This systematic review provides supporting evidence that biologic skin substitutes are more effective than SOC dressings at healing diabetic foot ulcers by 12 weeks. Future studies must address the relative benefits of different skin substitutes as well as the long-term implications of these products and their financial considerations.
File 13, p. 324.

N.) ***Diabetic Foot Disorders: A Clinical Practice Guideline (2006 revision),*** **The Journal of Foot & Ankle Surgery vol. 45, number 5 (September/October 2006)**

Bioengineered tissues. Bioengineered tissues have been shown to significantly increase complete wound closure in venous and diabetic foot ulcers. Currently, two bioengineered tissues have been approved to treat diabetic foot ulcers in the US: ApligrafM (Organogenesis Inc., Canton, MA), and Dermagraft™ (Smith & Nephew, Inc., London, UK); both have demonstrated efficacy in randomized, controlled trials. Tissue-engineered skin substitutes can provide the cellular substrate and molecular components necessary to accelerate wound healing and angiogenesis. They function both as biologic dressings and as delivery systems for growth factors and extracellular matrix components through the activity of live human fibroblasts contained in their dermal elements Bilayered skin substitutes (living cells) include bilayered skin equivalent (ApligrafM) and cultured composite skin (OrCeI™ bilayered cellular matrix, Ortech International, Inc., New York City, NY). ApligrafM has been shown to significantly reduce the time to complete wound closure in venous and diabetic ulcers.
File 13, pp. 337, 360-361.

O.) Martinson (2016), ***A comparative analysis of skin substitutes used in the management of diabetic foot ulcers,*** **Journal of Wound Care, North American Supplement, Vol. 25, No. 10, October 2016.**

Objective: To compare the relative product cost and clinical outcomes of four skin substitutes used as adjunctive treatments for diabetic foot ulcers (DFUs).
Method: Medicare claims data from 2011 to 2014 were used to identify beneficiaries with diabetes and foot ulcers. Patients treated with one of four types of skin substitute (Apligraf, Dermagraft, OASIS, and MatriStem) were identified. The skin substitutes were compared on episode length; amputation rate; skin substitute utilization; and skin substitute costs.
Results: There were 13,193 skin substitute treatment episodes: Apligraf (HML) was used in 4926 (37.3%), Dermagraft (HSL) in 5530 (41.9%), OASIS (SIS) in 2458 (18.6%) and MatriStem (UBM) in 279 (2 .1 %). The percentage of DFUs that healed at 90 days were: UBM 62%; SIS 63%; HML 58%; and HSL 58%. Over the entire time, UBM was non-inferior to SIS ($p<0.001$), and either was significantly better than HML or HSL ($p<0.005$ in all four tests). HML was marginally in skin substitutes per episode) and SIS ($1901) appeared to be equivalent to each other, although non-inferiority tests were not significant. Both were less than HML ($5364) or HSL ($14,424) ($p<0.0005$ in all four tests). HML was less costly than HSL ($p<0.0005$).
Conclusion: Various types of skin substitutes appear to be able to confer important benefits to both patients with DFUs and payers. Analysis of the four skin-substitute types resulted in a demonstration that UBM and SIS were associated with both shorter DFU episode lengths and lower payer reimbursements than HML and HSL, while HML was less costly than HSL but equivalent in healing.
File 13, p. 402.

DFUs that do not heal with standard care alone can successfully treated with skin substitutes. However, these skin substitutes can be expensive, and once their use is initiated, treatment may still be required for several months. In total, these episodes can be long and expensive, so therapies that can decrease the duration of the episode without creating a financial burden should be encouraged. A recently published systematic review from the Cochrane Wounds Group concluded that the clinical effectiveness and cost-effectiveness of skin substitutes in the treatment of DFUs still remains uncertain and that no specific type of skin substitute could be recommended. The present study has begun to address this uncertainty. This study has provided data on clinically based evidence from CMS claims that two skin substitutes, HSL and HML, did not appear superior to the lesser-used types of skin substitute, UBM and SIS. At 90 days, UBM and SIS healed about 62-63% of DFUs, while HML and HSL healed about 58%, which was statistically significant due to the large sample sizes available in the claims data. The 4% difference in healed wounds may not be considered significant to the clinicians using skin substitutes but the cost difference could be compelling to clinicians and payers. While HML and HSL cost over $5000 to heal a DFU, UBM and SIS were less than $2000. If payers can save even a portion of that difference on every DFU on which skin substitutes are used, the financial benefit will be substantial.
File 13, p. 409.

P.) Singh, et al. (2005) *Preventing Foot Ulcers in Patients with Diabetes,* American Medical Association, JAMA January 12, 2005, Vol. 293, No 2, 217-228.

Among persons diagnosed as having diabetes mellitus, the prevalence of foot ulcers is 4% to 10%, the annual population-based incidence is 1.0% to 4.1%, and the lifetime incidence may be as high as 25%. These ulcers frequently become infected, cause great morbidity, engender considerable financial costs, and are the usual first step to lower extremity amputation.
File 13, p. 411, 1005.

Q.)Laurent et al, (2017). *Efficacy and Time Sensitivity of Amniotic Membrane treatment in Patients with Diabetic Foot Ulcers: A Systematic Review and Meta-analysis*. Diabetes Ther (2017) 8:967-979.

All randomized controlled trials (RCTs) comparing human amnion/chorion membrane+ standard therapy and standard therapy alone in patients with DFUs were included in the analysis. Eligible studies were reviewed and data extracted into standard form. The Cochrane Collaboration's tool for assessing the risk of bias was used. Review manager version 5.3 software was used for statistical analysis. Data were analyzed using a random effect model. The results showed that patients receiving amniotic membrane + standard therapy had far fewer incomplete healing wounds than those receiving standard of care alone. Assessment of the wound healing state at 4 and 6 weeks revealed that the wound healing state was almost the same, but there was a net difference of wound healing state at 12 weeks.
Conclusion: Human amnion/chorion membrane + standard of care treatment heals DFUs significantly faster than standard of care alone. When using the amnion in patients with

DFUs, the optimal times to assess progress in wound healing should be 4 and 12 weeks.
File 13, p. 423.

R.) Ramsey (1999), *Incidence, Outcomes, and Cost of Foot Ulcers in Patients with Diabetes*, Diabetes Care, Vol. 22, Number 3, March 1999, 382-387.

Results: Among 8,905 patients identified with type 1 or type 2 diabetes, 514 developed a foot ulcer over 3 years of observation (cumulative incidence 5.8%). On or after the time of diagnosis, 77 (15%) patients developed osteomyelitis and 80 (15.6%) required amputation. Survival at 3 years was 72% for the foot ulcer patients versus 87% for a group of age- and sex matched diabetic patients without foot ulcers ($P < 0.001$). The attributable cost for a 40- to 65-year-old male with a new foot ulcer was $27,987 for the 2 years after diagnosis.
Conclusions: The incidence of foot ulcers in this cohort of patients with diabetes was nearly 2.0% per year. For those who developed ulcers, morbidity, mortality, and excess care costs were substantial compared with those for patients without foot ulcers. The results appear to support the value of foot-ulcer prevention programs for patients with diabetes.
File 13, p. 441.

S.) Brownrigg et al. (2012), *The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis*, Diabetologia (2012) 55:2906-2912

Aims/hypothesis: It is well established that diabetes mellitus increases the risk of cardiovascular disease (CVD) and all cause mortality. Observational studies suggest that a history of diabetic foot ulceration (DFU) may increase this risk further still. We sought to determine to what extent DFU is associated with excess risk over and above diabetes.
Methods: We identified studies reporting on associations of DFU with CVD and all-cause mortality. We obtained data on incident events of all-cause mortality, fatal myocardial infarction and fatal stroke. Study-specific estimates were pooled using a random-effects meta-analysis and the statistical heterogeneity of included studies was assessed using the J2 statistic.
Results: The eight studies included reported on 3,619 events of all-cause mortality during 81,116 person-years of follow-up. DFU was associated with an increased risk of all-cause mortality (RR 1.89, 95% CI 1.60, 2.23), fatal myocardial infarction (2.22, 95% CI 1.09, 4.53) and fatal stroke (1.41, 95% CI 0.61, 3.24). CVD mortality accounted for a similar proportion of deaths in DFU and non-DFU patients.
Conclusions/interpretation: Patients with DFU have an excess risk of all-cause mortality, compared with patients with diabetes without a history of DFU. This risk is attributable, in part, to a greater burden of CVD. If this result is validated in other studies, strategies should evaluate the role of further aggressive CVD risk modification and ulcer prevention in those with DFU.
File 13, p. 447.

T.) Markakis, et al. (2016), *The diabetic foot in 2015: an overview, Diabetes/ Metabolism Research and Reviews,* Diabetes Metab Res Rev 2016; 32 (Suppl. 1): 169-178

Human skin equivalents have been developed and are under evaluation. Bioengineered skin (Apligraf) and human dermis (Dermagraft) are types of biologically active implants for ulcers and contain human fibroblasts that deliver growth factors and extracellular matrix components. Results for studies of these in DFUs support their efficacy in promoting and accelerating wound healing, but, although such studies show statistically significant results, many have questioned the clinical efficacy of such methods. In any case, further large-scale RCT are still needed, especially to compare these treatments with other less expensive ones in order to evidence the benefits.
File 13, pp. 454, 456.

U.) William J. Jeffcoate and Keith G. Harding (2003), *Diabetic foot ulcers,* The Lancet Vol. 361, May 3, 2003.

Ulceration of the foot in diabetes is common and disabling and frequently leads to amputation of the leg. Mortality is high and healed ulcers often recur. The pathogenesis of foot ulceration is complex, clinical presentation variable, and management requires early expert assessment. Interventions should be directed at infection, peripheral ischemia, and abnormal pressure loading caused by peripheral neuropathy and limited joint mobility. despite treatment, ulcers readily become chronic wounds. Diabetic foot ulcers have been neglected in health-care research and planning, and clinical practice is based more on opinion than scientific fact. Furthermore, the pathological processes are poorly understood and poorly taught and communication between the many specialties involved is disjointed and insensitive to the needs of patients.
File 13, p. 464.

W.) Peters et al. (2020), *Interventions in the management of infection in the foot in diabetes: a systematic review,* Diabetes Metab Res Rev 2020; 36 (S1): e3282.

The optimal approaches to managing diabetic foot infections remain a challenge for clinicians… There is insufficient high-quality evidence to assess the effect of various adjunctive therapies, such as negative pressure wound therapy, topical ointments or hyperbaric oxygen, on infection related outcomes of the diabetic foot.
File 13, p. 471.

X.) Santema, et al. (2016), *Systematic review and meta-analysis of skin substitutes in the treatment of diabetic foot ulcers: Highlight of a Cochrane systematic review,* Wound Rep Reg (2016) 24 737-744

Skin substitutes are increasingly used in the treatment of various types of acute and chronic wounds. The aim of this study was to perform a systematic review and meta-analysis to evaluate the effectiveness of skin substitutes on ulcer healing and limb salvage in the treatment of diabetic foot ulcers. Randomized clinical trials were searched and

assessed following the methodology of The Cochrane Collaboration. We included 17 trials, totaling 1655 randomized participants. Risk of bias was variable among included trials. Thirteen trials compared the skin substitutes with standard care. The pooled results showed that skin substitutes can, in addition to standard care, increase the likelihood of achieving complete ulcer closure compared with standard care alone after 6-16 weeks (risk ratio 1.55, 95% confidence interval [CI] 1.30-1.85). Four of the included trials compared two types of skin substitutes but no particular product showed a superior effect over another. Two trials reported on total incidence of lower limb amputations. Pooling the results of these two trials yielded a statistically significantly lower amputation rate among patients treated with skin substitutes (risk ratio 0.43, 95% CI 0.23-0.81), although the absolute risk difference was small (-0.06, 95% CI -0.10 to -0.01). This systematic review provides evidence that skin substitutes can, in addition to standard care, increase the likelihood of achieving complete ulcer closure compared with standard care alone in the treatment of diabetic foot ulcers. However, effectiveness on the long term, including lower limb salvage and recurrence, is currently lacking and cost effectiveness is unclear.
File 13, p. 486.

The ultimate goal of treating diabetic foot ulcers is the prevention of lower limb amputations and is therefore a main outcome parameter of trials evaluating the effectiveness of novel therapies. This requires a long-term follow-up to provide evidence on ulcer recurrence and the occurrence of lower limb amputations. However, most of the trials found in this study fell short of this requirement. In this systematic review, we focused on three clinical relevant endpoints: incidence of complete closure of the ulcer, time to complete closure of the ulcer, and the incidence of lower limb amputations. Unfortunately, the majority of trials did not assess these outcome parameters as their primary study outcome, but mainly focused on the reduction in wound size or the healing speed. If complete ulcer healing was never achieved, the clinical relevance of these surrogate endpoints remains unclear. In conjunction to the benefits reported in this review, the use of skin substitutes might have secondary advantageous effects as well. One may consider a shortening of the clinical course and hospital stay, fewer painful dressing changes, shorter off-loading period, and a possible protection barrier against wound infection. These possible beneficial effects may tip the balance toward a more cost-effective outcome Not many data are currently available on the cost-effectiveness of skin substitutes Gilligan et al. performed a cost-effectiveness analysis of the use of OASIS compared to Dermagraft as studied by Landsman et al. They reported that the total treatment costs were 54% higher in the patients treated with Dermagraft compared to the total costs of the treatment with OASIS, despite similar clinical outcomes. Other cost-effectiveness studies such as performed by Redekop et al. and Allenet et al. indicate that treatment with skin substitutes may result in favorable economic outcomes, but stronger evidence is necessary to generalize these findings. Although this review presents some evidence for the beneficial effect of skin substitutes, the potential benefits should be weighed against the high costs of these products.
File 13, pp. 492, 815.

Y.) Haugh (2017), *Amnion Membrane in Diabetic Foot Wounds: A Meta-analysis*, (Plast Reconstr Surg Gwb open 2017;5:el302; doi: 10.1097/GOX.0000000000001302; Published online 25 April 2017.)

Background: Amniotic membrane is tissue obtained from human placenta rich in cytokines, growth factors, and stem cells that possess the ability to inhibit infection, improve healing, and stimulate regeneration.
Methods: A meta-analysis was performed examining randomized controlled trials comparing amniotic tissue products with standard of care in nonhealing diabetic foot ulcers including PubMed, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews.
Results: A search of 3 databases identified 596 potentially relevant articles. Application of selection criteria led to the selection of 5 randomized controlled trials. The 5 selected randomized controlled trials represented a total of 311 patients. The pooled relative risk of healing with amniotic products compared with control was 2.7496 (2.05725-3.66524, $P < 0.001$).
Conclusions: The current meta-analysis indicates that the treatment of diabetic foot ulcers with amniotic membrane improves healing rates in diabetic foot ulcers. Further studies are needed to determine whether these products also decrease the incidence of subsequent complications, such as amputation or death, in diabetic patients.
File 13, pp. 494, 1008.

Z.) Lipkin, et al., Effectiveness *of Bilayered Cellular Matrix in Healing of Neuropathic Diabetic Foot Ulcers: Results of a Multicenter Pilot Trial*

Patients with diabetes are at increased risk of developing foot ulcers. Peripheral neuropathy increases the likelihood of foot injury, and peripheral vascular disease reduces normal healing of minor trauma, allowing development of ulcers. It is estimated that 15 percent of patients with type 1 or type 2 diabetes will develop an ulcer on a foot or ankle within the course of the disease. Current standard care for diabetic foot ulcers includes removal of mechanical stress, sharp wound debridement, and use of dressings to maintain a moist wound environment. In addition, infections of the wound site must be managed. Rates of healing with standard care are 24 percent after 12 weeks. A majority of patients with failure of wound healing ultimately require surgery or amputation, and ulcers contribute to 85 percent of lower-extremity amputations for patients with diabetes Biologic dressings, such as cultured epidermal allografts, can promote healing of a variety of wounds, including burns, venous ulcers, and split-thickness skin graft donor sites. Because the allograft cells survive only briefly and do not become a permanent part of the regenerating tissue, the postulated mechanism of action of cultured grafts is stimulation of wound repair through the release of multiple cytokines and matrix components. Bilayered cellular matrix (BCM, OrCel™, Ortec International, New York, New York. The objective of the current study was to examine the effectiveness and safety of treatment of diabetic neuropathic foot ulcers using BCM plus standard care compared with standard care alone.
File 13, p. 500.

Within the 12-week study period, 35 percent of all ulcers in the BCM treatment group were completely healed, compared with 20 percent of ulcers in the control treatment group (Figure 2). Examining the stratum of ulcers with baseline size less than or equal to 6cm2 showed that 47 percent of ulcers in the BCM treatment group were completely

healed (7/15), compared with 23 percent (3/13) of those in the control treatment group. Ulcers with a baseline area of greater than or equal to 6cm2 showed that none of the ulcers in the BCM group were completely healed (0/5), while 14.3 percent of the wounds receiving standard care alone healed by the 12-week endpoint (1/7).
Rate of reepithelization. The rate of wound closure was calculated based on planimetrically measured total epithelialized area at each visit. The mean rate of wound closure per day was higher for the BCM treatment group (1.8 ± 2.5% per day) than for the control treatment group (1.1 ± 1.9% per day) over the 12-week treatment period (p = 0.0087). The mean rate of wound closure per day in BCM-treated wounds was 2.2 ±percent per day) compared to 1.1 ± 1.9 percent per day in those wounds receiving standard care alone (p = .001).
File 13, p. 501.

