

# Placental Allograft Reconstruction of Cutaneous Wounds Following Mohs Surgery: A Propensity Score-Matched Comparative Cost-Effectiveness Analysis

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## ABSTRACT

**Background:** The purpose of this study was to examine the cost-effectiveness of placental allograft as a nonoperative surrogate to autologous tissue-based methods of defect reconstruction on the face, head, and dorsal hand following Mohs micrographic surgery (MMS).

**Methods:** This study was a 5-year retrospective, analysis comparing propensity-matched cohorts of eligible Mohs surgery patients treated with a placental allograft (dHACM, dehydrated human amnion/chorion membrane) vs autologous tissue-based repairs. Costs on day 0 through discharge were used for a cost-effectiveness analysis (CEA) and an incremental cost-effectiveness ratio (ICER).

**Results:** Four-hundred-twenty-nine propensity-matched patients meeting the entry/exclusion criteria were divided into treatment (dHACM) and Standard of Care (SOC) cohorts in a 1:2 match. The study population was 78.8% male, with a mean age of  $77.8 \pm 9.3$  years. The primary reconstruction cost increased with dHACM ( $P < .0001$ ), while the cumulative cost of care was similar between groups ( $P > 0.05$ ). MMS defects treated with dHACM had significantly lower rates of adverse post-repair sequelae; infection ( $P = 0.0114$ ), dehiscence ( $P = 0.0189$ ), necrosis ( $P = 0.0349$ ), hematoma ( $P = 0.0066$ ) and scar revisions ( $P = 0.0044$ ), resulting in an average savings of \$409.55 for high-risk post-MMS defects and a dominant ICER.

**Conclusion:** In subjects meeting the entry/exclusion criteria, closure of post-MMS defects with dHACM resulted in significantly lower rates of adverse post-repair sequelae (2.8% vs 21.3%,  $P < .0001$ ), which offset the upfront cost of dHACM, resulting in shorter lengths of care and favorable cosmetic outcomes. dHACM may be a cost-effective approach for surgical wounds in select patient populations.

*J Drugs Dermatol.* 2025;24(5):450-456. doi:10.36849/JDD.8436

## INTRODUCTION

Basal and squamous cell carcinomas are the most common cancers in the United States with an alarming 80% increase in recent years.<sup>1,2</sup> This is likely to increase as the population ages.<sup>3</sup> Mohs micrographic surgery (MMS), known for its low recurrence rates, is among the preferred techniques for resecting these skin tumors when complex, large, or recurrent.<sup>4</sup> The subsequent cutaneous reconstruction plays a pivotal role in restoring form, function, and quality of life for patients post-MMS.<sup>5</sup> The impact of altered appearance or reduced function or well-being underscores the importance of effective interventions.<sup>6</sup> In anatomical sites with elevated

cosmetic and functional risk (such as the face, scalp, hands, and feet), innovative approaches are essential.<sup>7,8</sup> For elderly patients who are not suitable surgical candidates for autologous flaps, skin grafts, or second-intent healing is contraindicated, nonoperative techniques such as placental allografts, have emerged as a promising solution<sup>9</sup> that improve cosmesis and preserve functional ability.<sup>10</sup> Allografts promote dermal reconstruction and have demonstrated positive outcomes in various scenarios, including randomized controlled trials for hard-to-heal wounds,<sup>11-15</sup> pediatric burns,<sup>16</sup> and post-MMS defects.<sup>17</sup> However, concerns regarding overall costs have hindered their widespread adoption.<sup>18,19</sup>

A cost-effectiveness analysis (CEA) was conducted to compare placental allografts with autologous tissue-based methods for defect reconstruction following MMS.<sup>20</sup> This study aimed to assess both the monetary and non-monetary variables that affect the value of placental allografts as a treatment option in dermatologic surgery.

