Dehydrated human amnion/chorion membrane to treat venous leg ulcers: a cost-effectiveness analysis

Objective: To evaluate the cost-effectiveness of dehydrated human amnion/chorion membrane (DHACM) in Medicare enrolees 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 enrolees 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 favour 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, DHACM FPFU was the dominant strategy compared to NAT, as it was cost-saving and generated a greater number of QALYs over three years from the US Medicare perspective. A companion VLU Medicare outcomes analysis revealed that patients who received AT with a cellular, acellular and matrix-like product (CAMP) compared to patients who received NAT had the best outcomes. Given the added clinical benefits to patients at lower cost, providers should recommend DHACM FPFU to patients with VLU who qualify. Decision-makers for public insurers (e.g., Medicare and Medicaid) and commercial payers should establish preferential formulary placement for reimbursement of DHACM to reduce budget impact and improve the long-term health of their patient populations dealing with these chronic wounds.

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CAMPs • cellular, acellular and matrix-like products • cost-effectiveness • dehydrated human amnion/chorion membrane • Medicaid • Medicare • venous leg ulcer • wound • wound care • wound dressing • wound healing

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Approximately 1–3% of total healthcare expenditures are devoted to hard-to-heal wounds in high-income countries, and these rates are likely to increase as the population ages.[1] In 2021, the US Medicare programme covered over 63.8 million lives, at a cost of $839 billion USD or 3.9% of the US gross domestic product (GDP), and is projected to increase to 6.5% of GDP by 2096.[2] Hard-to-heal or chronic wounds, defined as wounds which have failed to close by 40–50% after four weeks of good standard care,[3] affected about 10.5 million US Medicare beneficiaries in 2019 and cost projections for all wounds ranged from $22.5–67.0 billion USD.[4] In the US, it has been estimated that 500,000–600,000 people experience a venous leg ulcer (VLU) annually,[5] accounting for approximately 2% of total US healthcare costs.[6] A retrospective analysis highlighted Medicare spending for wound care per beneficiary with the principal diagnosis of VLU

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Table 1. Medicare is divided into four parts[2]

- **Part A:** covers hospital (inpatient, formally admitted only), skilled nursing (only after being formally admitted to a hospital for three days and not for custodial care), home healthcare and hospice services
- **Part B:** covers outpatient services, including some providers' services while inpatient at a hospital, outpatient hospital charges, most provider office visits, even if the office is 'in a hospital', durable medical equipment, and most professionally administered prescription drugs
- **Part C:** after enrolling in Parts A and B, Managed Medicare or Medicare Advantage gives choice of health plans with at least the same service coverage as Parts A and B (and most often more), with the benefits of Part D, and always an annual out-of-pocket expense limit which A and B lack
- **Part D:** covers mostly self-administered prescription drugs.

increased from a mean value of $1206 USD in 2014 to $1803 USD in 2019.[4] If medical resources and work absenteeism are taken into account, the annual US payor burden was estimated at $14.9 billion USD in 2014 for Medicare and private insurers, excluding generic payors.[7]

Payroll taxes, beneficiary premiums, surtaxes from beneficiaries, copayments, deductibles and general US Treasury revenue fund Medicare.[1] Revenue is used to create two funds:

1. The Hospital Insurance (HI) trust fund or Medicare Part A
2. The Supplementary Medical Insurance (SMI) trust fund or Medicare Parts B and D (Table 1).

The HI trust fund will likely be <90% funded beginning in 2028, as the ratio of working contributors to the programme relative to beneficiaries decreases from 4:1 in 2000 to about 2.5:1 in 2030.[2] The SMI trust fund is adequately financed for several decades because general revenues are reset annually.[2]

To maintain Medicare enrolee health, continued improvements in healthcare must be accompanied by policies that promote cost efficiency, economies of scale, cost-containment measures, or increases in taxes and fees. These issues are acutely evident in wound care, where new and innovative methods of wound care management have improved healthcare outcomes,[8,9] but which, in some instances, have resulted in steeply rising costs.[10]

Patients with VLUs often enter a cycle of infection and remission followed by recurrence.[11] Studies on patients with VLUs reveal significant variations in the duration of ulcers and recurrence rates.[12–14] When compression therapy, the consensus standard of care,[15] is provided in conjunction with surgical correction of superficial venous reflux, VLU recurrence rates decrease; however, trends in closure rates have not improved.[16,17] The Early Venous Reflux Ablation randomised controlled trials (RCT) conducted in the UK demonstrated greater VLU-free time for patients treated early with an endovenous intervention,[18,19] in addition to faster VLU closure. The study concluded that venous intervention is cost-effective in the long term.[18] A cost-effectiveness analysis of this RCT from the US Medicare perspective, comparing compression therapy to early endovenous ablation, found that early intervention was 90.8% likely at a threshold of $45,995 USD per quality-adjusted life year (QALY) over three years. Zheng et al.[20] concluded that payors should cover early ablation to prevent costly VLU complications and improve patient wellbeing. Unfortunately for patients, despite the favourable medical evidence, most providers do not follow parameters for use established for advanced therapy (AT), a situation which may be remedied with additional education.[21]

To address the economic impact of hard-to-heal wounds on the Medicare programme, cost-effective strategies for prevention, early intervention and effective wound care management are essential and need to be taken into consideration by policy decision-makers. Efforts on patient education on wound prevention and self-care,[20] the use of multidisciplinary wound care teams[22] and, ultimately, the continued promotion of evidence-based practices that improve wound closure while reducing use of healthcare resources and costs are ongoing goals among thought leaders in the field. The present study retrospectively examined the cost-effectiveness of using an AT with dehydrated human amnion/chorion membrane (DHACM) compared with no advanced therapy (NAT) among Medicare enrolees who developed a VLU.[11] Studies of Medicare enrolees suggest that when wounds fail to close in a timely fashion (40–50% by four weeks), only 9.8% of patients with a lower extremity diabetic ulcer[9,23] and 21% of patients with a VLU[19] receive an AT at weekly to biweekly intervals as consensus experts suggest.[24–26]