AA.) Brantley et al, *Use of Placental Membranes for the Treatment of Chronic Diabetic Foot Ulcers,* Wound Healing Society, Advances in Wound Care, Volume 4, Number 9 (2015)

Significance: Chronic diabetic foot ulcers (DFUs) remain a challenge for physicians to treat. High mortality rates for DFU patients have pointed to the low effectiveness of standard care and lack of quality wound care products. The composition (collagen-rich tissue matrix and endogenous growth factors and cells) and functional properties (anti-inflammatory, anti-bacterial, and angiogenic) of placental membranes are uniquely suited to address the needs of chronic wounds. This led to the commercialization of placental membranes, which are now widely available to physicians as a new advanced wound treatment option.
Recent Advances: Progress in tissue processing and preservation methods has facilitated the development of placental products for wounds. Currently, a variety of commercial placental products are available to physicians for the treatment of chronic DFUs and other wounds. This review summarizes the key factors that negatively impact DFU healing (including social factors, such as smoking, vascular deficiencies, hyperglycemia, and other metabolic abnormalities), describes the structure and biology of placental membranes, and overviews commercially available placental products for wounds and data from the most recent DFU clinical trials utilizing commercial placental membranes.
Critical Issues: Although the effects of diabetes on wound healing are complex and not fully understood, some of the key factors and pathways that interfere with healing have been identified. However, a multidisciplinary approach for the assessment of patients with chronic DFUs and guidelines for selection of appropriate treatment modalities remain to be implemented.
Future Directions: The biological properties of placental membranes show benefits for the treatment of chronic DFUs, but scientific and clinical data for commercially available placental products are limited. Therefore, we need (1) more randomized, controlled clinical trials for commercial placental products; (2) studies that help to understand the timing of placental products' application and criteria for patient selection; and (3) studies comparing the functional properties of different commercially available placental products.
File 13, p. 503.

Chronic DFUs are often stalled in the inflammatory phase and are characterized by an excess of proinflammatory cytokines, oxygen free radicals, and proteases preventing wounds from healing. Accumulated data indicate that placental membranes, including the amnion and chorion, have a composition and properties that are beneficial for chronic wound treatment. The anti-inflammatory activity of placental membranes, in particular, is critical for downregulation of inflammation and for assistance of wound transition from the inflammatory to the regenerative phase of wound healing. Advances in tissue preservation methods have resulted in the development of commercial placental membrane products, which represent a promising new wound treatment modality available to physicians. More than 25 commercial placental membrane products are on the market, and the number is growing rapidly. However, with a few exceptions, the majority of placental products have neither scientific nor clinical data to support their use. File 13, p. 515.

• Chronic DFUs remain challenging to treat. Such wounds often do not respond to standard wound care treatments and require advanced therapies.
• Before wound treatment, DFU patients have to be assessed for multiple factors that negatively affect wound healing. Each factor should be addressed before wound treatment.
•Placental membrane (amnion and chorion) composition and biological activities are beneficial for wound treatment, particularly for chronic, difficult-to-close wounds.
•Advances in tissue processing and preservation techniques have resulted in the development of commercial placental membrane products. These products represent a new advanced wound treatment modality available for nonhealing wounds.
•Clinical data for commercial placental membrane products is limited. Among more than 25 placental membrane products, only two have been evaluated in randomized, controlled clinical trials.
File 13, p. 1097.

BB.) Veves, et al. (2001), *Graftskin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers. A prospective randomized multicenter clinical trial,* Diabetes Care, Volume 24, Number 2, February 2001

Research, Design, and Methods: In 24 centers in the U.S., 208 patients were randomly assigned to ulcer treatment either with Graftskin (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, which included extensive surgical debridement and adequate foot off-loading, was provided in both groups. Graftskin was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of five applications) or earlier if complete healing occurred. The major outcome of complete wound healing was assessed by intention to treat at the 12-week follow-up visit.
Results: At the 12-week follow-up visit, 63 (56%) Graftskin-treated patients achieved complete wound healing compared with 36 (38%) in the control group (P = 0.0042). The KaplanMeier median time to complete closure was 65 days for Graftskin, significantly lower than the 90 days observed in the control group (P = 0.0026). The odds ratio for complete healing for a Graftskin-treated ulcer compared with a control-treated ulcer was

2.14 (95% CI 1.23-3. 7 4). The rate of adverse reactions was similar between the two groups with the exception of osteomyelitis and lower-limb amputations, both of which were less frequent in the Graftskin group.
Conclusions: Application of Graftskin for a maximum of four weeks results in a higher healing rate when compared with state-of-the-art currently available treatment and is not associated with any significant side effects. Graftskin may be a very useful adjunct for the management of diabetic foot ulcers that are resistant to the currently available standard of care.
File 13, p. 518.

CC.) Zelen, et al. (2015), *Chronic diabetic ulcers, comparative effectiveness, treatment outcomes,* International Wound Journal.

Prospective, randomized, controlled, parallel group, multi-centre clinical trial was conducted at three sites to compare the healing effectiveness of treatment of chronic lower extremity diabetic ulcers with either weekly applications of Apligraf® (Organogenesis, Inc., Canton, MA), EpiFix® (MiMedx Group, Inc., Marietta, GA), or standard wound care with collagen-alginate dressing. The primary study outcome was the percent change in complete wound healing after 4 and 6 weeks of treatment. Secondary outcomes included percent change in wound area per week, velocity of wound closure and a calculation of the amount and cost of Apligraf or EpiFix used. A total of 65 subjects entered the 2-week run-in period and 60 were randomized (20 per group). The proportion of patients in the EpiFix group achieving complete wound closure within 4 and 6 weeks was 85% and 95%, significantly higher (all adjusted P-values ~ 0-003) than for patients receiving Apligraf (35% and 45%), or standard care (30% and 35%). After 1 week, wounds treated with EpiFix had reduced in area by 83-5% compared with 53 • 1 % for wounds treated with Apligraf. Median time to healing was significantly faster (all adjusted P-values ~0-001) with EpiFix (13 days) compared to Apligraf (49 days) or standard care (49 days). The mean number of grafts used and the graft cost per patient were lower in the EpiFix group compared to the Apligraf group, at 2-15 grafts at a cost of $1669 versus 6-2 grafts at a cost of $9216, respectively. The results of this study demonstrate the clinical and resource utilization superiority of EpiFix compared to Apligraf or standard of care, for the treatment of diabetic ulcers of the lower extremities.
File 13, p. 524.

Advanced therapies such as bioengineered skin substitutes (BSS) and dehydrated human amnion/chorion membrane (dHACM) have been shown to promote healing of chronic diabetic ulcers. An interim analysis of data from 60 patients enrolled in a prospective, randomised, controlled, parallel group, multi-centre clinical trial showed that dHACM (EpiFix®, MiMedx Group Inc., Marietta, GA) is superior to standard wound care (SWC) and BSS (Apligraf®, Organogenesis, Inc., Canton, MA) in achieving complete wound closure within 4-6 weeks. Rates and time to closure at a longer time interval and factors influencing outcomes remained unassessed; therefore, the study was continued in order to achieve at least 100 patients. With the larger cohort, we compare clinical outcomes at 12 weeks in 100 patients with chronic lower extremity diabetic ulcers treated with weekly applications of Apligraf *(n* = 33), EpiFix *(n* = 32) or SWC *(n* = 35) with collagen-alginate dressing as controls. A Cox regression was performed to analyse the time to heal within

12 weeks, adjusting for all significant covariates. A Kaplan-Meier analysis was conducted to compare time-to-heal within 12 weeks for the three treatment groups. Clinical characteristics were well matched across study groups. The proportion of wounds achieving complete closure within the 12-week study period were 73% (24/33), 97% (31/32), and 51% (18/35) for Apligraf, EpiFix and SWC, respectively (adjusted *P* = 0·00019). Subjects treated with EpiFix had a very significant higher probability of their wounds healing [hazard ratio (HR: 5-66; adjusted *P:* 1·3 x 10-11 compared to SWC alone. No difference in probability of healing was observed for the Apligraf and SWC groups. Patients treated with Apligraf were less likely to heal than those treated with EpiFix **[**HR: 0-30; 95% confidence interval (CI): 0· 17-0•54; unadjusted *P:* 5-8 x 10-5]. Increased wound size and presence of hypertension were significant factors that influenced healing. Mean time-to-heal within 12 weeks was 47•9 days (95% CI: 38-2-57·7) with Apligraf, 23·6 days (95% CI: 17-0-30·2) with EpiFix group and 57.4 days (95%CI: 48•2-66·6) with the SWC alone group (adjusted *P* = 3·2 x 10-7). Median number of grafts used per healed wound were six (range 1-13) and 2-5 (range 1-12) for the Apligraf and EpiFix groups, respectively. Median graft cost was $8918 (range $1,486-19,323) per healed wound for the Apligraf group and $1,517 (range $434-25,710) per healed wound in the EpiFix group *(P* < 0·0001). These results provide further evidence of the clinical and resource utilization superiority of EpiFix compared to Apligraf for the treatment of lower extremity diabetic wounds.
File 13, p. 533

DD.) Zelen, et al., ***A prospective randomized comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers,*** **International Wound Journal.**

Our purpose was to compare healing characteristics of diabetic foot ulcers treated with dehydrated human amniotic membrane allografts (EpiFix®, MiMedx, Kennesaw, GA) versus standard of care. An IRE-approved, prospective, randomized, single-centre clinical trial was performed. Included were patients with a diabetic foot ulcer of at least 4-week duration without infection having adequate arterial perfusion. Patients were randomized to receive standard care alone or standard care with the addition of EpiFix. Wound size reduction and rates of complete healing after 4 and 6 weeks were evaluated. In the standard care group *(n* = 12) and the EpiFix group *(n* = 13) wounds reduced in size by a mean of 32-0%±47-3% versus 97-1%±7-0% (P<0-001) after 4 weeks, whereas at 6 weeks wounds were reduced by -1-8% ± 70-3% versus 98-4% ± 5-8% *(P* < 0-001), standard care versus EpiFix, respectively. After 4 and 6 weeks of treatment the overall healing rate with application of EpiFix was shown to be 77% and 92%, respectively, whereas standard care healed 0% and 8% of the wounds *(P* < 0-001), respectively. Patients treated with EpiFix achieved superior healing rates over standard treatment alone. These results show that using EpiFix in addition to standard of care is efficacious for wound healing.
File 13, p. 544.

EE.) Lavery, et al., ***The efficacy and safety of Grafix for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomized, blinded, clinical trial.*** **International Wound Journal.**

In a randomized, controlled study, we compared the efficacy of Grafix ®, a human viable wound matrix **(**h VWM**)** (N = 50), to standard wound care *(n* = 47) to heal diabetic foot ulcers (DFUs). The primary endpoint was the proportion of patients with complete wound closure by 12 weeks. Secondary endpoints included the time to wound closure, adverse events and wound closure in the crossover phase. The proportion of patients who achieved complete wound closure was significantly higher in patients who received Grafix (62%) compared with controls (21 %, *P* = 0-0001). The median time to healing was 42 days in Grafix patients compared with 69-5 days in controls (P = 0-019). There were fewer Grafix patients with adverse events (44% versus 66%, *P* = 0-031) and fewer Grafix patients with wound-related infections (18% versus 36-2%, *P=0-044).* Among the study subjects that healed, ulcers remained closed in 82-1 % of patients (23 of 28 patients) in the Grafix group versus 70% (7 of 10 patients) in the control group *(P* = 0-419). Treatment with Grafix significantly improved DFU healing compared with standard wound therapy. Importantly, Grafix also reduced DFU-related complications. The results of this well-controlled study showed that Grafix is a safe and more effective therapy for treating DFUs than standard wound therapy.
File 13, p. 550.

FF.) DiDomico, et al. (2016), ***Aseptically Processed Placental membrane Improves Healing of Diabetic Foot Ulcerations: Prospective, Randomized Clinical Trial,*** **Plast Reconstr Surg Glob Open 2016;4:el095; doi: 10.1097/GOX.0000000000001095; Published online 12 October 2016.)**

Background: Allogeneic grafts derived from amnion/ chorion are known to be efficacious in healing chronic diabetic foot ulcerations (DFUs). The goal of this study was to compare aseptically processed dehydrated human amnion and chorion allograft (dHACA) versus standard of care (SOC) in facilitating wound closure in nonhealing DFUs. Methods: Patients with DFUs treated with SOC (off-loading, appropriate debridement, and moist wound care) after a 2-week screening period were randomized to either SOC or wound-size-specific dHACA (AmnioBand, Musculoskeletal Transplant Foundation, Edison, NJ.) applied weekly for up to 12 weeks plus SOC. Primary endpoint was the percentage of wounds healed at 6 weeks between groups. Results: At 6 weeks, 70% (14/20) of the dHACA-treated DFUs healed compared with 15% (3/20) treated with SOC alone. Furthermore, at 12 weeks, 85% (17 /20) of the DFUs in the dHACA group healed compared with 25% (5/20) in the SOC group, with a corresponding mean time to heal of 36 and 70 days, respectively. At 12 weeks, the mean number of grafts used per healed wound for the dHACA group was 3.8 (median 3.0), and mean cost of the tissue to heal a DFU was $1400. The mean wastage at 12 weeks was 40%. One adverse event and 1 serious adverse event
occurred in the dHACA group; neither was graft related. Three adverse events and 1 serious adverse event occurred in the SOC group. Conclusion: Aseptically processed dHACA heals diabetic foot wounds significantly faster than SOC at 6 and 12 weeks with minimal graft wastage.
File 13, p. 562.

GG.) Schaper et al. (2020), *Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update),* Diabetes Metab Res Rev. 2020.

Diabetic foot disease results in a major global burden for patients and the health care system. The International Working Group on the Diabetic Foot (IWGDF) has been producing evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. In 2019, all lWGDF Guidelines have been updated based on systematic reviews of the literature and formulation of recommendations by multidisciplinary experts from all over the world. In this document, the IWGDF Practical Guidelines, we describe the basic principles of prevention, classification, and treatment of diabetic foot disease, based on the six IWGDF Guideline chapters. We also describe the organizational levels to successfully prevent and treat diabetic foot disease according to these principles and provide addenda to assist with foot screening. The information in these practical guidelines is aimed at the global community of health care professionals who are involved in the care of persons with diabetes. Many studies around the world support our belief that implementing these prevention and management principles is associated with a decrease in the frequency of diabetes-related lower extremity amputations. We hope that these updated practical guidelines continue to serve as reference document to aid health care providers in
reducing the global burden of diabetic foot disease.
File 13, p. 571.

HH.) Vecin et al, *Skin substitutes as treatment for chronic wounds: current and future directions.* Frontiers in Medicine.

Chronic wounds are those that do not heal in a timely manner and may have various etiologies such as vascular disease, changes in the nervous system, or a combination of etiologies. They affect approximately 2% of the population and may provide complications
such as osteomyelitis, amputation, and sepsis with some ulcers such as diabetic foot ulcers conferring 5-year mortality rates comparable to cancer. Despite their prevalence and severity, they remain difficult to manage. The development of skin substitutes in the 1980s
revolutionized the treatment of chronic wounds. Since then, numerous skin substitutes have been implemented, each boasting their respective advantages and disadvantages. The purpose of the present review is to present RCT data to support the use of skin substitutes while also suggesting future directions in tissue engineering. Much of the RCT data available regarding skin substitutes compares a substitute to the standard of care but there is a lack of abundance of literature comparing the efficacy of skin substitutes to one another. Additional RCT data is necessary to compare substitutes and gain understanding
of which substitute best suits a specific clinical picture. This data can serve to guide clinicians in their decision-making. In addition, while available skin substitutes show improvement of healing outcomes in several chronic wound types, they provide barriers such as cost and accessibility. The authors of this review introduced several potential future directions in tissue engineering that may serve to create skin substitutes that are

effective and mitigate these challenges. Amnion-derived skin substitutes include dHAM, vCPM, and
dHACM and pose the advantages of pain-relieving qualities, antibacterial and non-immunogenic properties, and reduction in inflammation and scar development in treatment of DFUs and VLUs but are fragile and costly. Epidermal substitutes are not commonly used due to their fragility. Dermal substitutes such as DSS and SIS are commonly used due to their ease of use and reduced scarring and contractures but are costly. CHSA decreases pain, stimulates angiogenesis, prepares the wound bed for autografting, controls infection, and is low cost but confers the risk of disease transmission. Xenografts such as fish skin grafts promote efficient wound healing, but potential of rejection must be considered. Lastly, tissue engineered skin substitutes such as BLCC and DRT promote healing but provide the challenge of cost. In addition to current products, there are several prospective
future directions for the development of new alternatives. The implementation of stem cells in skin substitutes, pre-vascularization of substitutes, and 3D printing are methods currently being explored for their wound healing capacity. These technologies may provide a promising future for wound healing. With a multitude of products on the market, it is challenging to determine which product is appropriate for a given clinical scenario.
File 13, pp. 581, 590.

