A review of the proposed draft CAMPs LCDs compared to evidence-based medicine: a letter to the MACs for consideration

In the field of wound care, skin substitutes, also known as cellular tissue products (CTPs) and now referred to as CAMPs (cellular, acellular and matrix-like products),[1] have shown improved healing rates and cost-effective usage. Prospective randomised controlled trials (RCTs) (level-one evidence) supported this as early as 2001 and were confirmed by more recently published real-world data (RWD) analyses.[2–7] When used appropriately, this therapeutic class of products can create a protective barrier over hard-to-heal wounds. Such barriers reduce inflammation, support the growth of granulation tissue, and promote the migration of epithelial cells across the extracellular matrix. As a result, the trajectory of the healing cascade can be re-established towards closure. Adjunctive CAMP therapy can also alleviate pain and decrease fluid loss, risk of infection, amputation rates and associated mortality rates,[8–10] all important factors in improving patients' quality of life (QoL).

Over the past two decades, wound care specialists have increasingly integrated the use of CAMPs into their practice as part of their treatment algorithms to close hard-to-heal wounds. This adoption has been driven by multiple evidence-based factors:

- Well-established level-one evidence from prospective multicentre RCTs demonstrating superior closure rates when standard of care (SoC) is combined with CAMP usage compared to SoC alone[2–5,11–14]
- Supportive observational case series/reports (level-four evidence) showcasing extraordinary outcomes published in peer-reviewed journals by wound care providers using a CAMP to treat a broad range of hard-to-heal wounds (e.g., lower extremity diabetic ulcers (LEDUs), venous leg ulcers (VLUs), complex surgical wounds, pressure injury ulcers, ischaemic ulcers and traumatic wounds) in the outpatient wound care settings[15–17]
- Multiple propensity-matched retrospective analyses of Medicare claims data (2015–2020) (level-three evidence) that validate the findings of previous level-one RCTs and highlight the benefits of CAMPs to lower one-year mortality, improve clinical outcomes, shorten treatment episode duration, decrease wound recurrences and significantly reduce associated healthcare costs, while concurrently providing patient quality-adjusted life years or, in other words, improved QoL.[9,18,19]

These benefits are particularly accentuated when a CAMP is deployed while following parameters for use (FPFU) as defined in an analysis of 2015–2018 Medicare claims data from over 9,000,000 Medicare beneficiaries.[18] FPFU is defined as initiating a CAMP within 30–45 days from the date of the first wound care visit in the claim submissions, and once started, a CAMP should be applied regularly within the range of every 7–14 days until episode resolution or signs of treatment failure.[18]

In this dataset, only 9.2% of providers applied CAMPs while FPFU, and the average time to the first application of a CAMP from the date of the first wound-care-related visit claim was >69 days.[18] These trends reflect the need for wound care providers to be better educated on the use of CAMPs, which should also include education on optimal wound bed preparation before and during the concomitant application of a CAMP.[20–22] Educational opportunities targeting the appropriate use of CAMPs have gained momentum in the wound care community. For example, 2024 witnessed the inauguration of a highly successful CAMP-specific education-oriented conference called the *Cellular, Acellular, and Matrix-like Products (CAMPs) Wound Care Summit 2024*. Yet achieving broad standardised wound care training, including the use of CAMPs, remains a distant goal. An alternative approach to standardise the use of CAMPs would be to create regulations using medical evidence to influence clinical practice habits.

The Medicare Administrative Contractors (MACs) recently proposed Local Coverage Determinations (LCDs) focusing on CAMPs, with the aim of driving best practice based on available medical evidence. Evidence-based decision-making has become the foundation of 21st-century medicine[23] and is a welcome approach within the wound care area.

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However, for medical evidence to favourably impact real-world clinical outcomes, policy makers and frontline providers must be attentive to correctly interpret and understand published evidence. These tenets support at least two of the fundamental principles of ethics dating back to the time of Hippocrates: 'to help and do no harm'.[24]

Clarification of the supporting data

As wound care professionals, we and our colleagues would like to acknowledge that the currently proposed LCDs focusing on 'Skin Substitute Grafts/ Cellular and Tissue-Based Products for the Treatment of Diabetic Foot Ulcers and Venous Leg Ulcers'[25] were developed with good intentions, and we appreciate the challenges to develop coverage parameters that are consistent, evidence-based and apply to all covered CAMPs. Yet, we feel obligated to respectfully highlight that data interpretation of certain referenced articles was applied out of context during the development of the LCDs.