DHACM (EPIFIX, MiMedx Group, Inc., US) has been identified as the most widely applied AT among Medicare patients with VLUs[11] within the increasingly expanding selection of over 100 that are commercially available.[27] ATs, or high reimbursement skin substitutes, have recently been categorised in a peer-reviewed publication as cellular, acellular and matrix-like products (CAMPs).[24–26] DHACM allografts are immune-privileged, minimally manipulated, non-viable cellular human placental-derived tissue that provides a collagen scaffold to support the development of granulation tissue. In vitro[28–31] and in animal models,[31,32] DHACM has been shown to influence inflammation, cell proliferation, metalloproteinase activity and recruitment of stem cells, all of which play a role in the wound healing cascade.[31–33] Additionally, DHACM is known to contain >300 preserved regulatory factors, which, in utero, are essential to tissue generation.[29,31]

Closure rates of 50–60% when DHACM was an adjuvant for standard comprehensive VLU therapy with either intent-to-treat (p=0.0473) or per protocol (p=0.0128) calculations were demonstrated by two prospective RCTs.[34,35] At four weeks, wound area reductions were 63% for DHACM-treated cohorts combined with multilayer compression therapy versus 32% for multilayer compression therapy cohorts treated without DHACM (p=0.005).[36] The use of CAMPs in

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wounds that have stalled along the healing cascade is considered best practice among consensus experts as well as being supported by level one data.[24,25,35] Appropriate usage and integration of CAMPs into wound care practices have been shown to improve outcomes and reduce costs for Medicare patients with lower extremity diabetic ulcers.[9,23]

The Ontario Health Technology Assessment (OHTA)[37] found that adjunctive CAMP usage was more effective than standard care alone in hard-to-heal diabetic foot ulcers and VLUs. Additionally, patients were open to using CAMPs as a treatment option. However, within the parameter limits of the OHTA study, CAMPs were highly unlikely to be cost-effective compared with standard care for adults with VLUs. The OHTA used a three-state Markov model to evaluate cost-effectiveness,[37] and input parameters from only a single 128-patient intent-to-treat RCT with common inclusion/exclusion criteria.[35] Markov models are a mathematical stochastic process to predict possible health events in which the probability of each outcome depends only on the current state of the patient.

In contrast, the research presented in the present study builds upon the analysis of 530,220 Medicare enrolees with VLUs from 2015–2019, detailing their comorbidities, treatments, health outcomes and hospital use.[20] Patients with hard-to-heal VLUs, determined at 90 days and of any ulcer size and location below the knee, were evaluated over four years and labelled as 'chronic' in this article. Notably, patients with multiple comorbidities and other complications were included in a four-state Markov cost-effectiveness model. A complex VLU is one of the Markov states, and occurs when a patient develops an infection, leading to a health state of higher risk, cost and significance to patients, providers and payors. The model was developed from the US healthcare perspective and reflects real-world scenarios. The resulting economic analysis can be used by providers and payors participating in Medicare programmes or those with insured lives of comparable demographics to evaluate population applicability for coverage of CAMPs, specifically DHACM, compared with alternatives.

Methods

Ethical statement

The Medicare Limited Data Set (LDS) Files (1 October 2015–2 October 2019) were acquired under a Data Use Agreement (DUA) between the Center for Medicare and Medicaid Studies (CMS) and MiMedx Group, Inc. The Medicare LDS was previously collected, deidentified and available from CMS. LDS files do not contain specific direct identifiers as defined in the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. All analysis and reporting of Medicare data was performed in compliance with relevant laws and institutional guidelines approved by the CMS.

Table 2. Markov model health states (modified from Cheng et al.[48])

Health state	Description
Chronic or recurrent VLU	Patients receive treatment and have a chronic wound that is not initially infected. This health state has higher costs, higher hospital use and lower QoL than the healed state, but lower costs, lower hospital use and higher QoL than the complex state. This state subsumes previously closed wounds that remain unresolved and wounds that are no longer complex but require treatment and costs
Post-VLU (healed)	Patients no longer have an active wound. Patients in this health state have the lowest costs, lowest hospital use and highest QoL. Patients are susceptible to recurrent VLUs
Complex VLU	An unresolved VLU develops an infection. Patients in this health state have the highest costs, highest hospital use and lowest QoL. Added costs include hospitalisations, amputations, etc.
Death	Patients die related or unrelated to the VLU. There are no additional costs or benefits accrued

QoL—quality of life; VLU—venous leg ulcer

Retrospective cohort design and clinical definitions

This retrospective study design was developed as previously described.[8,19] ATs were high-cost CAMPs reported under Current Procedural Terminology (CPT) codes 15271–15278 and the applicable Healthcare Common Procedure Coding System (HCPCS) Q codes.[38] In this research, all DHACM applications were assumed to be FPFU, defined as the initiation of DHACM within 30–45 days of the first clinic visit or submitted claim date and, once started, DHACM was applied routinely within the range of every 7–14 days during the episode of care.[9,11,23] NAT referred to episodes treated without high- or low-cost CAMPs.[38] Clinical health states for the Markov model included chronic (hard-to-heal) or recurrent, complex, post-VLU, and death states (Table 2). A chronic VLU was defined as an ulcer that had not resolved within 90 days of the first claim. During this time, the patient received NAT, or if a VLU transitioned to AT, the VLU was also considered chronic. A complex VLU was defined as any chronic wound that developed an infection.

Cost-effectiveness analysis study design

We developed a Markov model from the US Medicare perspective to analyse the cost-effectiveness of DHACM FPFU in treating chronic VLUs in accordance with the Second Panel on Cost-Effectiveness in Health and Medicine.[39] The model compared DHACM FPFU to NAT in a Medicare cohort with chronic VLUs (that were currently uninfected). The model projected health outcomes over a three-year time horizon, using monthly cycles and roll-back periods at years one and two. Costs were adjusted to 2023 USD values, and clinical effectiveness was measured in units of QALYs. All parameters were discounted at 3% where appropriate. Results were reported using an incremental cost-effectiveness ratio (ICER), net monetary benefit (NMB) and one-year budget impact. The