II.) Mari, et al. (2019), ***Use of a Natural Porcine Extracellular Matrix with negative pressure wound therapy hastens the healing rate in stage 4, pressure ulcers***

A total of 16 patients, 8 study and 8 control, completed this study. After the 12-week study period, the average control patient healing rate was 45.79% as compared with the 89.98% healing rate in the study group. The difference in healing rate between control and study patients was optimal by 12 weeks. The studies suggest that ECM (extracellular matrix) dressings may be a promising adjunctive treatment option for stage 4 pressure ulcers.
File 13, p. 595.

JJ.) Dehghani, et al. (2017), ***Grafting with cryopreserved amniotic membrane versus conservative wound care in the treatment of pressure ulcers: a randomized clinical trial*****, Bull Emerg Trauma; 5(4): 249 – 258.**

To compare the healing process of pressure ulcers treated with cryopreserved human amniotic membrane allograft and routine pressure ulcer care in our hospital.
From January 2012 to December 2013, in a prospective randomized clinical trial (IRCT201612041335N2), 24 patients with second and third stage of pressure ulcers were enrolled in this study. All patients needed split thickness skin grafts for pressure ulcer-wound coverage. Selected patients had symmetric ulcers on both upper and lower extremities. The patients were randomly divided into two groups: amnion and control. In the amnion group, the ulcer was covered with cryopreserved amniotic membrane and in the control group it was treated with local Dilantin powder application. The duration and success rate of complete healing was compared between the two groups. The study group

was composed of 24 pressure ulcers in 24 patients (19 males and 5 females) with a mean age of 44±12.70 years. The demographic characteristics, ulcer area, and underlying diseases were similar in both groups. The early sign of response, such as decrease in wound discharge, was detected 12-14 days after biological dressing. Complete pressure ulcer healing occurred only in the amnion group (<0.001). Partial healing was significantly higher in the amnion group (<0.03). Healing time in this group was faster than that the control group (20 days versus 54 days). No major complication was recorded with amniotic membrane dressing. Cryopreserved amniotic membrane is an effective biologic dressing that promotes re-epithelialization in pressure ulcers.
File 13, p. 601.

KK.) Brown-Etris, et al. (2019), ***An extracellular matrix graft (Oasis wound matrix) for treating full-thickness pressure ulcers: A randomized clinical trial,*** **Journal of Tissue Viability 28, 21-26**

The purpose of the study was to evaluate clinical safety and effectiveness of Oasis Wound Matrix as a treatment for full-thickness pressure ulcers and compare it to Standard Care.
Methods: A total of 130 adults with Stage III or Stage IV pressure ulcers were randomly assigned, received either multiple topical treatments of SIS plus standard care (n = 67), or standard care alone (n = 63), and were subsequently evaluated. Ulcer size was determined at enrollment and weekly throughout treatment. Healing was assessed at each visit for a period of up to 12 weeks, with incidence of complete healing and 90% reduction in ulcer area being the primary outcome measures.
Results: The proportion of complete healing in the SIS group was 40% as compared to 29% in the standard of care group (p = 0.111); the percentage of patients having a 90% reduction in ulcer surface area was 55% in the SIS group versus 38% in the standard of care group (p = 0.037).
Conclusions: The results of this study suggest that within the setting of a comprehensive wound care program, weekly treatment of chronic pressure ulcers with SIS wound matrix increases the incidence of 90% reduction in wound size versus standard of care alone.
File 13, p. 610.

LL.) Snyder DL, Sullivan N, Margolis DJ, 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) Rockville, MD: Agency for Healthcare Research and Quality. February 2020. Available at: http://www.ahrq.gov/research/findings/ta/index.html.**

We identified 76 commercially available skin substitutes and categorized them based on the Davison-Kotler classification system. Sixty-eight (89%) were categorized as acellular dermal substitutes, mostly replacements from human placental membranes and animal tissue sources. Three systematic reviews and 22 RCTs examined use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Twenty-one ongoing clinical trials (all RCTs) examined an additional nine skin

substitutes with similar classifications. Studies rarely reported clinical outcomes, such as amputation, wound recurrence at least 2 weeks after treatment ended, or patient-related outcomes, such as return to function, pain, exudate, and odor. The lack of studies examining the efficacy of most skin substitute products and the need for better-designed and -reported studies providing more clinically relevant data in this field are this Technical Briefs clearest implications.
File 13, p. 625.

Acellular dermal substitutes versus standard of care:
Three systematic reviews reported more than a 2-fold increased risk for complete healing of diabetic foot ulcers with AlloPatch Pliable, AmnioBand, AmnioExcel, DermACELL, EpiFix, Grafix GraftJacket, and Integra Dermal Regeneration Template versus standard of care. Two reviews also reported a shorter time to heal favoring AlloPatch Pliable, AmnioBand, Grafix, and GraftJacket over standard of care. None of the reviews reported an overall risk-of-bias rating for included studies. Ten (77%) RCTs comparing acellular dermal substitutes with standard of care reported statistically significant findings up to 16 weeks favoring the interventions for complete wound closure, and shorter time to heal in diabetic foot ulcers and venous leg ulcers. Three studies rated severity of diabetic foot ulcers as Grade I-A (University of Texas Wound Classification System),48 Wagner 1 or 2,55 and mostly Wagner 2.56 One study rated severity of pressure ulcers as 52 percent to 58 percent Stage 111,58 while another study rated severity of venous leg ulcers as CEAP 6.49 The most commonly reported enrollment criteria included> 1 cm2 to <25 cm2 wound surface, >4-weeks duration, ankle brachia! index (ABI) 0.7 to ::Sl.2, and HbAlc <12 percent. Severe adverse events occurring with acellular dermal substitutes included diabetic foot infections, cellulitis, and osteomyelitis. Six (46%) studies reported less-frequent recurrence with a skin substitute. One study reported recurrence more frequently with Oasis Wound Matrix than standard of care. File 13, p. 663.

Cellular epidermal and dermal substitutes versus cellular epidermal and dermal substitutes: Authors reported no statistically significant difference between Apligraf and Theraskin for venous leg ulcer healing (at 12 and 20 weeks) and number of grafts per subject. Authors reported recurrence did not occur at 26 weeks. Eligible patients had wounds greater than 30-days duration and area less than 40 cm. File 13, p. 664.

85 percent of studies examining acellular dermal substitutes described the experimental intervention as favorable over standard of care for wound healing and shorter time to heal, insufficient data are available to determine whether wound recurrence or other sequela are less frequent with acellular dermal substitutes. The 2012 report had similar conclusions: "All the studies in the evidence base reported some benefit of skin substitutes over the control treatments when number of wounds completely healed was measured between 8 and 16 weeks but the reported results varied widely across studies."
File 13, pp. 682.

MM.) Sierra-Sanchez et al. (2021), *Cellular human tissue-engineered skin substitutes investigated for deep and difficult to heal injuries,* Regenerative Medicine

Wound healing is an important function of skin; however, after significant skin injury (burns) or in certain dermatological pathologies (chronic wounds), this important process can be deregulated or lost, resulting in severe complications. To avoid these, studies have focused on developing tissue-engineered skin substitutes (TESSs), which attempt to replace and regenerate the damaged skin. Autologous cultured epithelial substitutes (CESs) constituted of keratinocytes, allogeneic cultured dermal substitutes (CDSs) composed of biomaterials and fibroblasts and autologous composite skin substitutes (CSSs) comprised of biomaterials, keratinocytes and fibroblasts, have been the most studied clinical TESSs, reporting positive results for different pathological conditions. However, researchers' purpose is to develop TESSs that resemble in a better way the human skin and its wound healing process. For this reason, they have also evaluated at preclinical level the incorporation of other human cell types such as melanocytes, Merkel and Langerhans cells, skin stem cells (SSCs), induced pluripotent stem cells (iPSCs) or mesenchymal stem cells (MSCs). Among these, MSCs have been also reported in clinical studies with hopeful results. Future perspectives in the field of human-TESSs are focused on improving in vivo animal models, incorporating immune cells, designing specific niches inside the biomaterials to increase stem cell potential and developing three-dimensional bioprinting strategies, with the final purpose of increasing patient's health care. In this review we summarize the use of different human cell populations for preclinical and clinical TESSs under research, remarking their strengths and limitations and discuss the future perspectives, which could be useful for wound healing purposes. File 13, p. 792.

NN.) Serena et al., *A randomized controlled clinical trial of a hypothermically stored amniotic membrane for use in diabetic foot ulcers,* Journal of Comparative Effectiveness Research

Clinical studies have demonstrated the efficacy of cellular or tissue-based products such as placental-derived allografts in accelerating healing of chronic wounds. The proposed mechanism of action is the delivery of growth factors and the reduction in proteases. Novel processing technologies and hypothermic storage conditions of amniotic membranes that more completely preserve amnion and/ or chorion components maintain viable differentiated cell populations, stem cells, growth factors, cytokines and ECM proteins. Preservation of these components may improve chronic wound management outcomes. To date, clinical trials have evaluated only dehydrated and cryopreserved grafts. This trial is the first to examine hypothermically stored amniotic membrane. File 13, pp. 846-847.

This was the first prospective, comparative effectiveness research randomized control trial that compares efficacy of a fresh hypothermically stored amniotic membrane (HSAM) to an active control standard of care {SOC) for the treatment of diabetic foot ulcers (DFUs).

• Treatment with HSAM significantly improved the incidence and time to DFU wound closure.

• Cox adjusted survival data for wound closure showed that HSAM was superior to SOC at 4 weeks (11 vs 3%), 8 weeks (36 vs 23%), 12 weeks (60 vs 38%) and 16 weeks (63 vs 38%); p = 0.04.

• HSAM shows a 75% greater probability of wound closure on a weekly basis for the entire 16 week study period compared with SOC-treated ulcers; Hazard ratio= 1.75 {95% Cl: 1.16-2.70).
• The unadjusted frequency of wound closure for HSAM-treated ulcers was significantly greater than SOC by 12 weeks {55 vs 29%; p = 0.02) and 16 weeks {58 vs 29%; p = 0.01).
• HSAM showed a higher incidence of >60 percent reductions in area (82 vs 58%; p = 0.02) and depth (65 vs 39%; p = 0.04).
• Improvements in the probability, wound closure rate and frequency of wound closure support use of HSAM plus SOC for DFU wound management.
• Comparative Effectiveness Research studies of real-world data comparing HSAM to other amniotic membrane allografts for the management DFUs are warranted.
File 13, p. 854.

OO.) Gunasekaran (2025), ***Clinical Efficacy of Type I Collagen Skin Substitutes Versus Human Amnion/ Chorion in Treating Diabetic Foot Ulcers Using 55 Patient Randomized Controlled Independent Two Trials, one in India and the Other in the USA,*** Biomedical Materials & Devices.

The purpose of this study is to compare whether the results of two separate studies simulates each other. As one would expect, the results are duplicative of each other that's what we are planning to discuss in this research article. In a nutshell, the first study was conducted by Professional Education & Research Institute (PERI) at 9825 Kenwood Road, Suite 100, Blue Ash, OH 45242, USA which was managed by prestigious Dr. Charles M. Zelen, DPM who has over 20 years of clinical, academic, and industry experience in extremities, wound care, and biologic development programs. Over 22 Clinical Study publications have been published in reputed peer-reviewed journals. Another similar study was conducted by a distinguished plastic surgeon with immense experience in conducting randomized controlled clinical studies by name Dr. Naveen Narayan, MS, MCh (Plastic Surgery) at Adichunchanagiri Institute of Medical Sciences (AIMS), BG Nagara, Karnataka, India. To add to his credentials, he has 57 Clinical Study publications in respected journals with peer review. Both studies were registered on clinicaltrials.gov where one study was enrolled with 28 patients (NCT06470087) and the other study had a total no. of 27 patients (NCT06557122). It was intended to enroll 28 patients for each study. However, in the USA study, the Contact Research Organization (CRO) was able to recruit only 27 patients for the study in order to start the study on time. The first study of 28 patients were randomized into 2 groups of 14 patients each. The other study randomized into 2 groups of 12 patients each with exclusion of 3 patients who were rejected for the study due to their non-compliance with the approved protocol. Among the tested skin substitutes, one group consisted of standard of care (SOC) with High-Purity Type I Collagen based Skin Substitute (HPTC) and the other group is the standard of care (SOC) with Dehydrated Human Amnion/Chorion Membrane (dHACM) in the treatment of Diabetic Foot Ulcers (DFUs). Each group was followed for 4 weeks of treatment as described in the methods section. The wound healing outcomes were evaluated on days 7, 10, 14, 17, 21, and 28. Both the study results were compared. The results from both India (AIMS) and the USA (PERI) studies showed that the HPTC group achieved significantly better healing outcomes compared to the dHACM group. Over the

28-day study period, HPTC demonstrated a healing recovery rate of 62%, while dHACM showed a recovery rate of 38%. These findings highlight that HPTC not only facilitated faster healing but also more complete wound closure, suggesting it as a potentially more effective treatment for managing chronic diabetic foot ulcers and reducing the risk of long-term complications. Even though they were conducted independently and separated continents apart, the clinical outcomes for both the studies were statistically significant proving the clinical efficacy of High-Purity Type I Collagen-based Skin Substitute (HPTC) was much higher than the other group, Dehydrated Human Amnion/Chorion Membrane (dHACM).
File 13, p. 858.

PP.) Weiying Lu, BS et al (2025), *Meta-analysis of cellular and acellular tissue-based products demonstrates improvement of diabetic foot ulcer healing despite age and wound size*. JSV – Vascular Insights, Volume 3, Number C, 100-215.

Background: Patients with diabetes are at an increased risk of developing chronic adverse events owing to diabetes associated complications. Diabetic foot ulcers (DFUs) occur in approximately 15% of all diabetic patients. Patients with larger wound sizes and increasing age are often excluded from clinical trials.
Methods: A meta-analysis to compare the complete wound healing rates of patients receiving cellular and acellular matrix products (CAMPs) with standard of care (SOC) and with SOC alone was conducted. A total of 29 randomized controlled trials involving 2255 patients with DFU were included in the meta-analysis.
Results: The results indicated that the complete healing rate for CAMPs plus SOC patients was higher than for patients receiving SOC only. The aggregated odds ratio is 2.9 (95% confidence interval. 2.3-3.8). Patients in the CAMPs plus SOC group were almost three times more likely to achieve 100% wound closure than those treated with SOC only through final follow-up in each study. The median follow-up duration across studies was 12 weeks (Ql-Q3: 12-16 weeks). with no significant differences in follow-up length between the two arms.
Conclusions: Patients receiving CAMPs for DFUs were more likely to achieve wound closure. Meta-regression analysis of the moderators indicated that both moderators. average patient age and average wound size (baseline). displayed a nonsignificant relationship to the main outcome of wound closure. These findings suggest that patient age and wound size should not be excluded from clinical trials.
File 13, p. 866.

QQ.) Journal of Wound Care, North American Supplement, Vol. 30, No. 7 (2021) *Observed impact of skin substitutes in lower extremity diabetic ulcers: lessons from the Medicare Database (2016-2018*)

Objective: To evaluate large propensity-matched cohorts to assess outcomes in patients receiving advanced treatment (Al) with skin substitutes for lower extremity diabetic ulcers (LEDUs) versus no (12,676 episodes per cohort), AT patients had statistically fewer minor amputations ($p=0.0367$), major amputations ($p<0.0001$), ED visits ($p<0.0001$), and readmissions ($p<0.0001$) compared with NAT patients. In propensity-

matched Group 2 (1131 episodes per cohort), AT FPFU patients had fewer minor amputations (p=0.002) than those in the AT not FPFU group. AT (NAl) for the management of LEDUs. Method: The Medicare Limited Dataset (1 October 2015 through 2 October 2018) were used to retrospectively analyze people receiving care for a LEDU treated with AT or NAT (propensity matched Group 1). Analysis included major and minor amputations, emergency department (ED) visits and hospital readmissions. In addition, AT following parameters for use (FPFU) was compared with AT not FPFU (propensity-matched Group 2). A paired t-test was used for comparisons of the two groups. For comparisons *Conclusion:* AT for the management of LEDUs was associated with significant reductions in major and minor amputation, ED use, and hospital readmission compared with LEDUs managed with NAT. Clinics should implement AT in accordance with the highlighted parameters for use to improve outcomes and reduce costs.
File 13, p. 874.