## MATERIALS AND METHODS

### Study Design

This retrospective comparative cohort study evaluated the outcomes of two methods of primary Mohs defect reconstruction, placental allograft vs autologous tissue-based repair. Specifically, it compared the average cost and effectiveness between dehydrated human amnion/chorion membrane (dHACM) (EpiFix®; MIMEDX Group Inc., Marietta, GA) to skin flaps and autologous skin grafts. This analysis focused on defects with Mohs Appropriate Use Score  $\geq 7$  that could not be closed primarily or second-intention healing not appropriate. Lower-risk defects were excluded, as were cases receiving primary closure, delayed closure, or no repair.

Administrative practice databases were queried for patients undergoing Mohs surgery with same-day reconstruction between 2014 to 2018.<sup>17</sup> Deidentified cost and outcome data related to the index reconstruction were gathered from electronic medical records (ModMed Dermatology, Modernizing Medicine®, Boca Raton, FL) linked to automated charge captures. This study assumed the analytic perspective of the healthcare provider to calculate cumulative cost according to allowable fee schedules and excluded subject costs such as medications and co-pays. Ethical approval and waiver of informed consent for protocol AFSUR008.2; Pro00031033 was obtained from Advarra IRB, Columbia, MD.

### Outcome Measures

A cost analysis of patient care postoperative day 0 through discharge, was performed for all subjects. The primary endpoint was the cost difference between dHACM and Standard of Care (SOC) for initial reconstruction, post-repair sequelae, and cumulative cost of care. Cost profiles were verified using Current Procedural Terminology (CPT®) codes from provider documentation. Patient encounters were audited for clinical event charges prior to determining the final cost estimates. Ancillary procedures (eg, hematoma evacuation, wound debridement, scar excision, laser, dermabrasion, corticosteroid injection, and additional reconstruction) were included in cost calculations. All monetary values were reported in US dollars (\$), inflation-adjusted to 2024 using the US Consumer Price Index (CPI).<sup>21</sup>

Intervention effectiveness was defined as the proportion of patients without any adverse post-repair sequelae in this study. These events included bleeding, wound infection,

wound dehiscence, hematoma, flap or graft necrosis, graft loss, outside referral, donor site infection, persistent wound or scar erythema, distortion of surrounding tissue, and widened, hypertrophic, or keloid scarring. A subgroup analysis focused on specific complications; the total incidence of wound infection, hematoma, and flap or graft necrosis. Clinical documentation and ICD-10-CM coding (International Classification of Diseases, Tenth Revision, Clinical Modification) were used to investigate these metrics. The incremental cost-effectiveness ratio (ICER) was calculated as a measure of intervention effectiveness value,  $ICER = (Average\ cost_A - Average\ cost_B) / (Effectiveness_A - Effectiveness_B)$ , where A and B represent dHACM vs SOC interventions, respectively.

### Propensity Score Methods

A propensity-score-matching model was constructed to ensure covariate balance before making statistical comparisons. The dependent variable was the method of reconstruction, placental allograft vs autologous tissue. Potential confounders (covariates) included patient demographics (age, sex, and functional status), comorbidities, Charlson Comorbidity Index (CCI) score, smoking status, tumor characteristics, number of extirpative stages performed, surgery time (minutes), and defect size (cm<sup>2</sup>). To mitigate confounding by time biases, the placental allograft initiation date was used to delineate historical and contemporary controls (before vs on or after 01 January 2017) from within the 5-year control arm continuum. Propensity scores were estimated using binary logistic regression and a greedy nearest-neighbor-matching algorithm without replacements. This strategy matched a placental allograft subject to an autologous tissue control (both historical and contemporaneous) with the nearest propensity score, yielding a case-control ratio of 1:2 without sacrificing precision.

### Statistical Analysis

Continuous variable comparisons were evaluated using independent samples Student's *t*-test or Mann-Whitney *U* test, depending on distribution of data. Pearson's  $\chi^2$  test or Fisher's Exact test were used to compare categorical variables between groups and to assess differences in proportions. Multivariable linear regression was used to predict cost. Statistical significance was set at a two-tailed *P*-value of  $< .05$ . All analyses were performed using SAS/STAT® v9.4 (SAS Institute Inc., Cary, NC).