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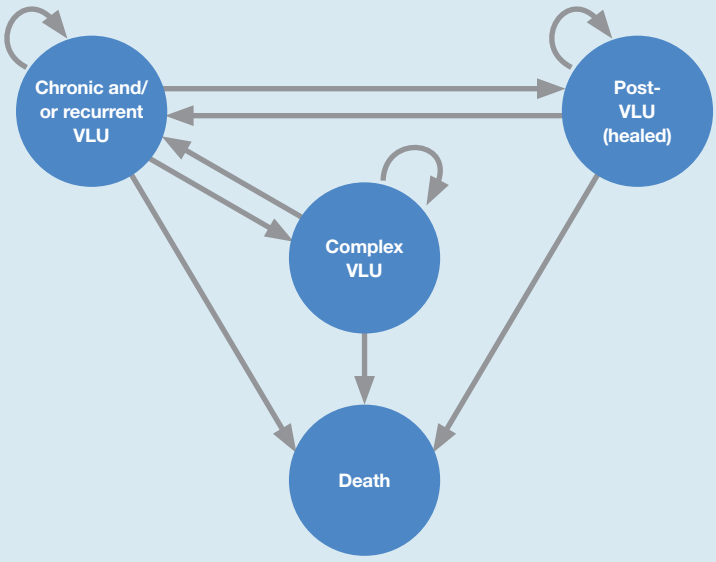
Fig 1. Markov model diagram. Four-state Markov model. Treatment arm 1: intervention with dehydrated human amnion/chorion membrane (DHACM) following parameters for use (FPFU) or treatment arm 2: no advanced therapy (NAT). Venous leg ulcers (VLUs) can remain chronic, become healed (Post-VLU), or develop complications (Complex VLU) after receiving treatment. Healed VLUs can remain healed or recur (Recurrent VLU). Complex VLUs can remain complex or return to chronic. All health states transition to death throughout the time horizon. Health states are defined in Table 2. Model parameters are provided in Table 3, and the outcomes of the Markov model are shown in Table 6



cost-effectiveness of DHACM FPFU was measured at a $100,000 USD/QALY willingness-to-pay (WTP) threshold. All modelling and analyses were conducted in 2023 using Microsoft Excel (Microsoft Inc., US).

Markov model structure

Medicare patients with a chronic uninfected VLU began the model in a chronic VLU health state (Fig 1). Patients were then treated with DHACM FPFU or NAT. Following treatment, VLUs either healed (Post-VLU), developed complications (Complex VLU), or remained unhealed. Individuals with healed VLUs either remained healed or regressed into a recurrent VLU (Recurrent VLU). Patients with complex VLUs either had their complications resolved and returned to a chronic VLU or transitioned to death. Recurrent VLUs followed the transition pathways of the original chronic VLU. Patients could transition to death from any health state.

Clinical inputs and transition probabilities

The initial transition probabilities from chronic VLUs were derived from a Medicare retrospective claims analysis.[11] The Medicare analysis provided complication rates, healing rates, and time to complication and healing (in days) for the DHACM FPFU and NAT arms (Table 3). These parameters were transformed into monthly transition probabilities. VLU recurrence and background mortality rates were derived from peer-reviewed literature and national databases.[40,41] Based on clinical opinion, the recurrence and mortality rates did not differ across treatment arms.

Costs

Monthly, health-state-specific costs were calculated by treatment arm. The Medicare analysis informed healthcare resource use and costs for inpatient admissions, readmissions, emergency department (ED) visits, outpatient observations, intensive care unit (ICU) stays, and amputations during treatment for a chronic, recurrent and complicated VLU (Table 3). The costs of DHACM treatment were calculated from 37,619 VLU episodes (34,698 patients), encompassing 166,227 outpatient claims that did not include any confounding ED visit, ICU or amputation charges. Other cost components of VLU chronic, recurrent and complicated care, such as home health visits, compression therapy and analgesics, were unavailable in the Medicare analysis and were derived from the literature.[20] AT costs were only applied to the DHACM FPFU arm. Recurrent VLUs were assumed to have the same treatment cost in both arms.

Health utility

Health utility weights, which measure effects on health, with a value between 0 (death) and 1 (perfect health), were used to estimate the quality of life (QoL) in each health state and were summed to calculate QALYs across the time horizon. A single QALY was equal to a year of perfect health. All utility weights were derived from the literature (Table 3). The baseline score for a healed skin ulcer was derived from a health-related QoL study on VLUs.[42] Baseline scores for chronic skin ulcers, venous insufficiency and additional conditions were estimated from a publication that used the US Medical Expenditure Panel Survey.[43] Patients in the chronic VLU health state were assumed to have venous insufficiency along with their chronic skin ulcer. The disutility associated with additional conditions was applied to individuals in the complex VLU health state. Patients with healed VLUs were assumed to have the baseline score, and those with recurrent VLUs were considered to have the same utility score as those with the original chronic VLU.

Sensitivity analyses

Univariate and probabilistic sensitivity analyses (PSA) were conducted to test the uncertainty of the base case results for the three-year time horizon. The univariate sensitivity analysis individually adjusted each base case parameter to an upper and lower bound value, while all other parameters were constant. The upper and lower bounds were based on reported standard error (SE) and a chosen statistical distribution.

For the PSA, all variables (both cost and QALYs) were simultaneously varied based on their point estimate, a measure of uncertainty and statistical distribution. The PSA was conducted over 10,000 Monte Carlo simulations. An assumed SE of ±10% of the base-case

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Table 3. Model parameters

Parameter	Base case	Lower bound	Upper bound	Distribution	Source
Clinical					
DHACM					
Time from chronic to healing, months, 75th percentile	3.25	3.14	3.37	Gamma	11
Chronic to complex percentage	15.83	12.85	19.05	Beta	11
Time from chronic to complex, months	3.20	3.04	3.36	Gamma	11
Time from chronic after complex to healed, months, 75th percentile	4.12	3.93	4.32	Gamma	11
NAT					
Time from chronic to healing, months, 75th percentile	5.52	5.38	5.67	Gamma	11
Chronic to complex percentage	19.84	16.09	23.86	Beta	11
Time from chronic to complex, months	5.18	4.98	5.38	Gamma	11
Time from chronic after complex to healed, months, 75th percentile	6.48	6.26	6.70	Gamma	11
Treatment independent					
Chronic to death percentage	2.15	1.75	2.59	Beta	41
History of ulcer, hazard ratio	1.47	1.20	1.77	Gamma	44
Costs and healthcare use					
DHACM use – chronic					
Treatments, n	4.80	4.63	4.97	Gamma	11
OP visits, n	12.64	11.86	13.44	Gamma	11
OP observations, n	0.03	0.03	0.03	Gamma	11
Average length of treatment, months	2.71	2.56	2.87	Gamma	11
NAT use – chronic					
Treatments, n	0.00	-	-	-	11
OP visits, n	16.39	15.25	17.56	Gamma	11
OP observations, n	0.05	0.05	0.06	Gamma	11
Average length of treatment, months	2.81	2.61	3.02	Gamma	11
Treatment independent use – chronic					
Home health visits, n	1.00	-	-	-	18
Amitriptyline usage (rate), %	40.00	-	-	-	18
Gabapentin usage (rate), %	10.00	-	-	-	18
Hydrocodone usage (rate), %	5.00	-	-	-	18
DHACM use – complex					
IP admission, days	8.44	7.83	9.08	Gamma	11
Readmission, days	2.99	2.75	3.25	Gamma	11
ICU, days	2.38	2.20	2.56	Gamma	11
Readmission ICU, days	0.96	0.88	1.05	Gamma	11
ED visits, n	1.70	1.50	1.93	Gamma	11
OP amputations, n	0.02	0.01	0.02	Gamma	11
IP amputations, n	0.05	0.04	0.06	Gamma	11