RR.) Felder, *A Systematic Review of Skin Substitutes for Foot Ulcers,* Plastic and Reconstructive Surgery July 2012

Background: Bioengineered and allograft-derived skin substitutes are increasingly available and marketed for use in the healing of chronic wounds. Plastic surgeons should have evidence-based information available to guide their use of these products. The authors systematically reviewed the literature to determine the published outcomes and effectiveness of different skin substitutes for healing chronic foot ulcers.
Methods: A broad literature search of the MEDLINE, EBSCO, EMBASE, and the Cochrane Central Register of Controlled Trials databases was undertaken. Relevant studies were selected by three independent reviewers to include randomized controlled trials or systematic reviews examining the use of skin substitutes on foot ulcers. Results were narrowed further by the application of predetermined inclusion and exclusion criteria. Studies were assessed for quality and data were extracted regarding study characteristics and objective outcomes.
Results: Of an initial 271 search results, 15 randomized controlled trials, one prospective comparative study, and five systematic reviews were included in the systematic review. Most of the included clinical studies were of moderate to low quality by objective standards and reported results using cell-based skin substitutes. The primary outcome examined, success rate of complete healing, was equivalent to or better than that of standard therapy for all skin substitutes examined.
Conclusions: A convincing body of evidence supports the effectiveness of living cell-based skin substitutes as an adjunctive therapy for increasing the rate of complete healing in chronic foot ulcers when basic tenets of wound care are also being implemented. Acellular skin substitutes also show some promise for treatment of foot wounds but require further study.
File 13, p. 886.

SS.) Y-Na Su et al. (2020), Human *amniotic membrane allograft, a novel treatment for chronic diabetic foot ulcers: A systematic review and meta-analysis of randomized controlled trials,* Int Wound j. 2020; 17:753-746

To evaluate the efficacy and safety of human amniotic membrane (HAM) allograft in treating chronic diabetic foot ulcers (DFUs), a comprehensive search of randomized controlled trials in MEDLINE, EMBASE, PubMed, CENTRAL and Web of Science was conducted to December 7, 2019. Two reviewers independently screened the studies, extracted data, and evaluated the quality of studies. The primary outcome was the proportion of complete healing. The secondary outcomes were mean time to complete healing and adverse events. Statistical analyses were performed using RevMan 5.3. We identified 257 articles, of which 7 articles (465 participants) were included in the meta-analysis. The proportion of complete wound healing in HAM plus standard of care (SOC) group was 3.88 times as high as that in SOC alone (RR: 3.88 [95% CI: 2.34, 6.44]) at 6 weeks, and 2.01 times at 12 weeks (RR: 2.01 [95%CI: 1.45, 2.77]). The intervention group had a significantly shorter time to complete healing (MD: -30.33 days, [95% CI: -37.95, -22.72]). The number needed to treat within 6 weeks was 2.3 ([95% CI: 1.8, 3.11). No significant difference was shown in adverse events. Results were consistent in a sensitivity
analysis. Hence, HAM plus SOC is effective and safe in treating chronic DFUs.
File 13, p. 906.

TT.) Gordan, et al., *Evidence for Healing Diabetic Foot Ulcers with Biologic Skin Substitutes A Systematic Review and Meta-Analysis,* Annals of Plastic Surgery, Volume 83, Supplement 1, October 2019 (Ann Plast Surg 2019;83: S31- S44)

Background: Development of diabetic foot ulcers is a common complication of diabetes. Standard-of-care (SOC) therapy alone is often not sufficient to heal these wounds, resulting in application of adjuvant wound therapies including biologic skin substitutes. Although a variety of products exist, it has been difficult to formulate conclusions on their clinical efficacy. We therefore performed a systematic review and meta-analysis on the efficacy of healing diabetic foot ulcers with biologic skin substitutes.
Methods: A systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Four electronic databases (PubMed/MEDLINE, EMBASE [Ovid], Cochrane CENTRAL [Ovid], and Web of Science) were searched from inception through February 27, 2019. Searches included keywords and subject headings pertaining to 3 main concepts: biologic skin substitutes, wound healing, and diabetic foot ulcers. Cochrane randomized controlled trial filters were used to narrow results. Data were extracted from 54 included articles, and risk-of-bias assessments were conducted by 2 independent reviewers. The primary objective was to calculate a pooled risk ratio for the proportion of wounds completely closed by 12 weeks. Secondary objectives included a pooled risk ratio for the proportion of wounds completely
closed by 6 weeks and mean time to healing.
Results: Twenty-five studies were identified that assessed the proportion of complete wound closure by 12 weeks. We found that wounds treated with biologic dressings were 1.67 times more likely to heal by 12 weeks than those treated with SOC dressings ($P < 0.00001$). Five studies assessed the proportion of complete wound closure by 6 weeks. Wounds treated with biologic dressings were 2.81 times more likely to heal by 6 weeks

than those treated with SOC dressings *(P* = 0.000 I). Descriptively, 29 of31 studies that assessed time to healing favored biologic dressings over SOC dressings.
Conclusions: This systematic review provides supporting evidence that biologic skin substitutes are more effective than SOC dressings at healing diabetic foot ulcers by 12 weeks. Future studies must address the relative benefits of different skin substitutes as well as the long-term implications of these products and their financial considerations.
File 13, p. 918.

UU.) Frykberg, et al., ***Diabetic Foot Disorders: A Clinical Practice Guideline (2006 revision),*** **Supplemental to The Journal of Foot & Ankle Surgery volume 45, number 5, September/October 2006.** [This clinical practice guideline (CPG) is based on the consensus of current clinical practice and review of the clinical literature. This guideline was developed by the Clinical Practice Guideline Diabetes Panel of the American College of Foot and Ankle Surgeons.]

The prevalence of diabetes mellitus is growing at epidemic proportions in the United States and worldwide. Most alarming is the steady increase in type 2 diabetes, especially among young and obese people. An estimated 7% of the US population has diabetes, and because of the increased longevity of this population, diabetes-associated complications are expected to rise in prevalence. Foot ulcerations, infections, Charcot neuroarthropathy, and peripheral arterial disease frequently result in gangrene and lower limb amputation. Consequently, foot disorders are leading causes of hospitalization for persons with diabetes and account for billion-dollar expenditures annually in the US. Although not all foot complications can be prevented, dramatic reductions in frequency have been achieved by taking a multidisciplinary approach to patient management. Using this concept, the authors present a clinical practice guideline for diabetic foot disorders based on currently available evidence, committee consensus, and current clinical practice. The pathophysiology and treatment of diabetic foot ulcers, infections, and the diabetic Charcot foot are reviewed While these guidelines cannot and should not dictate the care of all affected patients, they provide evidence-based guidance for general patterns of practice. If these concepts are embraced and incorporated into patient management protocols, a major reduction in diabetic limb amputations is certainly an attainable goal.
File 13, p. 930.

VV.) ***A comparative analysis of skin substitutes used in the management of diabetic foot ulcers*****. Journal of Wound Care North American Supplement, Vol. 25, No 10, October 2016**

Objective: To compare the relative product cost and clinical outcomes of four skin substitutes used as adjunctive treatments for diabetic foot ulcers (DFUs).
Method: Medicare claims data from 2011 to 2014 were used to identify beneficiaries with diabetes and foot ulcers. Patients treated with one of four types of skin substitute (Apligraf, Dermagraft, OASIS, and MatriStem) were identified. The skin substitutes were compared on episode length; amputation rate; skin substitute utilization; and skin substitute costs.
Results: There were 13,193 skin substitute treatment episodes: Apligraf (HML) was used in 4926 (37.3%), Dermagraft (HSL) in 5530 (41.9%), OASIS (SIS) in 2458 (18.6%) and

MatriStem (UBM) in 279 (2 .1 %). The percentage of DFUs that healed at 90 days were: UBM 62%; SIS 63%; HML 58%; and HSL 58%. Over the entire time, UBM was non-inferior to SIS (p<0.001), and either was significantly better than HML or HSL (p<0.005 in all four tests). HML was marginally in skin substitutes per episode) and SIS ($1901) appeared to be equivalent to each other, although non-inferiority tests were not significant. Both were less than HML ($5364) or HSL ($14,424) (p<0.0005 in all four tests). HML was less costly than HSL (p<0.0005).
Conclusion: Various types of skin substitutes appear to be able to confer important benefits to both patients with DFUs and payers. Analysis of the four skin-substitute types resulted in a demonstration that UBM and SIS were associated with both shorter DFU episode lengths and lower payer reimbursements than HML and HSL, while HML was less costly than HSL but equivalent in healing.
File 13, p. 996.

WW.) Dehghani et al. (2017), ***Grafting with Cryopreserved Amniotic Membrane versus Conservative Wound Care in Treatment of Pressure Ulcers: A Randomized Clinical Trial.*** **Bull Emerg Trauma. 2017;5(4):249-258. doi: I 0.18869/acadpub.beat.5.4.452.**

To compare the healing process of pressure ulcers treated with cryopreserved human amniotic membrane allograft and routine pressure ulcer care in our hospital.
From January 2012 to December 2013, in a prospective randomized clinical trial (IRCT201612041335N2), 24 patients with second and third stage of pressure ulcers were enrolled in this study. All patients needed split thickness skin grafts for pressure ulcer-wound coverage. Selected patients had symmetric ulcers on both upper and lower extremities. The patients were randomly divided into two groups: amnion and control. In the amnion group, the ulcer was covered with cryopreserved amniotic membrane and in the control group it was treated with local Dilantin powder application. The duration and success rate of complete healing was compared between the two groups. The study group was composed of 24 pressure ulcers in 24 patients (19 males and 5 females) with a mean age of 44±12.70 years. The demographic characteristics, ulcer area, and underlying diseases were similar in both groups. The early sign of response, such as decrease in wound discharge, was detected 12-14 days after biological dressing. Complete pressure ulcer healing occurred only in the amnion group (<0.001). Partial healing was significantly higher in the amnion group (<0.03). Healing time in this group was faster than that the control group (20 days versus 54 days). No major complication was recorded with amniotic
membrane dressing. Cryopreserved amniotic membrane is an effective biologic dressing that promotes re-epithelialization in pressure ulcers.
File 13, 1195.

XX.) Brown-Etris et al. ***An extracellular matrix graft (Oasis wound matrix) for treating full-thickness pressure ulcers: A randomized clinical trial*****, Journal of Tissue Viability 28 (2019) 21-26.**

Aim: The purpose of the study was to evaluate clinical safety and effectiveness of Oasis Wound Matrix as a treatment for full-thickness pressure ulcers and compare it to Standard Care.
Methods: A total of 130 adults with Stage III or Stage IV pressure ulcers were randomly assigned, received either multiple topical treatments of SIS plus standard care (n = 67), or standard care alone (n = 63), and were subsequently evaluated. Ulcer size was determined at enrollment and weekly throughout treatment. Healing was assessed at each visit for a period of up to 12 weeks, with incidence of complete healing and 90% reduction in ulcer area being the primary outcome measures.
Results: The proportion of complete healing in the SIS group was 40% as compared to 29% in the standard of care group (p = 0.111); the percentage of patients having a 90% reduction in ulcer surface area was 55% in the SIS group versus 38% in the standard of care group (p = 0.037).
Conclusions: The results of this study suggest that within the setting of a comprehensive wound care program, weekly treatment of chronic pressure ulcers with SIS wound matrix increases the incidence of 90% reduction in wound size versus standard of care alone.
File 13, p. 1205.

YY.) ***Technology Assessment Program. Skin Substitutes for Treating Chronic Wounds.*** **Technical Brief. Project ID WNDT0818. February 2, 2020.**

• We identified 76 commercially available skin substitutes to treat chronic wounds. The majority of these do not contain cells and are derived from human placental membrane (the placenta's inner layer), animal tissue, or donated human dermis.
• Included studies (22 RCTs and 3 systematic reviews) and ongoing clinical trials found during our search examine approximately 25 (33%) of these skin substitutes.
• Available published studies rarely reported whether wounds recurred after initial healing. Studies rarely reported outcomes important to patients, such as return of function and pain relief.
• Future studies may be improved by using a 4-week run-in period before study enrollment
and at least a 12-week study period. They should also report whether wounds recur during 6-month followup.
File 13, pp. 1211, 1213.

Findings - Care for chronic wounds involves removing necrotic tissue, applying dressings that maintain a moist wound environment, treating wound infections, and restoring blood flow to the wound site. If these procedures fail to restore the healing process, additional therapies may be considered. We identified 76 commercially available skin substitutes and categorized them based on the Davison-Kotler classification system. Sixty-eight (89%) were categorized as acellular dermal substitutes, mostly replacements from human placental membranes and animal tissue sources. Three systematic reviews and 22 RCTs examined use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers. Twenty-one ongoing clinical trials (all RCTs) examined an additional nine skin substitutes with similar classifications. Studies rarely reported clinical outcomes, such as amputation, wound recurrence at least 2 weeks

after treatment ended, or patient-related outcomes, such as return to function, pain, exudate, and odor. The lack of studies examining the efficacy of most skin substitute products and the need for better-designed and -reported studies providing more clinically relevant data in this field are this Technical Briefs clearest implications.
File 13, p. 1219

Standard of Care
Usual care or standard care for established chronic wounds incorporates common principles, as follows, that apply to managing all wound types:
• Remove necrotic tissue through debridement (typically sharp debridement).
• Maintain moisture balance by selecting the proper wound dressing to control exudate.
• Take measures to prevent or treat wound infections.
• Correct ischemia in the wound area.
• For venous leg ulcers, apply some form of compression.
• For diabetic foot ulcers, apply some form of offloading.
However, the methods for achieving each of these wound management principles varies among clinical practice guidelines and clinical studies. Therefore, in this document standard of care refers to the usual or standard care established by individual wound care facilities for the treatment of their patients rather than a standard approach that should be used for all wounds. Using saline wet-to-dry gauze on any chronic wound is no longer considered part of standard wound care. We excluded any studies that used saline wet-to-dry gauze. Four weeks of standard of care without achieving a 50 percent reduction in wound size may signal the need for a change or additional therapies. An RCT in patients with diabetic foot ulcers demonstrated that a 50 percent reduction in wound area at 4 weeks was a strong predictor of wound healing by 12 weeks when standard of care was used. 18 Only 9 percent of patients who did not meet the 50 percent reduction at 4-weeks threshold healed by 12 weeks. The positive predictive value was 58 percent, and the negative predictive value was 91 percent. For venous leg ulcers, Kantor and Margolis (2000) also showed that percent change in wound area after 4 weeks is predictive of complete wound healing by 24 weeks.19 The positive predictive value was 68 percent, and the negative predictive value was 75 percent.
Skin Substitutes
If chronic wounds fail to respond to standard of care, skin substitutes may be used as an adjunct to established chronic wound care methods to increase the likelihood of complete healing. We do not propose a definition for skin substitutes (see our product inclusion criteria on page 9), but several investigators have proposed definitions and outlined what skin substitutes should accomplish. According to Ferreira et al.,21 "skin substitutes are a heterogeneous group of biological and/or synthetic elements that enable the temporary or permanent occlusion of wounds. Although dermal substitutes can vary from skin xenografts or allografts to a combination of autologous keratinocytes over the dermal matrix, their common objective is to achieve the greatest possible similarity with the patient's skin." Ferreira et al. also noted that skin substitutes should have functional and structural characteristics that closely match those of autologous skin. According to Nathoo et al., "The ideal skin substitute should be durable, completely autologous, endothelialized and contain adnexal structures and adult stem cells." Other authors have stated that commercially manufactured skin substitutes should protect the integument from water loss and infection; provide a stable, biodegradable scaffold to promote the

synthesis of new dermal tissue; allow host or other cells to proliferate within the scaffold that will act as functional dermal cells rather than scar tissue; and resist tearing forces while being easy to handle. Eweida and Marei have suggested that growth factors and ECM components of the skin substitute may promote cell proliferation, reduce wound degradation caused by MMPs within the wound, and promote wound vascularization. The skin substitute properties these authors have noted may enhance a skin substitute' s wound healing potential beyond that of standard of care.
File 13, pp. 1225-1226.

ZZ.) Moreno et al. (2024), ***Purion processed human amnion chorion membrane allografts retain material and biological properties supportive of soft tissue repair.*** **Journal of Biomaterials Applications.**

The reparative properties of amniotic membrane allografts are well-suited for a broad spectrum of specialties. Further enhancement of their utility can be achieved by designing to the needs of each application through the development of novel processing techniques and tissue configurations. As such, this study evaluated the material characteristics and biological properties of two PU RION® processed amniotic membrane products, a lyophilized human amnion, intermediate layer, and chorion membrane (LHACM) and a dehydrated human amnion, chorion membrane (DHACM). LHACM is thicker; therefore, its handling properties are ideal for deep, soft tissue deficits; whereas DHACM is more similar to a film-like overlay and may be used for shallow defects or surgical on-lays. Characterization of the similarities and differences between LHACM and DHACM was conducted through a series of *in vitro* and *in vivo* studies relevant to the healing cascade: Compositional analysis was performed through histological staining along with assessment of barrier membrane properties through equilibrium dialysis. *In vitro* cellular response was assessed in fibroblasts and endothelial cells using cell proliferation, migration, and metabolic assays. The *in vivo* cellular response was assessed in an athymic nude mouse subcutaneous implantation model. The results indicated the PURION® process preserved the native membrane structure, nonviable cells and collagen distributed in the individual layers of both products. Although, LHACM is thicker than DHACM, a similar composition of growth factors, cytokines, chemokines and proteases is retained and consequently elicit comparable *in vitro* and *in vivo* cellular responses. In culture, both treatments behaved as potent mitogens, chemoattractants and stimulants, which translated to the promotion of cellular infiltration, neocollagen deposition and angiogenesis in a murine model.