For example, several points should be addressed when deriving the limit of four CAMP applications for diabetic foot ulcers (DFUs) and VLUs per a specified 12-week treatment episode:

- Averages, which are frequently presented in published research, are not the best metrics for establishing clinically useful limits
- The average of four CAMPs referenced for LEDUs is significantly higher for VLUs, wounds with a large surface area, wounds with significant depth or undermining, cases complicated with intermittent infection, and other easily stratified patient groups covered by the LCDs
- The proposed LCDs do not address the most impactful finding of the Medicare RWD, which revealed that clinically relevant parameters for use are not being followed
- The 12-week timeline does not align with the Medicare RWD on which the averages are based, and many of the 12-week RCTs employ products whose usage is too low to impact the real-world evidence (RWE).

Table 1 provides the average number of advanced treatments (AT) or CAMP applications from propensity-matched Group 1 and Group 2, respectively.[18] The LCD developers chose the average of 3.7±3.6 applications from propensity-matched Group 1. Rounding up to 4.0 applications, without the addition of a standard deviation (SD), can be construed as a significant shortcoming for multiple reasons. For one, considering the mean applications alone only represent approximately 50% of the episodes that used a CAMP. Clinically, this is not a statistically significant number to base best practice on. However, by applying one SD, which is typical and expected, the average number of CAMP applications expands to 7.0, which would incorporate close to 70% of the episodes that included a CAMP. Take note that propensity-matched Group 2 reflects more appropriate usage of CAMPs to treat hard-to-heal LEDUs, resulting in significantly lower amputation rates, emergency department visits, and a shorter average time to the first application of 34.7 days. To achieve these superior results, propensity-matched Group 2 used an average of 4.9±3.8 applications (Table 1).[18]

In contrast to LEDUs, very different results were observed when conducting a similar retrospective analysis on Medicare claims data (2015–2019) focused on the treatment of VLUs in the hospital outpatient department (HOPD) setting. The average or mean observed CAMP applications for all VLUs was 4.98±5.16 (Table 2).[7] When you separate out VLUs that became infected (complex) at any point during the observation period, the average number of CAMP applications increased to 6.65±6.80 (Table 2).[7] Allowing four CAMP applications within a 12 week episode of care aligns with one CAMP application every three weeks. A 2022 Medicare claims analysis focusing on the frequency of debridement of LEDUs, along with the concurrent use of a CAMP, revealed that the best outcomes were obtained when the beneficiaries received sharp debridement along with the simultaneous application of a CAMP every one to two weeks rather than every three weeks.[20] It is crucial to consider the context when applying research findings to a broad beneficiary population. In the retrospective Medicare evaluation from 2015–2019, patients were followed up to 12 months.[18,19] A retrospective evaluation period of 12 months differs significantly from the majority of prospective multicentre RCTs, which are classically limited to a 12-week treatment phase. Therefore, the results of a 12-month analysis may not be easily applicable to the structured assessment of a 12-week treatment period. Furthermore, the retrospective Medicare (2015–2019) analyses were solely derived from HOPD data, whereas prospective multicentre RCTs derived data from both HOPD and private clinics. RWD and RWE are used to verify or possibly bring into question the findings of prospective multicentre RCTs. In August 2023, the U.S. Food and Drug Administration (FDA) issued 'Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision Making for Drug and Biological Products'.[26] Within the document, the FDA defined RWD and RWE as follows:

- RWD are data relating to patient health status and/ or the delivery of healthcare routinely collected from a variety of sources
- RWE is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.[26]

The findings from retrospective Medicare database analyses (2015–2020) have confirmed that CAMPs, as a therapeutic class, have a favourable impact on outcomes and are cost-effective when used to treat

Table 1. Propensity-matched groups using CAMP or no CAMP while FPFU and not FPFU[18]