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Table 3. Model parameters (continued)

Parameter	Base case	Lower bound	Upper bound	Distribution	Source
Clinical					
NAT use – complex					
IP admission, days	11.65	10.62	12.71	Gamma	11
Readmission, days	4.53	4.11	4.97	Gamma	11
ICU, days	4.00	3.64	4.37	Gamma	11
Readmission ICU, days	0.98	0.91	1.05	Gamma	11
ED visits, n	1.48	1.37	1.60	Gamma	11
OP amputations, n	0.05	0.04	0.06	Gamma	11
IP amputations, n	0.08	0.07	0.10	Gamma	11
Utilisation costs (2023 USD)					
DHACM treatment	1700	1620	1782	Gamma	This work
OP visits	236	206	267	Gamma	11
OP observations	2034	1892	2180	Gamma	11
Home health visits	2979	2454	3554	Gamma	20
Amitriptyline	5.99	4.88	7.22	Gamma	45
Gabapentin	1.77	1.44	2.13	Gamma	45
Hydrocodone	2.26	1.84	2.72	Gamma	45
IP admissions days	1779	1664	1898	Gamma	11
Readmission days	1605	1420	1801	Gamma	11
ICU days	2054	1807	2316	Gamma	11
Readmission ICU days	1854	1478	2272	Gamma	11
ED visits	509	480	538	Gamma	11
OP amputations	2113	1687	2585	Gamma	11
IP amputations	22,742	18,553	27,352	Gamma	11
Compression therapy	76	63	91	Gamma	11
Health utilities					
Healed skin ulcer (utility)	0.7500	0.7444	0.7556	Beta	42
Chronic skin ulcer (utility)	0.6940	0.5503	0.8206	Beta	43
Venous insufficiency (disutility)	0.0380	0.0376	0.0384	Beta	43
2nd chronic condition (disutility)	0.0942	0.0940	0.0944	Beta	43

DHACM—dehydrated human amnion/chorion membrane; ED—emergency department; ICU—intensive care unit; IP—inpatient; NAT—no advanced treatment; OP—outpatient; USD—US dollars; VLU—venous leg ulcer

estimate was used for parameters without a reported SE or other measure of uncertainty. Parameters reported in percentages and utility scores (i.e., $0<x<1$) followed a Beta distribution, while all other parameters (i.e., $0<x<\infty$) followed a Gamma distribution.

A threshold analysis was conducted for three variables based on the model's relative sensitivity to each. The 12-month recurrence rate (the same for each arm), DHACM FPFU complication rate and NAT complication rate were adjusted to the point that they provided a value that yielded an NMB of $0 USD.

Budget impact analysis

Compared to NAT, a hypothetical one-million-member health plan was used to assess the one-year budget impact of treating patients with a hard-to-heal

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Fig 2. Hospital use increases when patients have a complex venous leg ulcer (VLU). Comparisons of episodes with a VLU (blue bars) or complex VLU (red bars) treated with DHACM FPFU (light colours) or NAT (dark colours) were tracked for their use of hospital resources (readmissions, ICU stays, admissions and ED visits). Significance was observed when comparing all DHACM FPFU (light bars) to all NAT (dark bars) for readmissions (p=0.03575), ICU stays (p=0.00062), admissions (p=0.00001), or ED visits (p=0.00036). DHACM—dehydrated human amnion/chorion membrane; ED—emergency department; FPFU—following parameters for use; ICU—intensive care unit; NAT—no advanced treatment