PURION® processed LHACM and DHACM differ in physical properties but possess similar *in vitro* and *in vivo* activities highlighting the impact of processing method on the versatility of clinical use of amniotic membrane allografts.
File 13, p. 1468.

AAA.) Tenenhaus (2016), ***Current Concepts in Tissue Engineering: Skin and Wound,*** **Plast. Reconstr. Surg. 138: 42S, 2016.**

Background: Pure regenerative healing with little to no donor morbidity remains an elusive goal for both surgeon and patient. The ability to engineer and promote the

development of like tissue holds so much promise, and efforts in this direction are slowly but steadily advancing.
Methods: Products selected and reviewed reflect historical precedence and importance and focus on current clinically available products in use. Emerging technologies we anticipate will further expand our therapeutic options are introduced. The topic of tissue engineering is incredibly broad in scope, and as such the authors have focused their review on that of constructs specifically designed for skin and wound healing. A review of pertinent and current clinically related literature is included.
Results: Products such as biosynthetics, biologics, cellular promoting factors, and commercially available matrices can be routinely found in most modern health care centers. Although to date no complete regenerative or direct identical soft-tissue replacement exists, currently available commercial components have proven beneficial in augmenting and improving some types of wound healing scenarios. Cost, directed specificity, biocompatibility, and bioburden tolerance are just some of the impending challenges to adoption.
Conclusions: Quality of life and in fact the ability to sustain life is dependent on our most complex and remarkable organ, skin. Although pure regenerative healing and engineered soft-tissue constructs elude us, surgeons and health care providers are slowly gaining comfort and experience with concepts and strategies to improve the healing of wounds.
File 13, p. 1483.

BBB.) ***Management of post-Mohs surgical wounds with a hypothermically stored amniotic membrane: a case series,*** **Journal of Wound Care, Vol. 33, No. 5.**

Results: This case series of seven wounds consisted of four fem ales and three males with a mean age of 8 7 .6 years. Mean wound size at first application of HSAM was l.34±1.20cm2. All wounds closed, with an average time to wound closure of 43.7±27.1 days. Patients received an average of 4 .6±2.5 HSAM applications. The four post- Mohs wounds with a history of being hard- to- heal had an average time to wound closure of 35.5±16.3 days, with an average duration of 86.5±32.4 days prior to the first HSAM application.
Conclusion: The results of this case series suggest that use of HSAM may provide an alternative approach to man aging post- Mohs wounds. In addition, these findings suggest that HSAM may be of greatest benefit when applied early after Mohs surgery.
File 13, p. 1493.

CCC.) Serena, et al. (2022), ***A Multicenter, Randomized, Controlled, Clinical Trial Evaluating Dehydrated Human Amniotic Membrane in the Treatment of Venous Leg Ulcers, Plast. Reconstr. Surg.*** **150: 1128, 2022.**

Background: This randomized controlled trial evaluated the safety and effectiveness of weekly and biweekly applications of dehydrated human amnion and chorion allograft (dHACA) plus standard of care compared to standard of care alone on chronic venous leg ulcers.
Methods: This open-label randomized controlled trial included patients with chronic venous leg ulcers at eight wound care centers across the United States. The primary

endpoint was the proportion of healed ulcers at 12 weeks. Secondary endpoints included the proportion of ulcers achieving 40 percent closure at 4 weeks and the incidence of adverse events.
Results: Among 101 patients screened for eligibility, 60 were eligible and enrolled. At 12 weeks, significantly more venous leg ulcers healed in the two dHACA-treated groups (75 percent) than in the standard-of-care group (30 percent) *(p* = 0.001) even after adjustment for wound area *(p* = 0.002), with an odds ratio of 8. 7 (95 percent Cl, 2.2 to 33.6). There were no significant differences in the proportion of wounds with percentage area reduction greater than or equal to 40 percent at 4 weeks among all groups. The adverse event rate was 63.5 percent. Among the 38 adverse events, none were graft or procedure related, and all were resolved with appropriate treatment.
Conclusions: dHACA and standard of care, either applied weekly or biweekly, significantly healed more venous leg ulcers than standard of care alone, suggesting that the use of aseptically processed dHACA is advantageous and a safe and effective treatment option in the healing of chronic venous leg ulcers.
File 13, p. 1495

DDD.) Snyder (2020), *Skin Substitutes for Treating Chronic Wounds,* Agency for Healthcare Research and quality.

For this report, we have not created a definition for a skin substitute product. Instead, we used the products listed under the Centers for Medicare & Medicaid Services (CMS) codes Q4101 to Q4207 as a starting point and looked for similar products to generate a list of products. We included only products primarily marketed for chronic wounds and commercially available in the United States. Some of the products that CMS listed were not included because they are not yet commercially available in the United States. We note that FDA does not refer to any product or class of products as "skin substitutes," and we are not proposing an official definition or classification system. The report includes many products cleared by the FDA as wound dressings via the 510(k) pathway which are not intended to treat wounds but only to cover wounds so that the natural healing process can take place.
File 13, 1504.

- Of the 76 commercially available skin substitutes, three systematic reviews and 22 RCTs (23 publications) examined use of 16 distinct skin substitutes, including acellular dermal substitutes, cellular dermal substitutes, and cellular epidermal and dermal substitutes in diabetic foot ulcers, pressure ulcers, and venous leg ulcers.
- Three systematic reviews examined the use of amniotic membranes and acellular dermal matrices (ADMs) in diabetic foot ulcers. Thirteen primary studies examined nine distinct skin substitutes. Most studies enrolled fewer than 25 patients per arm and measured outcomes up to 16 weeks.
- Twenty-two RCTs examined 16 distinct skin substitutes (7 skin substitutes not examined in the systematic reviews) in diabetic foot ulcers (15 studies), pressure ulcers (1 study), and venous leg ulcers (6 studies). Comparators were standard of care (16 studies) and another skin substitute (6 studies).

- Of the 16 distinct skin substitutes examined in 22 RCTs, seven skin substitutes were examined in more than one study. One skin substitute (EpiFix) was examined in five studies. One skin substitute (Dermagratt43-46) was examined in four studies. Five skin substitutes (Grafix/GrafixPrime, MatriStem Wound atrix/MatriStem Micromatrix, Apligraf, TheraSkin, DermACELL were examined in two studies each.
- Eligibility criteria in 22 RCTs were most commonly reported as a noninfected debrided wound of at least 4-weeks duration, with a wound size of 1 cm2 to 25 cm2. Conditions such as uncontrolled diabetes (HbA1c >12%), morbid obesity, peripheral vascular disease, severe malnutrition, severe liver disease, and severe renal disease were excluded.
- Most studies enrolled fewer than 60 patients per arm. Twenty (90%) studies were manufacturer-funded (one study did not report funding, and one study reported no funding). Most studies were conducted in U.S. wound care centers. Fourteen (64%) RCTs reported participants' race. Thirteen studies (59%) enrolled ~70 percent white/Caucasian patients, while one study enrolled 55 percent white and 45 percent black patients. Eight (36%) studies reported enrolling Hispanic/Latino individuals.
- Our risk-of-bias analysis indicated that 50 percent and 59 percent of included studies had more than a 15 percent difference between study arms in baseline mean wound size (range up to 53.5 cm2) and baseline mean wound duration (range up to 479 weeks), respectively.
- Successful wound closure was mostly described as 100 percent re-epithelialization without drainage or dressing.

File 13, p. 1515.

EEE.) Musa, M. *et al.* (2024). *Amniotic Membrane Transplantation: Clinical Applications in Enhancing Wound Healing and Tissue Regeneration*. In Advances in Experimental Medicine and Biology. Springer, Cham. https:// doi.org/ 10 .10 0 7 *I* 55 84 _ 2024 _ 834

Chronic wounds and non-healing tissue defects pose significant clinical challenges, necessitating innovative therapeutic approaches. A comprehensive literature review of amniotic membrane transplantation for wound healing and tissue repair evaluates the efficacy and safety of amniotic membrane transplantation in enhancing wound healing and tissue repair. Amniotic membranes promote wound closure and reduce inflammation and scarring via abundant growth factors, cytokines, and extracellular matrix components, which foster conducive environments for tissue regeneration. Amniotic membrane transplantation is effective in various medical disciplines, including ophthalmology, dermatology, and orthopedics. Low immunogenicity and anti-microbial properties ensure their safe application. Amniotic membrane transplantation offers a promising therapeutic approach for wound healing and tissue repair, and further research is warranted to explore its regenerative potential fully.

File 13, p. 1544.

FFF.) Gruss et al. (1978), *Human amniotic membrane: a versatile wound dressing,* CMA Journal/ May 20, 1978/ Vol. 118.

Human amniotic membrane was used successfully as a temporary biologic dressing for various wounds in 120 patients. The membrane is easily obtained, at little or no cost. It provides excellent wound coverage and has distinct advantages compared with other biologic dressings.
File 13, p. 1594.

III. *Q Codes*[4]

The QIC found that the HCPCS codes billed are experimental and investigational as denoted by the 'Q' code status nomenclature. The appellant argues that "Q" code status nomenclature does not denote a product is experimental and investigational. The witnesses – all physicians experienced in the standards of care relevant to complex wounds – provided sworn testimony that the services provided met the standard of care. File 15, (hearing recording); File 13, pp. 39-113.

For Medicare and other health insurance programs to ensure that claims for payment are processed in an orderly and consistent manner, standardized coding systems are used. The HCPCS Level II Code Set is one of the standards, national medical code sets specified by the Health Insurance Portability and Accountability Act (HIPAA) for this purpose. File 16.

HCPCS is a system for identifying items and certain services. It is not a methodology or system for making coverage or payment determinations, and the existence of a code does not, of itself, determine coverage or non-coverage for an item or service. While these codes are used for billing purposes, decisions regarding the addition, deletion, or revision of HCPCS codes are made independent of the process for making determinations regarding coverage and payment. Until national Medicare coverage and payment guidelines have been established for these codes, the Medicare coverage and payment determinations for these items may be made based on the discretion of the Medicare Administrative Contractors processing claims for these items.

The HCPCS is divided into two principal subsystems, referred to as Level I[5] and Level II. Relevant here is HCPCS Level II, the codes established for submitting claims a variety of services, supplies, and equipment that are not identified by CPT® codes. HCPCS Level II codes are maintained by CMS. CMS is responsible for making decisions about additions, revisions, and deletions to the national alpha-numeric codes. The Q codes are established

[4] CMS has published guidelines which contain the information set forth in this section, unless otherwise indicated. The guidelines were submitted by the Appellant (File 13) and are indexed for ease of reference, to the administrative record as File 16.

[5] HCPCS Level I is comprised of Current Procedural Terminology (CPT®) codes. CPT codes are a numeric coding system maintained by the American Medical Association (AMA). CPT® is a uniform coding system consisting of descriptive terms and codes that are used primarily to identify medical services and procedures furnished by physicians and other health care professionals. These health care professionals use CPT® to identify services and procedures for which they bill public or private health insurance programs. CPT® codes are republished and updated annually by the AMA.

to identify drugs, biologicals, and medical equipment or services not identified by national HCPCS Level II codes, but for which codes are needed for Medicare claims processing. Anyone can apply to modify a Level II code, and CMS sets forth evaluation criteria which includes the statement that "A new or modified code is not established for an item that is regulated by the FDA, unless the FDA allows the item to be marketed. Documentation of FDA approval is required to be submitted with the coding request application." File 16, p. 7.

Additionally, an email from HCPCS@cms.hhs.gov states, "the HCPCS Level II "Q" or "A" codes are generally not considered experimental." File 13, pp. 143-144.

In this case, in the absence of an applicable NCD, LCD, the proper and complete analysis of the reasonable and necessary standards are set forth in the MPIM. See MPIM, Ch. 3, §§ 3.3.3, 3.6.2.1-3.6.2.2; MPIM, Ch. 13, §§ 13.5.3, 13.5.4. All statutes and regulations pertaining to the Medicare program are binding on ALJs. 42 C.F.R. § 405.1063(a). And while not bound by the MPIM guidance, the ALJ must afford these guidance provisions substantial deference. 42 C.F.R. § 405.1062. The appellant must provide sufficient evidence to satisfy the Medicare coverage criteria.

FINDINGS OF FACT AND ANALYSIS

I. *Parties' Position*

The MAC initially paid the claims, which were subjected to post-payment review by the UPIC and denied. The MAC upheld the denial on redetermination. At these levels, the denials were based upon findings that the submitted documentation did not support medical necessity of the services. On reconsideration appeal, the QIC determined that the services at issue are experimental and investigational "as denoted by the Q code status nomenclature" and held that since the services (Q4180, Q4194, Q4197, and Q4217) are considered investigational and not payable as per CMS, these services do not meet the medically reasonable and necessary requirements of the Section 1862(a)(1)(A) of the Social Security Act. File 2, p. 10.

The Appellant argues that the differences in denial rationale between the MAC and UPIC versus the QIC, conflict with Medicare policy. The Appellant cites MLN Matters Number SE1521, which states that "[f]or redeterminations and reconsiderations of claims denied following a post-payment review or audit, CMS has instructed MACs and QICs to limit their review to the reasons(s) the claim or line item at issue was initially denied." Thus, the Appellant contends, it was improper for the QIC to find the skin substitutes experimental and investigational when the MAC and UPIC had not. The Appellant argues the skin substitutes applied are not experimental or investigational and have been long accepted in the field of plastic surgery wound care; citing, *inter alia,* the journal entries, case studies and clinical trials summarized above and Federal Register volume 78, No. 237, pgs. 74930-74931. File 13.

Physician witness testimony was that skin substitutes (or CAMPS) are not experimental or investigational. They are the standard of care to promote healing in complex wounds.

The witnesses described the high risk for complications including infection, morbidity and amputation, which risks were significantly lower where CAMPS are used in the wound treatment. The patients here, particularly, due to age and comorbidities were not amenable to other forms of treatment. The witnesses unanimously agreed that [redacted] followed the standard of care for treatment of complex wounds; they would have performed the same treatments in the same manner. File 15 (hearing recording).

II. *Medical Records*

Beneficiary A.G. (03/10/2023 – 01/12/2024)

A.G. presented to [redacted] on March 2, 2023, for wound care following Mohs procedure on February 28, 2023, referred by Dr. Lara Kelley. File 3, p. 370. He was diagnosed with chronic lymphocytic leukemia (CLL), a disease which impacts infections and bleeding due to its effects on production of healthy white blood cells, red blood cells, and platelets.[6] File 3, p. 375; File 15 (hearing recording). According to testimony, this diagnoses among other factors including his age of 89 years rendered A.G.'s wound care complex. File 15 (hearing recording). A.G.'s additional comorbidities were chronic heart failure, skin cancer, and history of right hip fracture. File 3, p. 369.

On wound assessment, it was full thickness, located on the left lower extremity and measured (in centimeters) 2.9 x 3.0 x 0.2. File 3, p. 378. There was zero percent granulation and a large amount of sanguinous drainage. Id. Initial treatment was a cleanse with Vashe wound solution, silver nitrate and OmniStat gauze to achieve hemostasis, then application of UrgoTul, 4 x 4's and 2-layer compression. Id. There was coordination of care with home health to change dressing twice weekly. Id. The treatment Plan was for application of antimicrobial skin substitute to prevent development of bioburden, provide a scaffold for collagen deposition which will stimulate granulation tissue formation an facilitate epithelialization. Id.

On return to [redacted] on March 10, 2023, the left leg preoperative wound measurement was 3.0 x 3.5 x 0.1 cm and postoperative measurement was 3.0 x 3.5 x 0.2 cm. File 3, p. 381. The skin substitute used was Puraply XT EF 4.91 x 4.91. Id. Pursuant to the treatment Plan, initial management of the wound this date included an excisional debridement of the wound in preparation for the application of the biologic graft. File 3, p. 381. Hemostasis was achieved through direct pressure to the wound, while the biologic graft was hydrated in saline, trimmed to the size of the defect, and then surgically affixed to the wound. Id. A nonadherent mesh and a bolster dressing was applied, followed by a multi-layer compression bandage. [redacted] evaluated A.G.'s vascular status and confirmed he had palpable pulses in the posterior tibial and dorsalis pedis vessels. Id. A.G. tolerated the compression well. Id. This procedure on subsequent dates herein is described as the skin substitute being "affixed" or "applied", without repetition of these specific steps in the process.