Result	Propensity-matched Group 1			Propensity-matched Group 2			
	No CAMP, n=12,510 Episodes of care: 12,676	CAMP, n=12,313 Episodes of care: 12,676	Paired t-test p-value	No CAMP, n=1131 Episodes of care: 1131	CAMP		p-value
					FPFU, n=1131 Episodes of care: 1131	Not FPFU, n=1128 Episodes of care: 1131	
Visits							
Minor amputations, n (%) Rates per thousand	551 (4.3) 43.47	490 (3.9) 38.66	0.0374	47 (4.2) 41.56	22 (1.9) 19.45	51 (4.5) 45.09	0.0048* 0.0040† 0.0020‡
Major amputations, n (%) Rates per thousand	402 (3.2) 31.71	197 (1.6) 15.54	<0.0001	30 (2.7) 26.53	<11 (<1.0)§	18 (1.6) 15.92	0.0027* 0.0008† 0.1007‡
ED visits, n (%) Rates per thousand	2932 (23.1) 231.30	2322 (18.3) 183.18	<0.0001	237 (21.0) 209.55	161 (14.2) 142.35	221 (19.5) 195.40	0.0018* 0.0004† 0.0697‡
Readmissions, n (%) Rates per thousand	805 (6.4) 63.51	508 (4.0) 40.08	<0.0001	73 (6.5) 64.54	27 (2.4) 23.87	39 (3.4) 34.48	0.001* <0.0001† 0.2275‡
Average days to AT (SD)		69.4 (83.3)			34.7 (5.7)	77.2 (88.0)	
Average number of AT applications (SD)	0	3.7 (3.6)		0	4.9 (3.8)	3.5 (3.3)	

*Kruskal–Wallis test; †No CAMP versus FPFU followed, paired t-test; ‡FPFU followed versus not FPFU, paired t-test; §<11 individuals requiring data suppression per CMS cell size policy. CAMP—cellular, acellular and matrix-like product; CMS—Centers for Medicare & Medicaid Services; ED—emergency department; FPFU—followed parameters for use; SD—standard deviation

hard-to-heal LEDUs and VLUs in the HOPD setting.[6,7,9,18,19] Although these results align with previously published prospective multicentre RCTs, one should be cautious when attempting to directly apply such findings outside the intended scope of the RWE, especially when the RWD lacks the same variety of sources as the intended treatment populations (e.g., HOPD clinics, private clinics, critical access hospitals, and the post-acute settings).

Beyond the risk of misinterpreting RWE, a substantial number of adequately powered prospective RCTs, even those involving CAMPs that have undergone the more rigorous FDA premarket approval (PMA) process, do not support the limitation of four skin substitutions or CAMP applications within a 12-week treatment episode (Table 3).

Of the currently proposed covered CAMPs, there are several RCTs demonstrating an average number of applications fewer than four; however, in the HOPD setting, these CAMPs do not necessarily reflect a

Table 2. Number of CAMP applications in VLU cohorts (per patient) (from: Tettelbach et al.[7])

	Cohort name	Cohort, n	Mean	SD	Min	Med	Max	Lower 95%	Upper 95%
All	All VLU CAMPs	30,547	4.98	5.16	1	3	108	4.92	5.03
	VLU CAMPs FPFU	6546	5.32	4.75	2	4	108	5.21	5.44
	VLU DHACM FPFU	1946	4.84	3.81	2	4	61	4.67	5.01
Chronic	All VLU CAMPs	23,486	4.47	4.44	1	3	108	4.42	4.53
	VLU CAMPs FPFU	5423	5.00	4.14	2	4	108	4.89	5.11
	VLU DHACM FPFU	1638	4.62	3.56	2	4	61	4.45	4.79
Complex	All VLU CAMPs	7061	6.65	6.80	1	5	95	6.49	6.80
	VLU CAMPs FPFU	1123	6.87	6.78	2	5	95	6.48	7.27
	VLU DHACM FPFU	308	6.03	4.74	2	5	34	5.50	6.56

CAMPs—cellular, acellular and matrix-like products; DHACM—dehydrated Amnion Chorion Membrane; FPFU—following parameters for use; Max—maximum; Med—median (the value separating the higher half from the lower half of the population); Min—minimum; SD—standard deviation; VLU—venous leg ulcer

Table 3. Number of CAMP applications and type of CAMP applied to ulcer per study duration