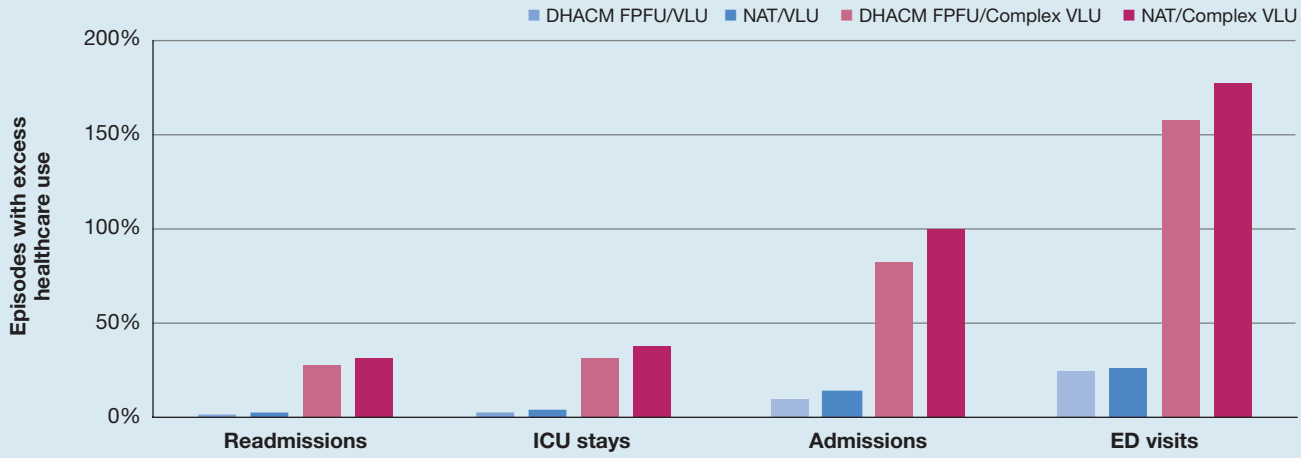
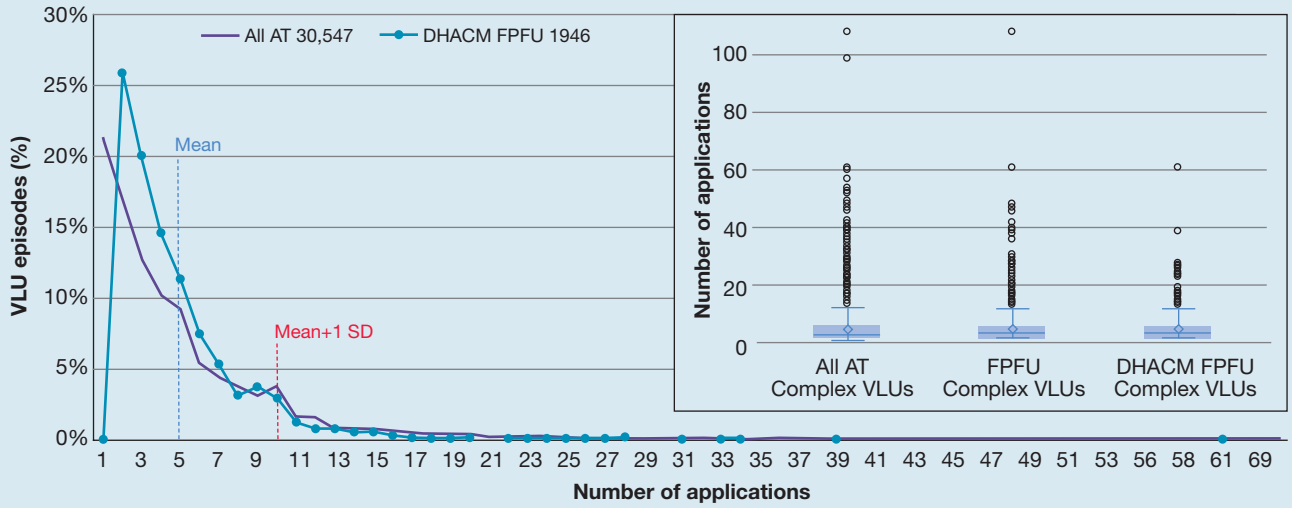


Fig 3. The number of AT applications required for claim closure (horizontal axis) versus the percentage of 2015–2019 Medicare episodes with a venous leg ulcer (VLU, vertical axis). All AT applications (purple line, 30,547 episodes) and enrolees receiving dehydrated amnion/chorion membrane applied following parameters for use (DHACM FPFU, blue line, 1946 episodes) were plotted. The mean CAMPs applications for all VLUs (dotted blue line, (area under the curve is 65% of the population)), plus one standard deviation (dotted red line, (area under the curve is 86% of the population)) are shown. Insert graph is the subset of complex VLU cohorts as box and whisker plots. DHACM—dehydrated human amnion/chorion membrane; FPFU—following parameters for use



(chronic) VLU with DHACM FPFU. The incidence rate of VLUs was estimated to be 251/100,000 patients annually, of which 30% become chronic. The market share of DHACM was calculated to be 28.6%, all based on the Medicare analysis. The treatment cost difference per patient was calculated over the first year and multiplied by the risk pool to determine the overall cost difference for all at-risk patients. The year-one cost difference per covered member and per member per month (PMPM) was then calculated.

Results

Cohorts were evaluated for the frequency of comorbidities in the chronic and complex health states (Table 4). Notably, all of the top comorbidities increased in the complex VLU state. The symptom frequency of pain increased more than threefold (9.5% to 31.9%). The overall Charlson Comorbidity Index score (CCI, a 10-year mortality prediction for a patient based on their comorbidities)[46] between the chronic and complex health states increased by 29% (+0.6 CCI) for patients

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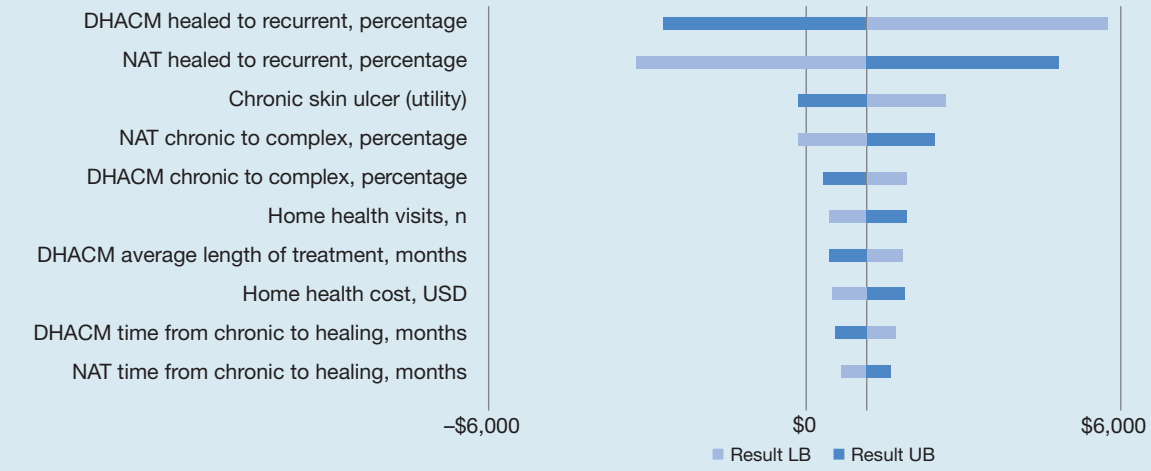
Fig 4. Tornado diagram: univariate sensitivity results. Three-year net monetary benefit (NMB). The threshold analysis identified the break-even values (where the NMB=$0) for the following parameters: 12-month VLU recurrence rate (78.17%), NAT complication rate (16.37%) and DHACM complication rate (20.41%). DHACM—dehydrated human amnion/chorion membrane; NAT—no advanced therapy; USD—US dollars; LB—lower bound; UB—upper bound



receiving NAT, while patients receiving DHACM FPFU had an increase in their CCI score of 68% (+1.3 CCI).