[6] https://www.cancer.gov/types/leukemia/patient/cll-treatment-(last visited 8/16/2025)

[redacted] documented the amount of product used as eleven square centimeters with five square centimeters of waste.[7] File 3, p. 381. He explained the reason for the waste was secondary to the size of the wound in comparison to the size of the product; the graft was selected because it would give the highest likelihood of both filling the void caused by the defect, controlling infection and inducing granulation and subsequent re-epithelialization. Id. The wound had 75 percent red granulation and 25 percent devitalized tissue consisting of sough and fibrin, and there was a moderate amount of bloody drainage. Id. The treatment Plan remained serial debridement to remove devitalized tissue and stimulate the inflammatory process in the wound bed to facilitate healing through the proper orderly phases. Id. Procedure Codes were 15002, 15271, Q4197 Puraply XT one square centimeter, 11 units and Q4197-JW Puraply XT 1 sq cm, 5 units. Id.

The process pursuant to the treatment Plan was repeated on March 17, 2023, to apply the second biologic graft. File 3, pp. 385-386. The amount of product used was 8 sq. cm and wasted was 17 sq. cm. File 3, p. 386. The wound size was 2.5 x 2.9 x .2 cm, with 40 percent red granulation and 60 percent devitalized tissue consisting of slough and fibrin. Id. Post-operatively, the wound measurement was 2.5 x 2.9 x 7.25 cm. Id. There was a moderate amount of serosanguinous drainage. Id. Procedure codes were 15271, Q4197 Puraply XT 1 sq cm, 8 units and Q1497-JW Puraply XT 1 sq. cm, 17 units. Id.

On March 31, 2023, A.G. presented with a bloody bandage on his right lower extremity, in addition to the Mohs-related wound on the left, reportedly a result of hitting his leg while fishing. File 3 p. 391. He requested assessment and dressing change on the right, which was completed. Id. [redacted] repeated the wound assessment and treatment process on the left leg wound according to the treatment Plan. The left lower extremity wound size was 2.6 x 2.2 x .2 cm; the right lower extremity wound measured 1.3 x 0.6 x 0.1 cm. Id. There was 40 percent granulation and 60 percent devitalized tissue of the left lower extremity wound with moderate serosanguinous drainage. The skin substitute was Puraply XT EF 4.91 x 4.91. File 3, p. 392. Procedure codes and amounts used were 15271, Q4197 Puraply XT 1 sq. cm. six units, Q4197-JW Puraply XT 19 units. File 3, p. 391.

Assessment on April 7, 2023, was unspecified open wound, right and left lower extremities (S81.801D and S81.802D). File 3, p. 395. Graft application number four using Code Q4197 Puraply XT EF 4.91 cm x 4.91 cm was completed on the left lower leg wound. Id. Five sq. cm of product was used, with 20 sq. cm of waste. Id. The left lower extremity wound size was 2.5 x 1.9 x .3 post-operatively. Granulation was 40 percent with 60 percent devitalized tissue; there was moderate serosanguinous drainage and the periwound was macerated with hemosiderin staining. Id. Procedure codes were 15271, Q4197 Puraply XT 1 sq. cm., 5 units and Q4197-JW Puraply XT 1 sq. cm, 20 units. File 3, p. 397.

[7] By addendum dated 7/19/2024, [redacted] offered a correction of these amounts due to mathematical error. The size of the skin substitute was 25 sq cm. The amount used was 11 sq. cm. Therefore, the amount wasted is calculated to be 14 sq cm. File 3, p. 383.

The wound treatment process was repeated April 17, 2024, for graft application number five using Puraply XT EF 4.91 x 4.91. File 3, pp. 400-401. There was bruising throughout the leg secondary to low platelets. File 3, p. 401. Codes identified were 15271, Q4197 Puraply XT 1 sq. cm., six units and Q4197-JW Puraply XT 1 sq. cm., 19.00 units. File 3, p. 402.

On April 21, 2023, 90 percent granulation of the wound with 10 percent devitalized tissue had been achieved; the wound gestalt was improved. File 4, p. 405. There was bruising throughout the leg secondary to low platelets. Id. Wound measurement pre-debridement was 1.8 x 1.5 x .1 cm, and post-operatively 1.8 x 1.5 x .2 cm. Id. Graft number six was affixed. Id. Codes were 15271, Q4197 Puraply XT 1 sq. cm., 3 units and Q4197-JW Puraply XT 1 sq. cm., 22 units. Id.

A.G. returned to [redacted] on April 26, 2023, arriving with Optifoam covering the wound, pitting from border of dressing due to lower extremity edema. File 3, p. 408. Compression was discontinued the prior week due to significant ecchymosis. Id. File 3, p. 408. Skin substitute Novachor was applied 1.5 x 2.75. Id. There was new onset of active bleed right posterior calf in the waiting room, likely etiology was trauma as the bleed was surrounded by ecchymosis, possibly from car transfer. File 3, p. 409. The left lower extremity anterior tibia wound was 2.2 x 2.0 x .3 cm; the right lower extremity posterior calf wound size was 2.0 x 1.2 x 0.1 cm. Graft seven was affixed to the left leg. File 3, p. 409. Procedure codes were 15271 and Q4194 Novachor 1 sq. cm, 5 units. File 3, p. 410.

On May 5, 2023, A.G.'s lower left leg wound was 100 percent granulation, zero percent devitalized tissue, measuring .3 x .8 x .1 cm. File 3, pp. 412-413. Novachor 1.5 x 2.75 was applied as graft number eight. Id. Five sq. cm of product was used, none was wasted. Id. The right lower extremity posterior wound was 90 percent granulation. Id. However, A.G. had arrived with another open wound on his right lower extremity, covered with a band aid. Id. On initial evaluation of the new wound, there was a moderate amount of sanguinous drainage. Id. The leg was erythematous, with hemosiderin staining, and ecchymosis. Id. The treatment Plan for the new right lower extremity wound was serial debridement to remove devitalized tissue and stimulate the inflammatory process in the wound bed to facilitate healing through the proper orderly phases of wound healing. Id. Procedure codes were 15271 and Q4194-JZ Novachor 1 sq. cm 5 units. File 3, p. 412.

Graft application number nine, Novachor 1.5 x 2.75 cm, occurred May 12, 2023, in treatment of open wounds to the lower left leg. File 3, p. 418. Wound to the left lower extremity lateral was 100 percent granulated, wound size was 1.1 x 1.0 x .1 cm. Wound on the left lower extremity medial was 90 percent granulated; left lower extremity anterior and measured 1.3 x 1.0 x .1 cm. Id. Right lower extremity wound on the posterior calf was scabbed. Id. Procedure codes were 15274 and Q4194-JZ Novachor 1 sq cm, 5 units. File 3, p. 418.

On May 19, 2023, the beneficiary returned for follow-up treatment of open wounds on the left lower leg and right lower leg. There was no edema of leg or thigh. File 3, p. 422. Graft application number ten was affixed. File 3, p. 423. Five square centimeters of Novachor 1.5 x 2.75 cm was used, there was no waste. Id. Wound measurements were

lower left extremity anterior tibia 0.5 x 0.5 x 0.1 cm, right lower extremity posterior calf wound was 0.8 x 0.5 x 0.2 cm, and the left lower extremity lateral wound was 1.1 x 1 x 0.1 cm. Id. The left lower leg lateral wound was 100 percent granulation, and the left lower extremity anterior wound was 90 percent granulated. Id. Procedure codes were 15271 and Q4194-JZ Novachor 1 sq. cm., five units. File 3, p. 424.

On May 26, 2023, there was no edema of leg or thigh, and the lower left leg distal wound totally epithelialized; the left leg anterior wound was 90 percent granulated. File 3, p. 426-427.

On October 23, 2023, A.G., now a 90-year-old man, returned to [redacted] for wound care for a pretibial open wound of the left lower extremity after excision and repair of biopsy-proven Squamous Cell Carcinoma performed October 17, 2023. File 3, p. 429-430. A.G. had a past medical history significant for active chronic lymphocytic leukemia (CLL), which he is on chronic oral therapy Imbruvica for, and immune thrombocytopenia (ITP) due to his illness. Id. He was due for an IVIG infusion to increase his platelets next week. Id. A.G. was taking a course of antibiotics (Doxycycline) which he began on October 20, 2023, for significant cellulitis of the left lower extremity. Id.

Wound assessment on November 10, 2023, shows left anterior wound size 4.3 x 3.3 x 0.4 cm. File 3, p. 429. The wound was larger, but granulation tissue was proliferating. Id. The "Plan" section of the procedure note identifies the product used as Puraply XT. Id. However, in the "Procedure" portion of the office note, the skin substitute used this date was identified as Revita 4 x 4 and the procedure codes were Q4180 Revita, per sq. cm, 15 units and 4180-JW, per sq. cm., 15721 and 15002. File 3, p. 429.

On November 17, 2023, diagnoses were local infection of the skin and subcutaneous tissue, unspecified (L08.9) and unspecified open wound, left lower leg, subsequent encounter (S82.802D [Primary]). File 3, p. 435. Skin substitute Revita 4 x 4 was used. Id. The amount of product used was 14 square centimeters with one square centimeter wasted.[8] Id. Wound assessment showed infection resolved, wound diameter was larger, but granulation tissue was proliferating and was much healthier appearing; the wound bed was 90% granulation tissue and 10% devitalized tissue consisting of slough, fibrin and eschar, and exudate was a copious amount, serosanguinous. File 3, p. 437. In the "Plan" section of the progress note, application of Puraply XT skin substitute was referenced, however procedure notes identify Revita as used this date, and the procedure codes were Q4180 Revita, per sq. cm, units 15, Q4180-JW, and 15271. Id. On November 27, 2023, A.G. presented for a bandage change prior to being away on a cruise for 12 days. File 3, pp. 440-44, 443 -444.

When A.G. returned to [redacted] on December 15, 2023, he had a new open wound to the right knee as well as the left lower leg wound; diagnoses were nonhealing wound left lower extremity (S81.802D) and right knee pre-debridement (S81.001). File 3, p. 446. Pre-debridement measurement was 3.0 x 2.8 x 0.1 cm left lower extremity and 2.1 x 1.9 x

[8] In an Addendum dated July 19, 2024, [redacted] identified a mathematical error in the amount of skin substitute that was wasted. File 3, p. 438. The size of the skin substitute was 16 sq. cm. The amount used was 14 sq. cm. Therefore, the amount wasted is 2.0 sq. cm. Id.

0 cm right knee. File 3, p. 446. The left lower extremity wound was improved, with 85 percent granulation tissue and 15 percent devitalized tissue. File 3, p. 447. The procedure code was 11042 debride skin/ tissue. File 3, p. 448.

The left lower extremity wound was improved on assessment December 22, 2023. File 3, p. 449. Preoperative Measurement was 2.9 x 2.7 x 0.1 cm and post-operative measurement was 3.0 x 2.9 x 0.3 cm. Id. The skin substitute was identified as Revita 4 x 4. Id. The procedure notes showed that graft application number three used three sq. cm. of product and wasted six sq. cm. File 4, p. 450[9]. Wound bed composition was 90 percent granulation tissue and 10 percent devitalized tissue, which was slough, fibrin, eschar, and hematoma. File 3, p. 451. There was a large amount of dried sanguinous/ serosanguinous exudate. Id. Procedure codes were Q4189-JC Revita, per sq. cm., nine units, Q4180-JW Revita, per sq. cm. six units; and 15271. File 3, p. 452.

On December 29, 2023, A.G. presented to [redacted] for application of skin substitute and compression therapy for treatment of his left lower leg wound. File 3, p. 456. The pre-operative wound measurement was 2.2 x 2.0 x 0.1 cm and postoperative size was 2.6 x 2.3 x 0.2 cm. Id. The skin substitute was Revita 4 x 4. Id. Graft Application Number four used six sq. cm. of product and waste was ten sq. cm. File 3, p. 457. Wound bed composition was 90 percent granulation and 10 percent devitalized tissue, which was slough and fibrin. Id. There was a moderate amount of serosanguinous exudate. Id. Procedure codes were Q4180-JC Revita, per sq. cm., six units, Q4180-JW Revita, per sq. cm. ten units, and 15271. File 3, p. 458.

On January 5, 2024, follow-up and application of biologic skin, preoperative wound measurements were 1.4 x 1.2 x 0.1 cm and post-operative measurements were 2.0 x 2.0 x 0.2 cm. File 3, p. 461. The skin substitute was Revita 2 x 3. Id. Graft application number five used 4 sq. cm. of product with 2 sq. cm. waste. File 3, p. 462. The wound was improved, with wound bed composition of 50 percent granulation tissue and 50 percent devitalized tissue, which was slough, fibrin and hyperkeratotic tissue. File 3, p. 463. There was hypergranulation, and a swab culture for PCR wound panel and sensitivity had been obtained. Id. Procedure codes were 15272, Q4180-JC Revita, per sq. cm., four units and Q4180-JW Revita, per sq. cm., two units. File 3, p. 463.

On January 12, 2024, Revita graft number six was affixed to the left lower leg wound. File 3, p. 467. Product used was four sq. cm and waste was two sq. cm. File 3 p. 468. The wound measured 1.9 x 2.0 x 0 cm, it was improved with 80 percent granulation tissue and 20 percent devitalized tissue. File 3, p. 469. There was hypergranulation, devitalized tissue was slough and fibrin, and there was a moderate amount of serosanguinous exudate. File 3, p. 469. Procedure codes were 15271, Q4180 Revita, per sq. cm., four units and Q4180-JW Revita, per sq. cm., two units. File 3, p. 469. The microculture report for the swab taken January 5, 2024, was positive for staph aureus and corynebacterium. File 3, p. 474.

[9] In an Addendum dated July 19, 2024, [redacted] identified a mathematical error in the amount of skin substitute that was wasted. File 3, p. 452. The size of the skin substitute was 16 sq. cm. The amount used was 9 sq. cm. Therefore, the amount wasted is 7.0 sq. cm. Id.

When A.G. returned to [redacted] on January 26, 2024, he had unspecified open wound, left lower leg, (S81.802D Primary) and Cellulitis of left upper limb (L03.114), with localized swelling, mass and lump, left upper limb (R22.32). File 3, p. 472. There was left upper extremity edema extending from hand/fingers proximally to the upper arm. Id. Erythema extended from wrist proximally to upper arm. Id. There was warmth in the extremity but no complaints of pain. Id. There was an intact blood blister on the proximal arm near the elbow and at the mid-forearm a bulla that was weeping and appeared to contain purulence. Id. A.G. was started on Doxycycline, 100 mg. Id. Wound measurement of the left anterior leg was 1.5 x 1.5 cm newly epithelialized with a small area in the center that remained open, measuring 0.5 x 0.5 x 0.1 cm. File 3, p. 474. Left lateral leg wound measurement was 0.4 x 0.5 x 0.2 cm. Id. The wound bed tissue composition was 95 percent epithelialized. Id. Procedure code was 97597 active wound care. File 3, p. 475.

Beneficiary H.P. (04/19/2023 – 09/25/2023)

Beneficiary H.P. saw [redacted] for wounds on the lower left limb and medial ankle following Mohs reconstruction for squamous cell and basal cell carcinoma, on referral from Dr. Lara Kelley. File 3, pp. 480-482. On initial assessment April 18, 2023, the lower extremity anterior/ pre-tibial wound measured 2.6 x 2.9 x 0.4 cm, and the left medial ankle wound was 2.2 x 2.2 x 0.3 cm. File 3, p. 482. There was a moderate amount of sanguinous drainage. Id. The treatment plan was application of amniotic skin substitute to donate growth factors to the wound bed to enhance collagen formation. Id.

Application of the biological grafts occurred April 19, 2023, with adjunct treatments of debridement, pressure-relief, compression, infection control, nutrition, management, and vascular assessment. File 3, p. 485. Graft application number one used 16 sq. cm of product, WoundFix 4.0 x 4.0, with no waste. File 3, p. 486. The left lower extremity anterior wound measured 2.6 x 2.9 x 0.4 cm, and the medial ankle wound was 2.2 x 2.2 x 0.3 cm. File 3, p. 486. There was moderate, continuous oozing of sanguinous drainage. Id. Procedure codes were 15002, 15271, and Q4217 Woundfix biowound plus xplus ("Woundfix"), 16 units. Id.

On return to [redacted] on April 26, 2023, the wounds were debrided of necrotic subcutaneous tissue and cleansed in preparation for application of graft number two, Woundfix 4.0 x 4.0. File 3, p. 491. Pre-operative measurement of the left extremity anterior wound was 3.2 x 3.0 x 0.4 and post-operative measurement was 3.7 x 3.1 x 0.4 cm. File 3, p. 491. The left medial ankle pre-operative measurement was 2.2 x 2.8 x 0.2 cm, and post-operative size was 2.2 x 2.9 x 0.5. File 3, p. 491. Sixteen square centimeters of product (Woundfix) was used without waste. File 3, p. 492. Wound assessment showed 25 percent granulation and 75 percent devitalized tissue, improved, with a moderate amount of sanguinous and serosanguinous drainage. Id. Procedure codes were 15271 and Q4217 Woundfix, 16 units. Id.