## RESULTS

### Baseline Characteristics

Of 4,402 Mohs surgery patients, 2,380 who underwent same-day reconstruction for high- and moderate-risk area defects met inclusion criteria. The final cohort consisted of 143 cases using dHACM and 286 autologous tissue controls (Figure 1). The covariate-balanced distributions are provided (Table 1). Among 429 patients, 335 were male (78.1%) and 401 were 65 years of age or older (93.5%). The mean patient age was  $77.8 \pm 9.3$

years. Over half (234/429; 54.5%) of the study population were routinely taking  $\geq 5$  or more medications. The CCI severity of comorbidity burden in two-thirds (328/429; 76.5%) of individuals was mild. The CCI estimated mean 10-year survival rate was  $88.0\% \pm 12.0\%$ . Tumor size (cm<sup>2</sup>), area of reconstructive risk, and the distributions of squamous cell vs basal cell carcinoma tumors were similar between groups ( $P>0.05$ ).

### Direct Cost Comparisons

For primary reconstruction (POD, postoperative day 0), allotransplantation of dHACM vs SOC was more costly in all areas combined (\$3171.36 vs \$2342.86,  $P<0.0001$ ), and high-risk areas (\$2,893.66 vs \$2376.86;  $P=0.0060$ ; Table 2). When comparing the cost of post-repair sequelae (POD 1 through discharge), dHACM patients incurred significantly lower costs than autologous tissue patients in all areas combined (\$15.87

vs \$940.66,  $P<0.0001$ ), and in high-risk areas (\$19.73 vs \$946.07,  $P<0.0001$ ). No significant differences were found in cumulative cost comparisons between dHACM cases (\$3,187.23) and control counterparts (\$3,283.52) ( $P=0.6812$ ).

### Intervention Effectiveness

Overall, dHACM patients experienced significantly less adverse post-repair sequelae, 2.8% vs 21.3% ( $P<0.0001$ ; Figure 2). Specifically, dHACM was associated with a significantly lower incidence of infection ( $P=.0114$ ), dehiscence ( $P=0.4189$ ), flap or graft necrosis ( $P=0.0349$ ), and hematoma ( $P=0.0066$ ). Method of reconstruction did not impact outpatient visit frequency ( $P=0.2185$ ). Distinctively, dHACM patients underwent fewer scar excisions than SOC (flap and graft) counterparts ( $P=0.0044$ ). This resulted in a cumulative cost for dHACM treatment that was lower for high-risk patients where average cumulative

**FIGURE 1.** Flow diagram demonstrating enrollment, exclusions, allocation, and analysis of study cohort. MMS, Mohs micrographic surgery; NMSC, nonmelanoma skin cancer.