Hospital resource usage increased by 6–10-fold in the complex VLU state compared to chronic VLUs without an infection. The use of DHACM FPFU demonstrated further reductions in hospital use in relation to NAT. Hospital use (readmissions, ICU stays, admissions and ED visits) was observed to add to the cost of a complex VLU.

Across the 30,547 episodes that received a CAMP in this study, a mean of 4.98±5.16 applications were required per completed claim (Fig 3, Table 5). The majority of episodes (n=23,486) were chronic VLUs with a slightly lower mean. However, the mean rose to 6.65±6.8 applications for those with a complex VLU (n=7061). Complex VLUs comprised 23% of the ulcers studied, requiring a statistically significant 2.2 further applications on average ($p<0.0001$, Table 5). Graphing the number of AT applications for the studied cohorts and those with complex VLUs revealed differential distributions (Fig 3).

Cost-effectiveness analysis base-case results

Over the three-year time horizon, DHACM FPFU was dominant over NAT, providing an additional 0.010 QALYs, while saving $170 USD per patient. The dominant result suggests that DHACM FPFU would be cost-effective compared to NAT in treating chronic VLUs at any WTP threshold over a three-year time horizon. The NMB at a $100,000 USD/QALY WTP threshold was $1178 USD (Table 6).

The advantage of DHACM FPFU over NAT increased throughout the time horizon. Over a one-year time horizon, DHACM FPFU was cost-effective compared to NAT before becoming dominant over the two- and three-year time horizons. The individual breakdown by time horizon is provided in Table 6.

Sensitivity analyses

The univariate sensitivity analysis identified only four scenarios in which DHACM FPFU would not be cost-effective compared to NAT at a $100,000 USD/QALY WTP threshold over a three-year time horizon. The most sensitive parameters were the VLU recurrence rates for DHACM and NAT, the utility score for a chronic skin ulcer, and the NAT complication rate (Fig 4).

Compared to NAT, over the three-year time horizon, the PSA estimated that DHACM FPFU had a 48.26% likelihood of being dominant and a 63.01% likelihood of cost-effectiveness at a $100,000 USD/QALY WTP threshold. DHACM FPFU had a >50% likelihood of cost-effectiveness at any WTP threshold (Figs 5, 6).

Budget impact results

The one-year budget impact of DHACM FPFU represented a <1 cent increase in PMPM spending in a hypothetical one-million-member plan. The $0.008 USD PMPM increase in spending represents a low barrier to treatment (Table 6). These results were estimated assuming 2510 patients of the one-million-member plan had a chronic VLU, of which 28.6% were treated with DHACM FPFU.

Discussion

This study addressed the cost-effectiveness of DHACM as an early treatment for patients with a VLU. Previous analysis of 854,266 VLU episodes demonstrated that using a CAMP reduces the time to VLU closure, results in fewer complications and decreases hospital usage.[11] When a CAMP, such as DHACM, was applied according to parameters for use, it provided the best outcomes.[11] This analysis determined that DHACM FPFU was a dominant treatment over NAT over a three-year time horizon. The upfront cost of DHACM FPFU for VLUs was offset by the significant reductions in hospital use,

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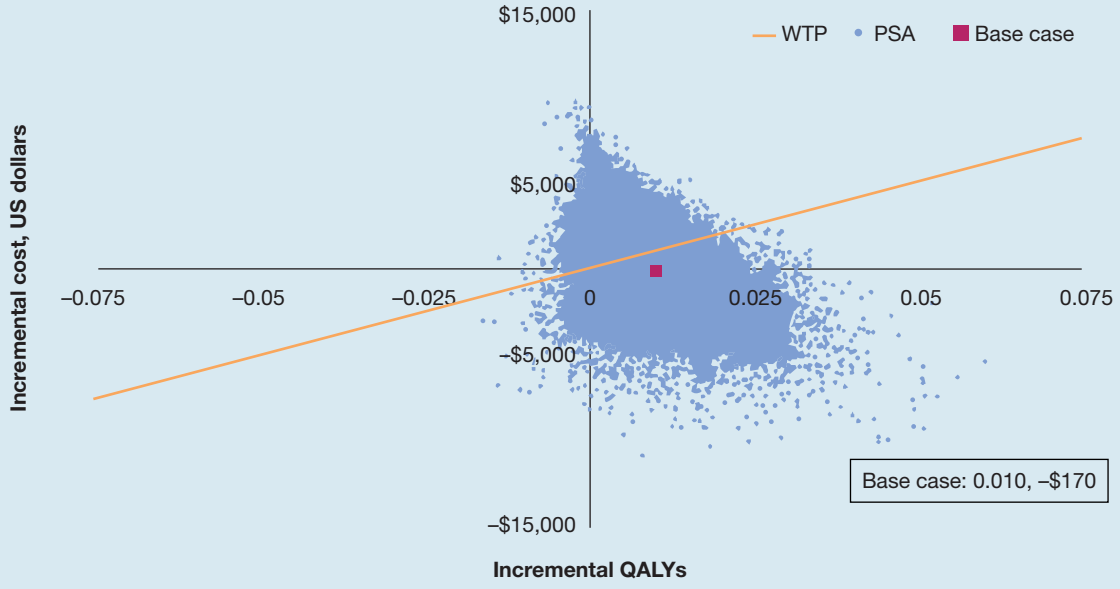
Fig 5. Probabilistic sensitivity analysis. Results: three-year scatterplot. WTP—willingness to pay; PSA—probabilistic sensitivity analysis; QALYs—quality-adjusted life years



infections, and improved patient QALYs over a three-year period from the Medicare perspective. The PSA highlights the robustness of these results.

Several cost-effectiveness models have been used to analyse patients with a VLU in the last 10 years, from the perspective of Europe,[47,48] Australia[49] and the US,[20,50,51] each of which found that intervention was cost-neutral-to-dominant. Studies supportive of intervention treatments analysed hydration response technology dressings,[47] single-use negative pressure wound therapy (NPWT) or traditional NPWT,[51] use of an antimicrobial wound dressing,[48] guideline-based use of compression therapy,[49] early endovenous ablation with compression therapy[18] and adjunctive use of CAMPs.[50] Most of the Markov models had three states, while, interestingly, guideline-based use of compression therapy required a five-health-state model to account for the high recurrence rate of VLUs and the excess costs of hospitalisations.[49] A review of the complex nature of patients with chronic venous insufficiency (CVI)[11] supports the concept that guidelines can stratify patients for intervention or best treatment modality upon the development of a VLU.