On May 3, 2023, pre-operative left anterior wound measurement was 3.6 x 2.7 x 0.2 cm and left medial ankle size was 1.9 x 2.3 x 0.4 cm. Skin substitute Woundfix was affixed

in graft number three. File 3, p. 500. Sixteen sq cm of product was used without waste. Id. There was 25 percent granulation and 75 percent devitalized tissue. File 3, p. 500. There was continuous oozing of a moderate amount (less than the previous week) of serosanguinous drainage. Id. Procedure codes were Q4217 Woundfix 16 units and 15271. Id.

Progress notes dated May 10, 2023, documents the fourth application of Woundfix 4.0 x 4.0. File 3, p. 506. The left anterior leg wound pre-operatively measured 2.9 x 2.5 x 0.2 cm and post-operatively 2.9 x 2.5 x 0.3 cm. Id. The left medial ankle measurements were pre-operative 1.7 x 2.8 x 0.3 cm and post-operative 1.7 x 2.8 x 0.4 cm. Id. The amount of product used was 13 square centimeters with three square centimeters of waste. File 3, p. 507. There was 40 percent granulation and 60 percent devitalized tissue consisting of slough and fibrin. Id. There was moderate serosanguinous drainage. Id. Procedure codes were 15271, Q4217-JC Woundfix, 13 units and Q4217-JW three units. Id.

On follow-up May 17, 2023, wound measurements were left anterior leg 2.3 x 2.5 x 0.2 cm and left medial ankle 1.8 x 2.5 x 0.2 cm. File 3, p 512. Post-operatively, the left anterior leg measured 2.7 x 2.5 x 0.3 and the left medial ankle was 1.8 x 2.5 x 0.4 cm. File 3, p. 512. For graft application number five, 12 square centimeters of produced was used and 4 square centimeters of product wasted. File 3, p. 513. Post-debridement there was 90 percent granulation 10 percent devitalized tissue consisting of fibrin and slough. Id. There was a large amount of serosanguinous drainage. Id. The amount of drainage was increased as demonstrated with strikethrough drainage on bandage; H.P. was reminded to limit activities and elevate his leg throughout the day. Id. Procedure codes were 15271 and Q4217-JC, 12 units and Q4217-JW, four units. File 3, p. 514.

The wound measurements on May 24, 2023, were pre-operative left anterior 2.2 x 1.7 x 0.1 cm and post-operatively 2.2 x 1.8 x 0.2 cm. File 3, p. 519. The left medial ankle measurement was pre-operative 1.1 x 1.7 x 0.2 cm and post-operative 1.1 x 1.9 x 0.6 cm. Id. Skin application Woundfix 4.0 x 4.0 was used for graft application number six. Id. Product used was seven square centimeters with nine square centimeters wasted. File 3, p. 520. Post-debridement there was 95 percent granulation and 5 percent devitalized tissue, consisting of slough and fibrin. Id. Drainage was moderate, which was a significant reduction from the week prior. Id. Procedure codes were 15271, Q4217-JC seven units and A4217-JW nine units. File 3, p. 521.

H.P. returned for graft application number seven on May 31, 2023, where Woundfix was applied with four square centimeters of product used and 4 square centimeters of waste. File 3, p. 527. The left leg anterior wound size was 1.6 x 1.3 x 0.1 cm, and the left medial ankle wound measured 0.8 x 1.5 x 0.2 cm. File 3, p. 527. There was a dramatic decrease in wound dimensions and significant reduction in drainage this week. Id. Procedure codes were 15271, Q4217-JC four units and Q4217-JW four units. File 3, p. 528.

On June 7, 2023, skin substitute Woundfix 2.0 x 2.0 was applied for graft number eight with 2 square centimeters of product used and 2 square centimeters of product wasted. File 3, pp. 533-534. The wound measurements were left anterior leg 2.0 x 2.0 cm, scab, and left medial ankle 1.3 x 1.7 cm scab. File 3, p. 534. Post-debridement there was 95

percent granulation and 5 percent devitalized tissue. Id. There was a dramatic decrease in wound dimensions and drainage was minimal. Id. Procedure codes were 15271 and Q4217-JC two units and A4217-JW two units. File 3, p. 535.

One hundred percent epithelialization had been achieved on June 26, 2023; the wound had healed. File 3, p. 540.

On September 1, 2023, H.P. returned to [redacted] for treatment of an open wound on the right leg posterior distal, measuring 2.3 x 2.5 x 0.3 cm. File 3, p. 543. The wound was post-Mohs excision, and the treatment plan was application of Amniotic Skin Substitute and compression therapy. File 3, p. 544. On September 11, 2023, the first graft application occurred using Woundfix 2.0 x 4.0. File 3, p. 546-547. The pre-operative wound measurement was 2.5 x 2.3 x 0.3 cm; post-operative size was 2.5 x 2.3 x 0.3 cm. File 3, p. 546. There was 50 percent granulation and 50 percent devitalized tissue of slough, with moderate serosanguinous drainage. File 3, p. 547. Procedure codes were 15002, 15271, Q4217 Woundfix, six units, and Q4217-JW Woundfix two units. File 3, p. 548.

Wound treatment on September 18, 2023, involved graft application number two, using four square centimeters of product without waste. File 3, p. 555. The wound measurement was 2.0 x 2.2 x 0.2 cm, it had 60 percent granulation and 40 percent devitalized tissue. Id. There was moderate serosanguinous drainage. Procedure codes were 15271 and Q4217-JZ Woundfix, four units. File 3, p. 556.

On September 25, 2023, the right posterior leg wound was 1. x 1.5 x 0.2 cm with 80 percent granulation and 20 percent devitalized tissue. File 3, p. 560. There was a moderate amount of serosanguinous drainage. Id. Woundfix 2.0 x 2.0 was used for graft application number three, with 3 square centimeters of product used and one square centimeter of waste. File 3, pp. 559-560. Procedure codes were 15271, Q4217, three units and Q4217-JW. File 3, p. 561.

H.P. followed up wound treatment with [redacted] on October 2, 2023, and October 9, 2023. File 3, p. 567. On October 16, 2023, the wound was 100 percent epithelialized. File 3, p. 566.

Beneficiary H.S. (01/25/2023 – 03/13/2023)

H.S., a 98-year-old woman who is prescribed the blood-thinner Eliquis, sought treatment with [redacted] on January 25, 2023, for non-healing wounds, left lower leg, referred by Dr. Boyes. File 3, p. 651. The left lateral wound postoperative measurement was 4.9 x 3.0 x 0.4 cm, and the left posterior wound size was 1.3 x 1.7 x 0.2. File 3, p. 651. The left lateral leg wound had 60 percent granulation and 40 percent devitalized tissue; the left posterolateral wound had 25 percent granulation and 75 percent devitalized tissue; the left proximal wound had 50 percent granulation and 50 percent devitalized tissue. File 3, p. 652. There was minimal serous drainage. Id. The skin substitute applied was Woundfix 4.0 x 4.0. Id. This was graft number one; there was 16.0 square centimeters used with

zero waste. File 3, p. 652. Procedure codes were 15002, 15271, and Q4217 Woundfix, 16 units. File 3, p. 654.

On February 1, 2023, wound measurements were left lateral lower extremity 4.7 x 3.0 x 0.4 and left posterior 1.4 x 1.7 x 0.2 cm. The left lateral wound was 65 percent granulation and 35 percent devitalized tissue; the left posterolateral wound was 40 percent granulation and 60 percent devitalized tissue; and the left proximal wound was 70 percent granulation and 30 percent devitalized tissue. File 3, p. 660. The devitalized tissue was fibrin and slough; there was minimal serous drainage. Id. Woundfix 4.0 x 4.0 was applied as graft number two; there was 16 square centimeters used and zero waste. File 3, pp. 559-660. Procedure codes were 15271 and Q4217 Woundfix, 16 units. File 3, pp. 661-662.

H.S. returned for wound treatment on February 8, 2023, where left lateral wound measured 4.5 x 2.6 x 0.3 cm, left posterior wound was 1.1 x 1.4 x. 0.2 cm, and left lateral wound size was 1.2 x 1.5 x 0.2 cm. File 3, p. 667. Woundfix 4.0 x 4.0 was the skin substitute applied with 15.0 square centimeters used and one square centimeter of waste. File 3, pp. 667-668. The left lateral wound had 65 percent granulation; the left posterolateral 40 percent granulation, and the left proximal wound was 70 percent granulated. File 3, p. 668. There was minimal serous drainage. Id. Procedural codes were 15271, Q4217 Woundfix, 15 units and Q4217-JW, Woundfix. File 3, p. 670.

Graft application procedure note on February 15, 2023, documents post operative wound sizes of left lateral 4.1 x 3.1 x 0.4 cm, left posterior 1.2 x 1.5 x 0.2 cm, and left proximal 4.3 x 2.7 x 0.3 cm. File 3, p. 672. The skin substitute used was Woundfix 4.0 x 4.0 (quantity two units). File 3, p. 672. Grafting application to the left proximal, left lateral and left posterior wounds was 27 square centimeters. File 3, p. 673. The amount of product wasted was 5 square centimeters. Id. On this date and February 27, 2023, there was 90 percent granulation to the left lateral and left proximal leg wounds. File 3, pp. 673, 683. There was minimal serous drainage, devitalized tissue was slough and fibrin. Id. Procedure codes were 15271, Q4217 Woundfix, 27 units, and Q4217-JW Woundfix, five units on February 15, 2023; and 15271, Q4217 Woundfix, 25 units, and Q4217[-JW], 7 units on February 27, 2023. File 3, pp. 675, 683.

On March 6, 2023, post-operative wound measurements were left lateral 4.7 x 3.1 x 0.4 cm, left posterior 1.4 x 1.7 x 0.2 cm and left proximal 3.2 x 2.2 x 0.3 cm. File 3, p. 689. This was the sixth graft application to the left lateral and posterior wounds, and the third to the left proximal wound. File 3, p. 690. Product used was 24 square centimeters and wasted was 8 square centimeters. Id. Granulation remained 90 percent in the left lateral and proximal wounds, there was minimal serous drainage. Id. Procedure codes were 15271, Q4217 Woundfix, 24 units and Q4217-JW, 8 units. File 3, p. 692.

The seventh and fourth graft applications occurred on March 13, 2023, to the left lateral and posterior, and left proximal wounds. File 3, p. 696. The percent granulation was 90 percent for all wounds; wound gestalt was improved. Id. Wound measurements were 4.7 x 3.1 x 0.4 cm (left lateral); 1.4 x 1.7 x 0.1 cm (left posterior). Id. The amount of product

used was 23 square centimeters, and 9 square centimeters was wasted. Id. Procedure codes were 15271, Q4217, 23 units, and Q4217[-JW], 9 units. File 3, p. 697.

Analysis

The evidence provided, including the beneficiaries' medical records, the Appellant's testimony, witness testimony, the attorney representative's arguments, and medical literature provided, demonstrates that the codes billed are medically reasonable and necessary and meet Medicare coverage criteria.

In making this determination, it is acknowledged that the "Q" codes alone do not signify non-coverage and do not conclusively determine whether an item is experimental and investigational. HCPCS is a system for identifying items and certain services. Pursuant to CMS guidance, it is not a methodology or system for making coverage or payment determinations, and the existence of a code does not, of itself, determine coverage or non-coverage for an item or service. See File 16. Additionally, an email from HCPCS@cms.hhs.gov states, "the HCPCS Level II 'Q' or 'A' codes are generally not considered experimental." File 13, pp. 143-144. Similarly, FDA approval or lack thereof is not determinative. The regulations clarify that CMS uses FDA categorization "as a factor in making Medicare coverage decisions." 42 CFR § 405.201(a)(1). Thus, under Medicare regulations, FDA approval or categorization alone is not determinative of Medicare coverage.

Next, the UPIC's Review Summary as upheld by the MAC enumerated several issues supporting denial, as follows.

1. The UPIC and MAC found that comprehensive evaluations weren't included in the documentation, and therefore did not support the underlying systemic conditions were stable or if conservative treatments were tried and failed, provided as examples A.G. date of service March 10, 2023, and H.P. date of service April 19, 2023.

Regarding A.G., [redacted] explained at the hearing that the beneficiary's diagnosis with CLL was one reason A.G.'s physician referred him to a plastic surgeon with expertise in biologic applications; the wound was complex, and the beneficiary's condition put him at high risk for complications. File 15 (hearing recording). When A.G. presented to [redacted] office on referral March 2, 2023, [redacted] noted he required treatment for a wound following Mohs procedure that occurred February 28, 2023. File 3, p. 370. A.G.'s diagnosis with CLL impacts susceptibility to infections and bleeding due to its effects on production of healthy white blood cells, red blood cells, and platelets. File 3, p. 375, File 15 (hearing recording). A.G.'s additional comorbidities were chronic heart failure, skin cancer, and history of right hip fracture. File 3, p. 369. According to testimony, these diagnoses among other factors including his age of 89 years rendered A.G. not amenable to other standard treatments. File 15 (hearing recording). A "wound history" is documented, where A.G. was asked about the duration of the wound and prior treatments. File 3, p. 377. On the initial encounter of March 2, 2023, treatment was not application of antimicrobial skin graft and was instead a cleanse with Vashe wound solution, silver

nitrate and OmniStat gauze to achieve hemostasis, then application of Urgotul, 4 x 4s and 2-layer compression, and coordination of care with home health to change dressing twice weekly. Id. Adjuncts to the application of the biologic grafts included a combination of debridement, pressure-relief, compression, infection control, nutrition, management, and vascular assessment. File 3, p. 381. Along the left margin of the March 10, 2023, progress notes and all other progress notes, is a detailed accounting of Current Medications, Past Medical History, Surgical History, Family History, Social History, Allergies, Hospitalizations/ Major Diagnostic Procedures, and Review of Systems. File 3, pp. 381-383. Accordingly, a comprehensive evaluation was included, and systemic conditions were taken into consideration as well as any prior wound treatments.

Regarding H.P., as with A.G., there is a detailed accounting of Current Medications, Past Medical History, Surgical History, Family History, Social History, Allergies, Hospitalizations/ Major Diagnostic Procedure, and Review of Systems along the left margin of the April 19, 2023, progress notes. File 3, pp. 485-486. The initial encounter on April 18, 2023, states H.P. presented following post-Mohs procedure performed by referring physician Dr. Kelley to excise two biopsy confirmed basal cell carcinoma lesions one from the left pre-tibial region and the second from the left medial ankle region. Patient was referred by Dr. Kelley for primary closure versus advanced wound care management for healing by secondary intention. File 3, p. 483. The April 18, 2023, encounter involved treatment of the wounds on H.P.'s lower left leg and ankle by cleansing with vashe, Omnistat granules applied to stop bleeding, application of endoform and secured with xeroform followed by application of a 2-layer compression bandage. File 3, p. 482. H.P. was educated to refrain from his activities of playing tennis and golf and instructed to elevate his leg. Id. He was to keep the bandage dry and intact. Id. Adjuncts to the application of the biologic graft included a combination of debridement, pressure-relief, compression, infection control, nutrition, management, and vascular assessment. File 3, p. 485. Testimony was that H.P.'s comorbidities of basal and squamous cell carcinoma and the location of the wounds on the tibial region and ankle, render him not amendable to other treatments which would put him at risk of adverse events, including creating new wound sites. File 15 (hearing testimony). Accordingly, a comprehensive evaluation was included in the documentation, and systemic conditions were taken into consideration as well as any prior treatments.

2. The UPIC and MAC found that the plan of care for A.G. on January 12, 2024, included the application of Puraply XT skin substitute; however, they noted Revita skin substitute was billed, making it unclear to the UPIC and MAC which type of skin substitute was used. File 4, p. 69.

It is correct the treatment *plan* portion of the progress note mentions Puraply. However, the *procedure* portion of the progress note, where the action taken on the date of the visit is described, Revita is identified as the graft used. File 3, p. 467. The Procedure Codes section of the note identifies Q4180 Revita. File 2, p. 469. There is no ambiguity as to which biologic graft was applied on January 12, 2024. It was clearly identified and coded as Revita.

3. The UPIC and MAC found absent in the documentation "sufficient information" about the beneficiary's failure to respond to prior conservative wound care measures with documented compliance. The example provided was A.G. date of service January 12, 2024, and H.S. date of service January 25, 2023. File 4, p. 69.