Product(s) (designation)	Ulcer type studied	Number of CAMPs applied during treatment phase	Average number of applications	Study type	Total study patients	Duration of CAMP treatment phase
Apligraf[3] (PMA)	DFU	Up to 5		Multicentre prospective RCT	208	4 weeks with follow-up phase at 12 weeks
Dermagraft[4] (PMA)	DFU	Up to 8		Multicentre prospective RCT	314	7 weeks with follow-up phase at 12 weeks
OASIS[27] (510k) Dermagraft (PMA)	DFU	Up to 8: Oasis Up to 3: Dermagraft		Multicentre prospective comparator RCT	26	12 weeks with follow-up phase at 20 weeks
Grafix Prime[11] (361)	DFU		6	Multicentre prospective RCT	97	12 weeks
EPIFIX[1] (361)	DFU		5	Multicentre prospective RCT	110	12 weeks with follow-up phase at 16 weeks
EPIFIX[10] (361)	VLU		7.2	Multicentre prospective RCT	128	12 weeks with follow-up phase at 16 weeks
EPICORD[2] (361)	DFU		7	Multicentre prospective RCT	155	12 weeks with follow-up phase at 16 weeks
Mirragen[12] (510k)	DFU		5	Multicentre prospective RCT	49	12 weeks

510k and 361 are regulatory pathways. CAMPs—cellular, acellular and matrix-like products; DFU—diabetic foot ulcer; PMA—pre-market approval; RCT—randomised controlled trial; VLU—venous leg ulcer. Products: Apligraf (Organogenesis, US); Dermagraft (Organogenesis, US); OASIS, Smith+Nephew, UK); Grafix Prime, Smith+Nephew, UK); EPIFIX (Marietta, US); EPICORD (Marietta, US); Mirragen (Rolla, US)

substantive portion of clinical adoption[6,19] (Fig 1a, b), thus confounding any calculations if the considered RCTs are taken into account individually. From 2015–2019, four CAMPs accounted for more than 74% of the usage to treat LEDUs (Fig 1a) and 65% of the usage to treat VLUs (Fig 1b) in the HOPD settings.[6,19] To more effectively determine the allowable number of applications of CAMPs, one should attempt to remove any significant statistical bias to suitably apply a determination to all covered CAMPs. One step would be to weight the RWD by taking into consideration the proportion of real-world usage.

Insights on billing, coding, diagnostics and recommendations

In an attempt to mitigate the four CAMP application restrictions, the MACs have proposed use of the KX modifier (a signal on a claim) to allow for additional applications in 'exceptional' cases. Except, the presented data contends that the need to apply more than four CAMPs during the specified 12-week treatment episode will be the rule rather than the exception. If the MACs plan to use the KX modifier as a metric for future evaluations of exceptional CAMP use, the marker will likely have little statistical value while potentially overwhelming the auditing process. Considering that CAMPs are an application, then bill modality, the KX modifier, depending on how it is managed by the Centers for Medicare & Medicaid Services (CMS), could potentially create barriers and patient access issues due to the inability to financially sustain continued applications while waiting weeks to months on potential payments. This is because, based on the current parameters, more than half of the 12-week treatment episodes will require additional CAMPs beyond the proposed four application limit.

There is added confusion where the LCDs state that 'the following is considered not reasonable and necessary:

1. Greater than four applications of a skin substitute graft/CTP within the episode of skin replacement therapy (defined as 12 weeks from the first application of a skin substitute graft/CTP). In exceptional cases in which four applications are not sufficient for adequate wound healing, additional applications may be considered with documentation that includes a progression of wound closure under the current treatment plan and medical necessity for additional applications.'[18]

To alleviate ongoing confusion, it may be prudent

for the authors of the draft LCDs to provide clarification on clinical findings that constitute demonstrable progression of wound closure, ensuring proper justification of a KX modifier. Suggested examples could include but are not limited to:

- Decreased wound surface area
- Reduction in wound volume
- Improvement in wound bed granulation tissue
- Decreased drainage from the wound bed.

In 2020, CMS launched the 'Patients over Paperwork' initiative, with the goal to eliminate or reduce overly burdensome regulations and guidance to allow providers to focus on their primary mission—improving their patients' health.[28] The requirement of reporting the KX modifier for medically necessary applications greater than four could create another regulatory burden for providers to track, and not just within their own practice. Since a CAMP can be unknowingly applied at other places of service, providers will need to track the use of CAMPs to avoid documentation mismatches with the KX modifier. This is important because the LCDs define the episode of skin replacement therapy as 12 weeks from the first CAMP application.

When it comes to Billing and Coding, the LCD Reference Articles,[29] as proposed, do not include diagnosis codes for wounds that involve deep structures such as muscle, tendon, joint capsule and bone. When an extremity wound with exposed deep structures cannot be closed with a surgical flap, the patient is at higher risk for amputation due to limited limb preservation options. Fortunately, multiple published observational studies report favourable outcomes when a CAMP was used to salvage limbs threatened by hard-to-heal wounds with exposed deep structures.[30–32] In the best interest of Medicare beneficiaries, the authors of the proposed LCDs may wish to review and give further consideration to include ICD-10 codes for wounds with muscle (L97.xx3) and/or bone (L97.xx4) involvement, specifically non-pressure hard-to-heal ulcers.