The two studies that examined adjunctive use of skin substitutes or CAMPs[37,50] used three-health-state Markov models and developed their data from four published studies[35,52–55] and a UK trial, which collectively enrolled approximately 1000 people across several countries after a run-in period of 14 days and typically strict run-in criteria, which included wound size.[37,50] Our model was informed by 530,220 Medicare patients with a VLU followed for four years. Study criteria included all VLU sizes below the knee and a broader range of comorbidities, providing direct relevancy of transition rates and cost efficiency to Medicare enrolees.

Running prospective studies with >500,000 patients,

Table 4. Percentage of comorbidities within study group episodes

	NAT		DHACM FPFU	
Patients	1558	386	1607	307
Episodes	1560	386	1638	308
Comorbidity/symptom	**VLU**	**Complex VLU**	**VLU**	**Complex VLU**
Venous insufficiency	100.0%	100.0%	100.0%	100.0%
Deep vein thrombosis	74.7%	81.6%	79.1%	85.1%
Hypertension	46.3%	77.7%	49.6%	77.3%
Diabetes	37.8%	52.6%	38.6%	53.6%
Varicose veins, oedema	32.9%	45.6%	37.8%	42.9%
Peripheral vascular disease	26.8%	52.1%	23.4%	53.9%
VLU Inflammation	20.6%	25.4%	21.2%	23.4%
Neuropathy	14.7%	37.3%	15.7%	42.9%
Lymphoedema	14.2%	26.9%	9.4%	23.1%
Renal insufficiency	12.9%	33.7%	10.4%	36.4%
Polyneuropathy	10.3%	26.9%	11.3%	31.5%
Pain	9.5%	31.9%	11.1%	25.6%
Atherosclerosis	8.9%	23.6%	7.9%	23.4%
Charlson Comorbidity Index	2.1	2.7	1.9	3.2

DHACM—dehydrated amnion/chorion membrane; NAT—no advanced therapy; VLU—venous leg ulcer

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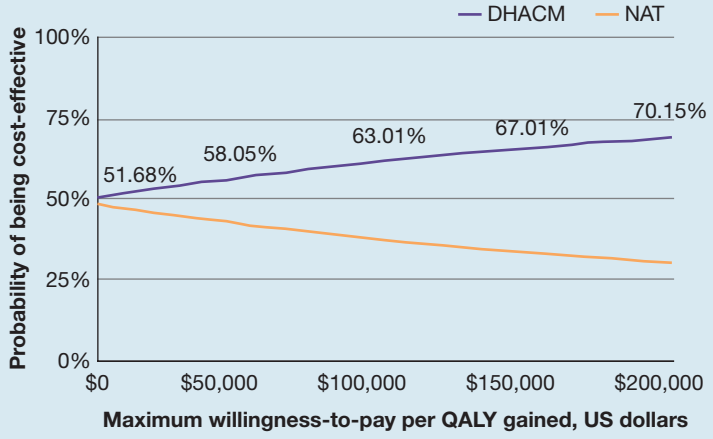
Table 5. Number of CAMP applications in VLU cohorts

		Cost-effectiveness results (per patient)							
	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; VLU—venous leg ulcer; SD—standard deviation

Fig 6. Cost-effectiveness acceptability curve. Likelihood of DHACM cost-effectiveness at different willingness to pay thresholds. DHACM—dehydrated human amnion/chorion membrane; NAT—no advanced therapy; QALY—quality-adjusted life years



with extended run-in, treatment and follow-up periods, is prohibitively expensive. This work highlights the value of extensive retrospective studies to identify population trends, generate data-backed hypotheses, and propose evidence-based best practices for achieving cost-efficient, positive patient outcomes in a resource-constrained system. The current study also supports previous work that suggests that most patients will benefit from early intervention in cases of a VLU,[20,47–49,51] using several other treatments and specifically with a CAMP, such as DHACM.[11,50]

Patients with CVI typically have multiple comorbidities, which complicate their treatment course. In this study, patients with a complex VLU treated with NAT had lower CCI scores than their DHACM FPFU counterparts (Table 4), yet still had worse outcomes. The Complex VLU state results in up to tenfold increases in hospital use compared to chronic VLU episodes from the NAT cohort (Fig 2), leading to cost increases, which will be the focus of future work. A 2.5-fold cost increase was calculated by comparing all chronic VLU episodes to the DHACM FPFU cohort. The benefits of treating patients with DHACM FPFU were observed across several outcomes (Fig 2). Other subgroup analyses, such as dual enrolee patients with Medicaid, saw substantial improvements and will be evaluated in future research.

Each patient may benefit from various prophylactic treatments (e.g., compression stockings, venous ablation). However, as long as a chronic ulcer remains open, infections increase hospital visits and potentially life-threatening complications. Of patients treated with DHACM, 24% use the ED (Fig 2), but this number rose to >175% when patients developed an infection and received NAT. A prospective RCT published in 2024 on patients in Asia concluded that closure of a VLU was vital to improving patient QoL and reducing costs. Patients with an open VLU at the six-month follow-up had costs that were 162% higher than those with a closed ulcer.[56] Shortening the time to ulcer closure and reducing recurrence rates are essential to ending the cycle and reducing healthcare expenditures.

We note that of the 530,220 patients with a VLU during 2015–2019, only those who transitioned to DHACM FPFU or whose VLUs were labelled as chronic entered the model. Indeed, 28% of all enrolees still had an open wound after six months. Previous models were not based on studies that evaluated patients with wounds of such duration or multimorbid state. Yet, they make up three to nearly four of every 10 Medicare enrolees with a VLU. We anticipate this model to be relevant to populations of similar demographics within the US.