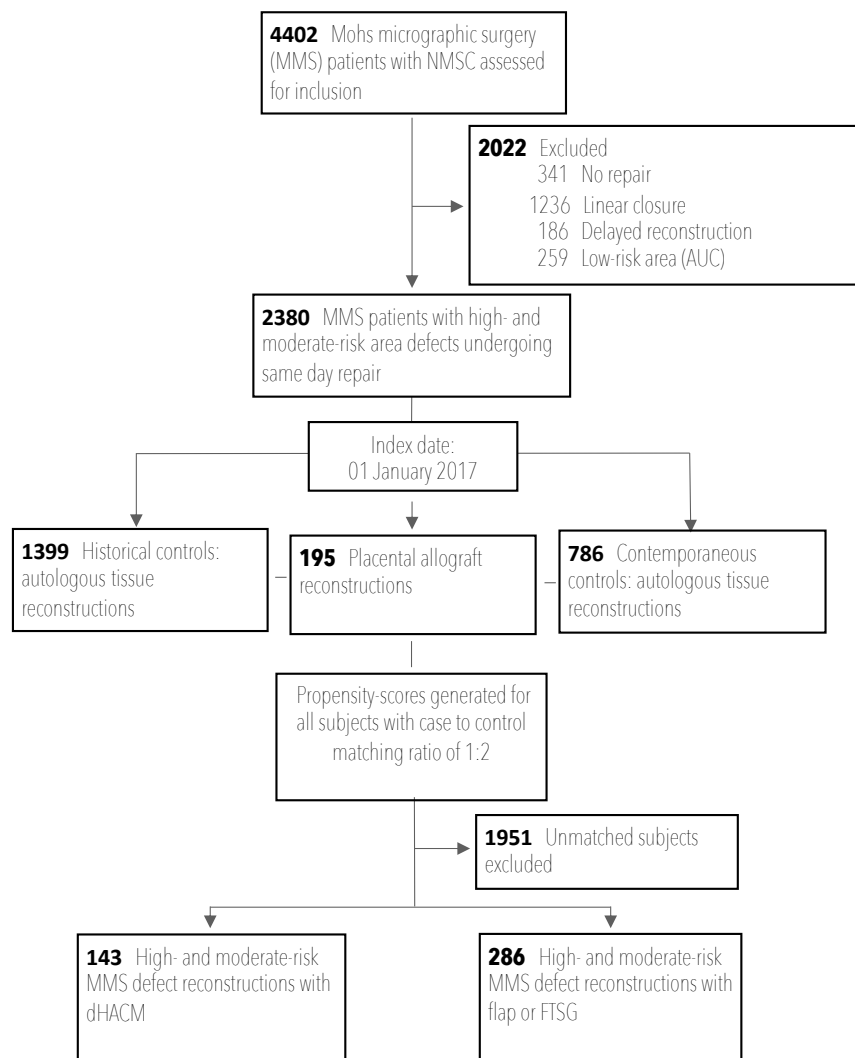


TABLE 1.

Study Population Characteristics and Covariate-Balanced Study Cohorts				
	Study Population	Matched Cohorts		P-Value
		dHACM	Autologous Tissue	
n	429	143	286	--
Age, years	77.8 ± 9.3	77.9 ± 9.6	77.8 ± 9.5	.9563
> 65 years	401 (93.5)	138 (96.5)	263 (92.0)	.0724
Male	338 (78.8)	115 (80.0)	223 (78.0)	.9342
Polypharmacy (≥ 5 medications)	234 (54.5)	75 (52.4)	159 (55.6)	.5372
Charlson Comorbidity Index Score <sup>a</sup>	--	--	--	.3761
Mild (1-2)	328 (76.5)	113 (79.0)	215 (75.2)	--
Moderate (3-4)	101 (23.5)	30 (21.0)	71 (24.8)	--
Severe (≥5)	--	--	--	--
Est. 10-yr survival rate, % <sup>a</sup>	88.0 ± 12.0	88.7 ± 11.0	87.9 ± 12.0	.4726
NMSC diagnosis	--	--	--	.9395
Squamous cell carcinoma	313 (73.0)	108 (75.5)	205 (72.0)	--
Basal cell carcinoma	116 (27.0)	35 (24.5)	81 (28.0)	--
Tumor location (AUC)	--	--	--	.3176
High-risk area	352 (82.1)	111 (77.6)	241 (84.0)	--
Moderate-risk area	77 (17.9)	32 (22.4)	45 (16.0)	--
Tumor size, cm <sup>2</sup>	1.4 ± 1.5	1.5 ± 1.7	1.4 ± 1.4	.6125

TABLE 2.