Within the section entitled *Evidence-Based Guidelines for Standard of Care*,[25] the authors make the following statement:

> *The use of a Class 3 (most supportive) high-compression method is strongly recommended in the treatment of venous ulcers.*

By US standards, Class 3 high compression is defined as a pressure >30mmHg and is not recommended for individuals with ankle–brachial indices <0.5 or >1.3 since this level of compression could place them at risk for an ischaemic event. Another reason for the authors to consider modifying this statement is to broaden the acceptable range of compression pressures, which would afford alternative compression ranges to beneficiaries who simply cannot tolerate compression levels >30mmHg. In

Fig 1a. The percentage of diabetic lower extremity ulcer episodes that used a cellular, acellular and matrix-like product (CAMP) are shown based on 16,735 episodes from propensity-matched Group 1 derived from the Medicare data files from 2015–2019.[6] Products: Apligraf (Organogenesis, US); Puraply (Organogenesis, US); Grafix (Smith+Nephew, UK); EPIFIX (Marietta, US); TheraSkin (LifeNet Health, US); Dermagraft (Organogenesis, US); NuShield (Organogenesis, US); Integra (Integra LifeSciences, US); PriMatrix (Integra LifeSciences, US)

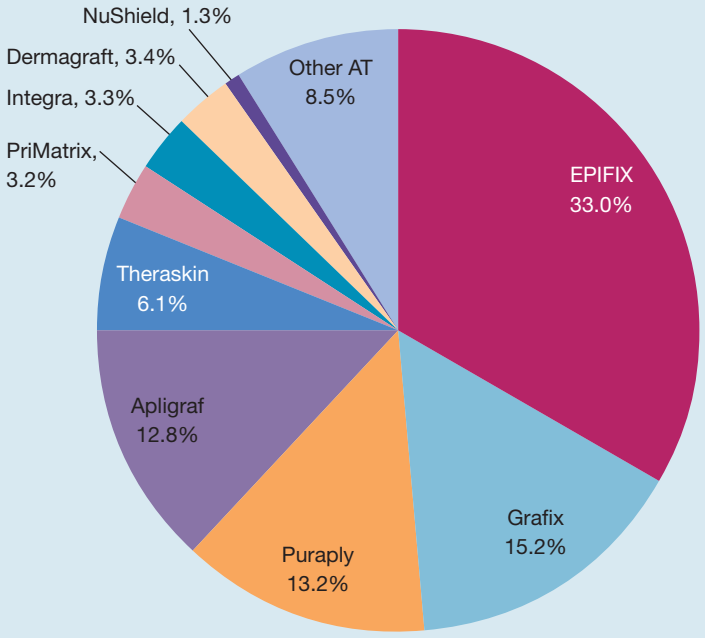
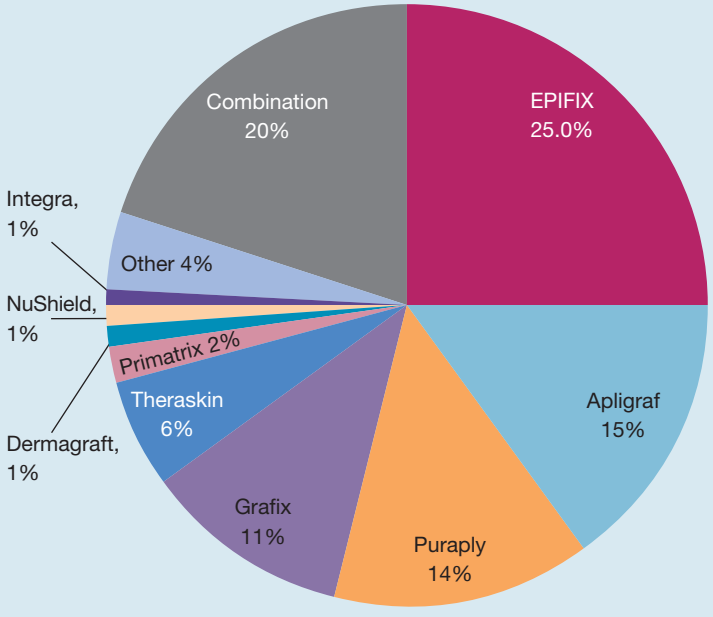