Medicare spends >$1.0 billion USD per year on the management of chronic VLUs.[4,57] The findings of this current study suggest that funds could be conserved if early interventional procedures, such as DHACM, were

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initiated at four weeks for all enrolees with a VLU which failed to close by 40%, and applied routinely thereafter until ulcer closure. Additionally, patients prone to infections or other complexities will likely achieve ulcer closure 14.3 days sooner when receiving DHACM FPFU.[20] When ulcers close in faster timelines,[34–36] patients avoid many VLU complications, opportunities for infection are reduced, and costly hospital use avoided[11] (Fig 2). When physicians effect the transition of Medicare enrolees with either a chronic VLU or those identified as having a complex VLU to DHACM FPFU, the NMB in the first year is positive at a WTP of $100,000 USD (Table 6). This current work provides patients, practitioners and payors with real-world insight into strategies to close VLUs, including a robust monetary incentive to invest upfront in patient health.

Another study[4] of Medicare patients with hard-to-heal wounds found that VLUs were the third most costly hard-to-heal wound per beneficiary, behind surgical wounds and pressure ulcers. Furthermore, while their research shows an overall decrease in hard-to-heal wound-related costs, expenditures for VLUs significantly increased from 2014–2019,[4] emphasising the importance of reducing costs while improving outcomes for patients with VLUs. While the specific reasons for the rise in VLU costs are unknown, contributing factors driving overall wound care costs down are hypothesised to include CMS prior authorisation programmes for non-emergent indications;[58] proposed changes in the payment of CAMPs which reduce access for patients with larger wounds;[59] and limitations to Medicare Advantage contracts for hospital facility fees. In general, CMS is driving the transition of healthcare from fee-for-service, which incentivises quantity of care, towards incentivising quality and cost-effective care.[60]

Value-based reimbursement strategies have been previously proposed,[61,62] and implemented by Medicare for chronic conditions, such as cardiovascular disease[63] and cancer.[64,65] Medicare should work with health systems to appropriately increase reimbursement rates or incentives for early intervention in chronic wounds, such as VLUs. Again, the Medicare data evaluated in this study indicate that DHACM FPFU provides a cost-effective solution for improving patient lives while reducing costs to Medicare.

Another take-home message highlighted by this analysis is that the number of applications per episode can vary considerably (Fig 3, Table 5), likely influenced by patient comorbidities, wound features and socioeconomic factors. Even the 23% of VLUs that were complex and treated with DHACM FPFU in this study provided cost-effective results. Fig 3 highlights an inflection point in the application distribution (dotted red line) where evaluating whether a patient is responsive to additional treatment may be prudent. While complex VLUs may require a greater number of applications to reach closure, this population would otherwise have very high hospital use (Fig 2) and subsequent costs. It is anticipated that early closure of a VLU reduces infections and subsequent hospital use, and powers the cost-effectiveness of DHACM FPFU.

Table 6. Cost-effectiveness and budget impact results

Cost-effectiveness results (per patient)	Year 1	Years 1–2 cumulative	Years 1–3 cumulative
Cost of DHACM, $USD	31,338	44,279	56,595
Cost of NAT, $USD	30,872	44,418	56,764
Cost difference, $USD	466	–139	–170
QALYs of DHACM	0.708	1.395	2.048
QALYS of NAT	0.699	1.385	2.038
QALYs difference	0.009	0.010	0.010
ICER ($/QALY)	51,059	Dominant	Dominant
NMB at $100,000/QALY WTP threshold, $USD	446	1142	1178
Budget impact for one million members in year one, $USD			
Cost difference for 753 people at risk			100,268
Cost difference per one-million-member health plan			0.10
Difference per member per month			0.008

DHACM—dehydrated amnion/chorion membrane; ICER—incremental cost-effectiveness ratio; NAT—no advanced therapy; NMB—net monetary benefit; QALY—quality adjusted life year; WTP—willingness to pay. Model assumes 0.251% incidence of venous leg ulcers of which 30% become chronic and a 28.6% market share of DHACM; all calculations have been rounded to the nearest second or third place

As the ratio of working contributors to Medicare beneficiaries decreases to about 2.5:1 in 2030,[2] there will be an increasing need to enact policies that promote cost efficiency. Health systems that implement early and regular intervention will need to be appropriately incentivised by Medicare payments for performance measures to be sustainable. Anticipated savings of over $81,000 USD per million enrolees when DHACM is applied FPFU exemplifies an opportunity for Medicare to reduce costs and improve outcomes (Table 6). Standards are still developing within the wound care field, and evidence-driven quality metrics have been published.[66] It should be expected that there will be upfront costs for treatments such as DHACM. Nevertheless, payors and providers should support programmes that incentivise early intervention when it averts the more considerable downstream chronic wound care costs and improves patient health.

Limitations

This study has several limitations. First, the work is based on retrospective analysis of claims data, and caution in assigning causality from retrospective data

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is warranted. The authors anticipate the lowest fidelity on qualitative data (e.g., subjective claim notations, such as pain or inflammation), and higher certitude on quantitative data (number of patients, VLUs, DHACM applications, etc.). The uncertainty of model assumptions was captured in sensitivity analyses (Figs 3, 4).

The economic model developed for this work did not control for variability in the population of patients with VLUs, of which there are many sociodemographic causes. The demographics of Medicare patients with VLUs in this study were quantified.[11] However, the model does not provide a mechanism to address patients predisposed to health disparities, who have access issues due to a rural geography, or have other challenges in accessing specialty care for VLUs, all of whom may have less predictable outcomes.[67] The intended effort of future research is to elucidate the socioeconomic variables of Medicare recipients.

Conclusion

DHACM FPFU, in this economic evaluation, is a cost-effective alternative to NAT for Medicare patients with a complex VLU. Medicare should update its reimbursement strategies to incentivise the deployment of AT in timely and routine applications, thus allowing providers to follow evidence-based best practices related to CAMP use more readily. Most patients will see benefits, but patients with a VLU at risk for complications should be eligible early in the treatment process. Establishing such policies would lower the elevated costs of healthcare use for those with chronic wounds while favourably impacting clinical outcomes for patients who currently face the arduous cycle of VLU formation, closure and recurrence. JWC

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Reflective questions

- What factors contribute to the cost of a venous leg ulcer (VLU)?
- Why are infections a challenging complication for patients with a VLU?
- Why might early intervention in the case of a VLU be warranted?
- How might dehydrated human amnion/chorion membrane (DHACM) applied following parameters for use be cost-effective in the first year?
- At what willingness-to-pay threshold do DHACM savings become cost-effective? Why?

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