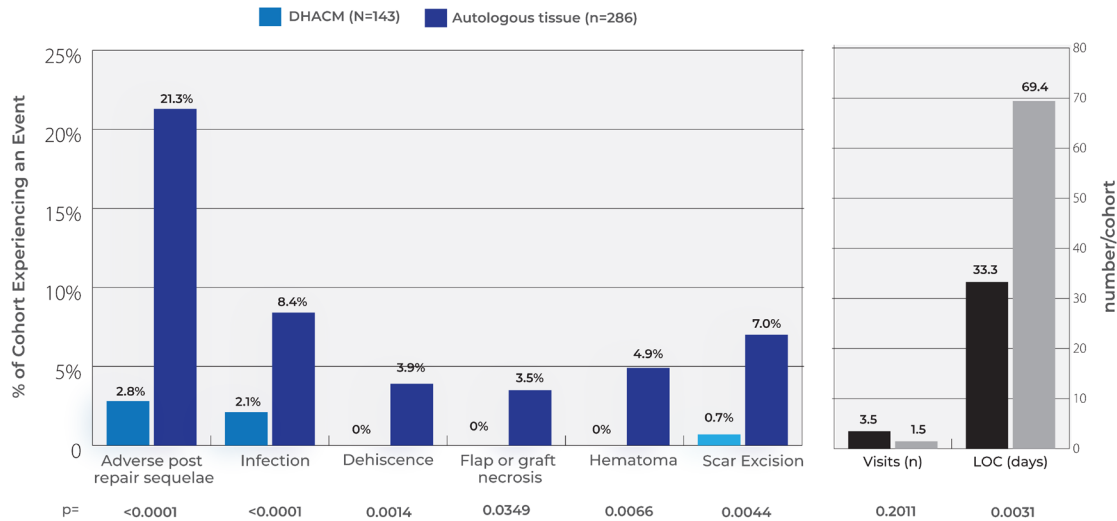
Cost and Defect Size Comparisons Between dHACM and Conventional Autologous Tissue-Based Reconstruction									
Cost Variable	Matched Cohorts								P-Value
	dHACM (\$)				Autologous Tissue (\$)				
	M	Mdn	SD	Range	M	Mdn	SD	Range	
All reconstructions									
n	143	--	--	--	286	--	--	--	--
Defect size, cm <sup>2</sup>	3.5	2.1	3.7	0.5 - 25.9	3.2	2.4	2.8	0.5 - 30.0	0.4302
Primary reconstruction <sup>a</sup>	\$3,171.36	\$2,389.21	\$2,419.30	\$377.59-\$13,199.86	\$2,342.86	\$2,146.44	\$626.71	\$1,429-\$4,614.72	<.0001
Postoperative sequelae <sup>b</sup>	\$15.87	\$0.00	\$132.06	\$0.00-\$1,495.44	\$940.66	\$0.00	\$1,773.38	\$0.00-\$12,165.64	<.0001
Cumulative cost of care	\$3,187.23	\$2,389.21	\$2,436.26	\$377.59-\$13,199.86	\$3,283.52	\$2,615.16	\$1,949.01	\$1,429.72\$14,081.44	0.6812
Cost differential	-\$96.29	--	--	--	--	--	--	--	--
Effectiveness	97.2%	--	--	--	78.7%	--	--	--	--
ICER	-\$520.49	--	--	--	--	--	--	--	--
High-risk area									
n	111	--	--	--	241	--	--	--	--
Defect size, cm <sup>2</sup>	3.3	2	3.7	0.5 - 25.9	3	2.3	2.7	0.5 - 30.0	0.4424
Primary reconstruction <sup>a</sup>	\$2,893.66	\$2,389.21	\$1,933.55	\$377.59-\$9,059.19	\$2,376.86	\$2,226.84	\$642.42	\$1,429.72-\$4,614.72	0.006
Postoperative sequelae <sup>b</sup>	\$19.73	\$0.00	\$147.13	\$0.00-\$1,495.44	\$946.07	\$0.00	\$1,792.67	\$0.00-\$12,165.64	<.0001
Cumulative cost of care	\$2,913.39	\$2,389.21	\$1,962.69	\$377.59-\$9,059.19	\$3,322.94	\$2,615.16	\$1,989.00	\$1,429.72-\$14,081.44	0.0689
Cost differential	-\$409.55	--	--	--	--	--	--	--	--
Effectiveness	96.5%	--	--	--	78.0%	--	--	--	--
ICER	-\$2,213.78	--	--	--	--	--	--	--	--

M, Mean; Mdn, Median; SD, Standard deviation; Effectiveness, % of patients free of adverse post-repair sequelae; ICER, incremental cost effectiveness ratio.