The beneficiaries were all referred to [redacted] by other physicians due to the complex nature of the wound and condition of the patients. The peer-reviewed medical literature of record and hearing testimony make clear that the application of biologic grafting is the standard of care in these high-risk patients who have complex wounds. The medical records document the use of conservative modalities and biologic grafting to promote faster hearing with fewer infections and to avoid amputation. [redacted] followed this standard of care. For example, Dr. [redacted] cleansed the wounds with Vashe wound solution, silver nitrate and OmniStat gauze to achieve hemostasis, then applied UrgoTul, 4 x 4's and 2-layer compression. He evaluated vascular status and confirmed A.G. had palpable pulses in the posterior tibial and dorsalis pedis vessels. The biologic grafts were used in conjunction with conventional standards of care, which the medical literature and hearing testimony supports as most effective. Indeed, by January 26, 2024, A.G.'s wound on the anterior leg was 1.5 x 1.5 cm newly epithelialized with a small area in the center that remained open, measuring 0.5 x 0.5 x 0.1 cm. File 3, p. 474. Left lateral leg wound measurement was 0.4 x 0.5 x 0.2 cm. Id. The wound bed tissue composition was 95 percent epithelialized. Id. There was sufficient evidence of the risks of conservative wound care measures, there is no suggestion of noncompliance on the part of any of the beneficiaries.

4. The UPIC and MAC state the Wound Care Consent form did not include a date or signature date and provided as an example A.G. dates of service March 10, 2023, through January 12, 2024. File 4, p. 69.

The Wound Consent form was signed by A.G. and among the packet of documents dated March 2, 2023, the initial encounter with [redacted] office. File 3, p. 372. Moreover, the progress notes for March 10, 2023, and each note thereafter affirmatively states that consent of the patient was obtained: "Consent: Prior to procedure, consent reviewed and signed." File 3, p. 381, see pp. 385, 390, 395, 401, 405, 408, 412, 417, 422, 429, 435, 446 ("Consent All of the risks, benefits, potential complications [including the need for further surgery] and alternative treatment options were fully discussed with the patient"), 450, 457, 461, 467.

Turning to medical reasonableness and necessity of the claims at issue, it is undisputed that there is no applicable LCD or NCD. Without an applicable NCD or LCD, the MPIM clarifies that reasonableness and necessity depends on whether the treatment is safe and effective, not experimental, or investigational, and appropriate. See MPIM, Ch. 3, §§ 3.3.3, 3.6.2.1-3.6.2.2; MPIM, Ch. 13, § 13.5.4. The MPIM provides that the evaluation of whether the products are "safe and effective," "not experimental or investigational," and "appropriate" are based on "the available evidence of general acceptance by the medical community." MPIM, Ch. 3, § 3.6.2.2; MPIM, Ch. 13, 5 § 13.5.3.

Greater than thirty peer-reviewed articles were submitted by the Appellant to document the general acceptance of the proper use of biologic grafts. They have proven in clinical trials to prevent and/ or significantly lower the incidence of amputation, infection and morbidity in complex wounds such as those at issue here. The medical records and witness testimony attests to the complexity of the wounds for each of the beneficiaries due to their ages, diagnoses, and for H.P. the location of the wounds on the tibia and ankle. The type and amount of biologic was methodically accounted for in the medical records. The wounds were closely monitored with measurements, type and quantity of exudate, color, and make-up of wound bed reported in every instance of application. The beneficiaries' other conditions, diagnostic testing and procedures were monitored and recorded in the progress notes; wound care was not applied in isolation. The beneficiaries at issue all experienced wound healing without infection at the initial site, and without other complications.

The record demonstrates that the treatment with Q4180 Revita, per sq cm, Q4194 Novachor, per sq cm, Q4197 PuraPly XT, per sq cm, Q4217 WoundFix, per sq cm and application codes 15271, 15002 is the standard of care for the beneficiaries' conditions, that they meet but do not exceed their medical need, and that they are at least as beneficial as existing and available medically appropriate alternatives. See MPIM, Ch. 3, § 3.6.2.2; see also MPIM, Ch. 13, § 13.5.4. The record demonstrates that they are generally accepted by the medical community as "appropriate," for the wounds affecting these beneficiaries.

Based on the foregoing, in accordance with the standards set forth in the MPIM, the appellant has demonstrated that Q4180 Revita, per sq cm, Q4194 Novachor, per sq cm, Q4197 PuraPly XT, per sq cm, Q4217 WoundFix, per sq cm and application codes 15271, 15002 are medically reasonable and necessary, under the applicable manual requirements, which is required to support coverage. 42 C.F.R. § 424.5(a)(6). Therefore, Medicare Part B covers the items and services at issue during the dates of service.

CONCLUSIONS OF LAW

The amniotic and/ or placental tissue biologics and related application services provide to multiple Medicare beneficiaries from January 25, 2023, through January 12, 2024, by [redacted] (the "Appellant") meet the requirements to be reasonable and necessary in the treatment of the beneficiaries.

ORDER

For the reasons discussed above, this decision is **FULLY FAVORABLE**. I direct the Medicare Administrative Contractor to process the claims in accordance with this decision.

SO ORDERED

Jaya Shurtliff
Administrative Law Judge

APPENDIX A

Executive Summary

Oliver Burckhardt, Co-CEO
Tiger BioSciences

(Sept. 12, 2025)

Company Overview:

- **Focus CAMPs:** Placental, Dermis & Adipose Tissue
- **Tissue Engineering:** Wound Care & Soft Tissue Reconstruction
- **Vertically Integrated:** Tissue Recovery, R&D, Sales & Marketing
- **Headquarters:** Philadelphia, PA & San Antonio, TX
- **Privately Owned:** 750 employees in 14 US locations

Proposed MPFS & OPPS Rules

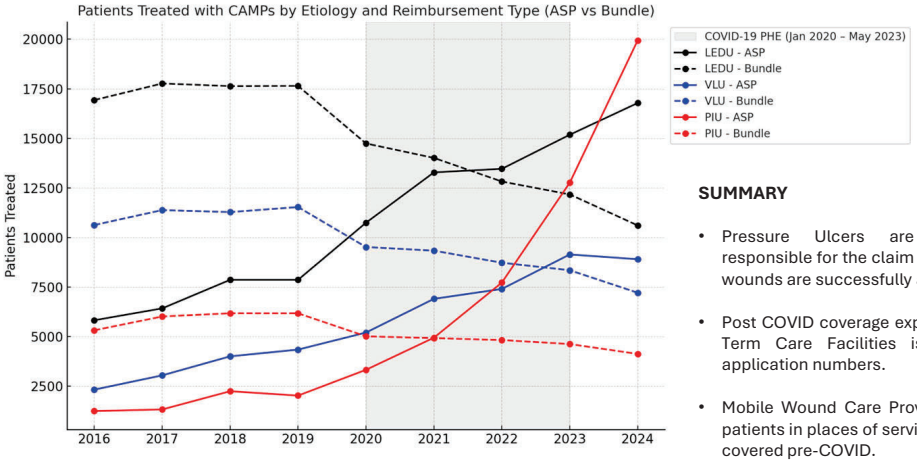
New Skin Sub LCD

Executive Summary

- **PATIENT ACCESS**: Tiger's strategy and proposal focuses on maximizing patient access to its regenerative technologies at a price point acceptable to the Medicare trust fund.
- **EMPIRIC EVIDENCE**: in Q1/2024 CMS requested that empiric/clinical data needs to be made available to justify Medicare coverage. No guidance was given what studies need to show. CMS does not allow companies sufficient time to conclude the requested, sophisticated clinical trials that the FDA never before required. We ask for more time to complete those clinical trials, a reasonable pathway to submit to secure timely coverage.
- **FEE SCHEDULE:** Tiger welcomes a consistent payment methodology but requests a realistic rate that is based on proper product usage & rates, place of service and real-world Medicare data.
- **FRAUD & ABUSE**: Tiger supports CMS to use all tools available to it to address fraud & abuse issues related to misuse of CAMPs. Tiger requests that the entire industry is not punished because of a small subset of bad market players.
- **SUPPORT OF MAHA**: Tiger supports the Trump administration's MAHA initiative to facilitate the use of regenerative medicine innovation by modernizing policies as clinical data is established.

2016-2024 Medicare CAMPs Claims Data Analysis

Professional Claim Drivers



*Bundle payment model represents the HOPD setting. ASP payment model represents the private office and post-acute care settings.

LEDU – lower extremity diabetic ulcer

VLU – venous leg ulcer

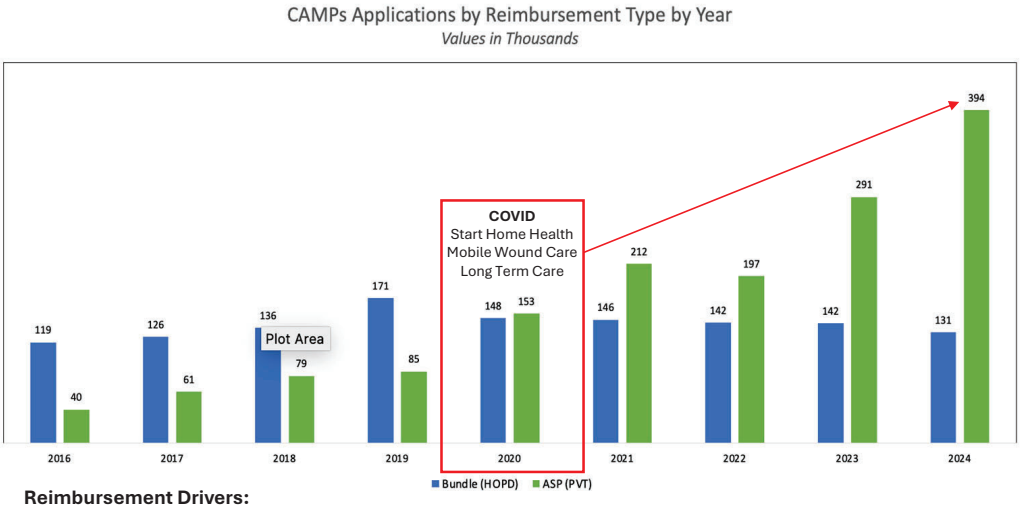
PIU – pressure Injury ulcer

SUMMARY

- Pressure Ulcers are predominantly responsible for the claim increases. Bigger wounds are successfully addressed.
- Post COVID coverage expansion into Long Term Care Facilities is driving CAMP application numbers.
- Mobile Wound Care Providers are seeing patients in places of services that were not covered pre-COVID.
- The clinical success of CAMPs is driving increased usage.
- More advanced CAMPs (multi-layer grafts) are driving wound closure rates up.

2016-2024 Medicare CAMPs Claims Data Analysis

CAMPs Reimbursement Drivers



Reimbursement Drivers:

- Mobile wound management in long-term care facility has expanded patient demographics (2020).
- Larger wounds (predominantly pressure inflicted wounds) drive average wound cost reimbursement.
- Forced ASP-based reimbursement framework (implemented 2022) has propelled Medicare spend significantly.
- More advanced CAMPs are driving higher price point/ASPs.

CY 2026 MPFS Proposed Rule

CY 2026 OPPS Proposed Rule

Tiger's Fee Schedule Concerns

Overall Observations from 90 Fed. Reg. 32352 and 33276

Comparison of Weighted Averages vs. CMS Published Rate

Methodology	Result ($ / cm^2)	Notes
CMS Published	$125.38	254 HCPCS, ASP → MUC → AWP/WAC We believe: Combined OPPS + Professional, undisclosed weighting, FY 2024
Weighted Average as Published (all claims, CMS pricing hierarchy)	$975.31	Transparent volume-weighted average across HCPCS with measurable volume, OPPS + Professional Claims
Weighted Average as published by CMS	$67.80	OPPS claims only, CMS pricing hierarchy. Illustrates effect of down-weighting Professional claims
Senate Bill 2561 (Professional + OPPS Claims)	$712.11	Volume-weighted average of published payment allowance limits (Q4/2023) using both Professional and OPPS claims

Key Takeaway:

- **CMS's $125.38 rate cannot be replicated using any transparent weighted calculation; actual defensible estimates range from $712–$975 per cm^2, depending on methodology and claim inclusion.**

CY 2026 MPFS Proposed Rule

CY 2026 OPPS Proposed Rule

Tiger's Suggested CAMP Payment Rate

Payment Rate Recommendation: $700/cm²

- **Rational:**
  - If CMS considers volume-weighted average of published payment allowance limits (Q4/2023) a rate of **$712 per cm²** is justifiable.
  - Dr. Tettelbach et al. published a fully burdened cost calculation based on real world data that supports a range of **$478-$704** per cm².
  - Amniotic membrane (per the NCD) used for ocular purposes is typically a 14 mm disc, which is approximately 1.5 per cm². That correlates to a range of **$557-776 cm²**.
  - Using CMS's calculation methodology from the proposed rules, a volume-weighted average across all categories results in **$975 per cm²**

RATE RANGE	Low Range $478/cm²	High Range $975/cm²

Table 3. Full cost burden ($ USD), justifying CAMP reimbursement range of $478–704 USD/cm²

Cost category	Entry-scale estimate (per cm²)	Late-stage estimate (per cm²)	Description
Clinical trials and R&D	$115	$185	Amortised cost of $11.5–15 million USD in past and future R&D over 3 years at early-stage volume (240,000–500,000cm²)
Procurement, manufacturing and processing	$38	$59	Includes GMP production, quality assurance/quality control, raw materials, tissue preparation, production batch loss and sterile packaging
SG&A expenses (including inflation)	$132	$151	Overhead for ~100 employees at $150,000 USD average salary, adjusted for inflation
Regulatory, legal and compliance	$37	$50	US FDA engagement, IP, safety monitoring, tissue bank compliance, audit readiness
Marketing, education and access	$95	$143	Sales force, provider education, payer contracting and outreach
Insurance, risk and fixed costs	$30	$70	Product liability insurance, risk mitigation, professional service fees
Subtotal (fully burdened cost)	$447	$658	Total cost to sustain product in market prior to margin
+ Margin (industry standard)	$31 (7%)	$46 (7%)	Operating margin to support reinvestment, future R&D, capital stability and pipeline continuity
Total justified reimbursement	$478 per cm²	$704 per cm²	Full reimbursement range needed to maintain innovation and ensure access for Medicare patients

FDA—Food and Frug Administration; GMP—good manufacturing practice; IP—intellectual property; R&D—research and development; SG&A—selling, general and administrative

Source: Safeguarding access, fiscal responsibility and innovation: a comprehensive reimbursement framework for CAMPs to preserve the Medicare Trust Fund. Journal of Wound Care, Tettelbach September 2025

CY 2026 MPFS Proposed Rule

CY 2026 OPPS Proposed Rule

Fee Schedule Summary

Summary:

- Suggested Payment Rate: **$700/cm²**
- Tiger supports the Proposed Rules: it creates a consistent, site-neutral reimbursement rate for skin substitutes irrespective of care settings and establishes a uniform reimbursement rate.
- The proposed reimbursement rate is **artificially** and **indefensibly low** without a factual basis and will greatly impede the continuation of care that our patient population requires.
- A separate payment rate established for skin substitute products and a rate for skin substitute application procedures must appropriately reimburse providers (especially Mobile Wound Care Providers) and suppliers for their product cost, services, and overhead expenses associated with the application procedures.
- Elimination of upward pricing spiral caused by ASP payment methodology urgently necessary.

Based on projected 2025 Medicare spending on skin substitutes in the Professional private office and post-acute care settings of $15.38 billion, implementing a fixed reimbursement rate of $700/cm² would result in:

IMMEDIATE SAVINGS

- **69%** reduction in CAMP reimbursements,
- Up to **$10.57 billion** savings in first year,
- Projected 10-year savings: **$105.7 billion**.

SECONDARY SAVINGS

- Use of CAMPs drives significant savings through reductions in infections, limb amputations, and hospital and care costs associated with non-healing wounds.

New Skin Sub LCDs

Tiger's Perspective

LCD CONCERNS

- The drastic limitation of product availability (221 to 17) under the proposed LCD will leave hundreds of thousands of patients **without valid treatment options**, especially for larger wounds in long term care facilities.
- The limitation on number of graft applications allowed in the proposed LCD will lead to **treatment failures**, clinical wound healing issues, loss of limbs and increased fatality rates.
- Pressure Ulcer is not specifically mentioned as covered indication in proposed LCD.
- **Recent FDA TRG responses have shown that the proposed LCD is contradicting current FDA regulations**

TIGER INITIATIVES & NEEDED CLARIFICATION:

- Tiger initiated 3 different RCTs to show clinical evidence for relevant CMAPs and indications (DLU/VLU/PIW).
- Unclear if Nov 1, 2025 data submission will lead to coverage under the proposed LCD (slated currently for Jan 1, 2026).
- Tiger submitted FDA "approval requests/TRG" using the proposed LCD product definitions and indications needed for coverage but received denials as inconsistent with FDA.
- Pressure Ulcers need to be considered/covered in proposed LCD.

The Ask to CMS:

Implement Fixed Payment Rate of $700/cm^2

Significant and immediate savings for Medicare without reducing patient access to life saving regenerative technology

Postpone LCD Effective Date to July 1, 2026

Extend the submission deadline for clinical effectiveness data, to ensure that full body of clinical data and evidence-backed products are included in the final LCD

Include Pressure Wounds in LCD

Allow access to medically necessary wound care, particularly for vulnerable populations and individuals managing complex chronic conditions who will be hurt without access to CAMPs.