Fig 1b. The percentage of venous leg ulcer episodes that used a cellular, acellular and matrix-like product (CAMP) is shown based on 30,547 episodes from propensity-matched Group 1 derived from the Medicare data files from 2015–2019.[19] Products: Apligraf (Organogenesis, US); Puraply (Organogenesis, US); Grafix (Smith+Nephew, UK); EPIFIX (Marietta, US); TheraSkin (LifeNet Health, US); Dermagraft (Organogenesis, US); NuShield (Organogenesis, US); Integra (Integra LifeSciences, US); PriMatrix (Integra LifeSciences, US)



various settings, such as critical access hospitals, and rural or post-acute settings, it may be difficult to obtain the suggested venous ulcer diagnostic test(s) (e.g., venous duplex ultrasound or plethysmography) in a timely manner. This could feasibly lead to a delay in starting adjunct CAMP therapy, putting patients at risk of complications such as infection and sepsis.[7,19]

To supplement ankle–brachial studies, toe blood pressure readings, pulse volume recordings, transcutaneous oxygen measurements (TCOMs), and skin perfusion pressure measurements have been suggested as acceptable benchmarks for the prediction of ulcer healing.[25] 'Suggested as acceptable benchmarks' is ambiguous and should be removed, especially since these diagnostic tests are already considered acceptable benchmarks.[33] Another modality to consider adding to the list is portable near-infrared spectroscopy imaging. This technology measures tissue oxygen saturation, oxyhaemoglobin and deoxyhaemoglobin in nearly all individuals at any location on the body in any care setting. Its ability to evaluate perfusion and tissue viability helps improve medical decision-making when determining whether the wound is ready to receive a CAMP or is responding to the applied treatment.

Conclusion

Although evidence was used in the development of this draft LCD, the manner in which the data have been interpreted should be re-evaluated, while providing clarification of the LCD restrictions and the use of the KX modifiers. Additional review of the prospective RCTs and proper weighting of the RWE found in recently published retrospective Medicare analyses of LEDUs and VLUs will aid in accounting for confounding variables. The presented data support the number of allowable CAMPs during a 12-week episode of care to be closer to eight, particularly in the HOPD setting. Expanding the number of allowable CAMP applications to eight would also make the KX modifier more meaningful as a measurable metric. Clarifying the clinical findings that constitute demonstrable progression of wound closure would also ensure the proper use of the KX modifier. Given there is supporting clinical evidence, ICD-10 codes for hard-to-heal wounds with exposed muscle (L97.xx3) and/or bone (L97.xx4) should be included in the proposed LCDs. Recommendations in the *Evidence-Based Guidelines for Standard of Care* section[25] that could be misinterpreted and potentially lead to patient harm should be modified or removed.

Finally, the current draft of the LCDs seems to prioritise reducing the excessive use of CAMPs rather than encouraging the adoption of best practices that can enhance beneficiaries' outcomes. Interestingly, developing policies that encourage providers using CAMPs to follow clinically relevant parameters would consequently increase their use, as indicated by the medical evidence, including the Medicare data analyses.[34] The LCDs also should not have removed the ability to treat wounds beyond LEDUs and VLUs by excluding the option to treat them based on medical necessity. For practising healthcare providers, medical necessity is still an evidence-based decision-making process bolstered by training and clinical experience. As the proposed LCD stands today, a patient without diabetes but with idiopathic peripheral neuropathy, who presents with a diabetic-like neuropathic ulcer which is refractory to conservative standard care, will no longer be afforded the opportunity to be treated with a CAMP based on medical necessity. In contrast, infectious disease specialists successfully treat infections on a routine basis with antibiotics that do not have an established indication for the targeted diagnosis, especially when other options fail or are not available. Given all the available medical evidence, which is counterbalanced by a significant lack of evidence, the authors of the proposed LCD should reconsider their stance on excluding the option of medical necessity, which, if included, would allow frontline providers to combine their clinical experience with evidence-based decision-making, thus enabling them to strive for best practices in all clinical settings. **JWC**

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Note from the Editor

Dear Reader, thank you for reading this open letter. We encourage replies, and we will publish any responses we receive as commentary pieces in future issues of *JWC*. Please contact jwc@markallengroup.com for further details.