High-risk areas, units (subunits): periorbital (brow, superior &amp; inferior eyelids, lateral and medial canthi), infraorbital cheek, nasal (dorsum, lateral wall, ala, tip, columella, upper &amp; lower lip (philtrum, vermillion, central and lateral cutaneous regions), auricular (helix, antihelix, concha, earlobe, retroauricular), temporal (temple), mental (chin), and hand (dorsal surface, including fingers and webbing). Moderate-risk areas, units (subunits): frontal (central forehead), cheek (buccal, parotid-masseteric, and zygomatic regions), and scalp (Frontal, vertex, parietal, and occipital regions)

<sup>a</sup>Direct cost of reconstructive procedure involving CPT 14020-14301, 15220-15260, 15576, 15630, 15731, 15733, 405XX, 4065X; CPT 15275 & HCPCS Q4186. <sup>b</sup>Post reconstruction costs, includes all billable CPT and ancillary procedures to address complication and post-repair appearance. All costs were inflated to 2024 values using the US bureau of labor statistics CPI calculator<sup>21</sup>

**FIGURE 2.** Comparison of complications and outpatient care utilization for dHACM (dehydrated amnion chorion membrane), and autologous tissue controls. Following MMS (Mohs micrographic surgery), patients received either dHACM (n=143 patients, blue) or an autologous tissue graft or flap (n=286 patients, grey).



Results for each cohort are presented as a percentage (dark shades), or averages: visits (n) and Length of care (LOC, in days) (light shades). Adverse post-repair sequelae is a unique count of patients who experienced any of the following: Infections, dehiscence, flap or graft necrosis, hematoma, and/or scar excision.

costs were reduced by \$409.55. Additionally, reconstructions managed with dHACM reached their final disposition at a much faster rate. The average length of care (LOC) for dHACM differed significantly when compared to autologous tissue controls,  $33.3 \pm 35.2$  days vs  $48.3 \pm 69.4$  days, respectively ( $P=0.0031$ ). Only 1.4% (2/143) of the dHACM group required care > 90 days vs 10.8% (31/286) of controls ( $P=0.0005$ ; Figure 2).

#### Predictors of Greater Cost

A significant multiple regression model with all predictors was produced  $R^2 = .398$ ,  $F(19,409) = 15.86$ ,  $P<0.001$ . Regression analysis revealed a cost increase of \$1,449.60 ( $P<0.0001$ ) for every instance of infection, and an additional \$2,196.60 ( $P<0.0001$ ) for each instance of flap or graft necrosis. A previous Mohs reconstruction at the study index site was also predictive within the model, increasing care totals by \$625.30 ( $P=0.0174$ ). Lastly, defect size was associated with greater cost by adding \$98.80 for every additional  $\text{cm}^2$  of wound treated > 1.0  $\text{cm}^2$ .

#### Cost-Effectiveness

The average cost of primary reconstruction for each method was calculated.<sup>17</sup> When compared to SOC, the intervention effectiveness of dHACM was significantly better, 97.2% vs 78.7% ( $P<0.0001$ ; Figure 2, Table 2). The ICER calculation for dHACM was:  $-\$96.29 / 18.5\%$  incremental improvement in intervention effectiveness. dHACM is thus a dominant treatment, \$520.49 is saved per complication-free individual (Table 2).

#### Example Cosmesis Results

High-risk areas such as the superior crus of antihelix in an 85-year-old white male, the right superior lateral eyelid (eyebrow) in a 74-year-old White female, or the 2nd web space by the left index

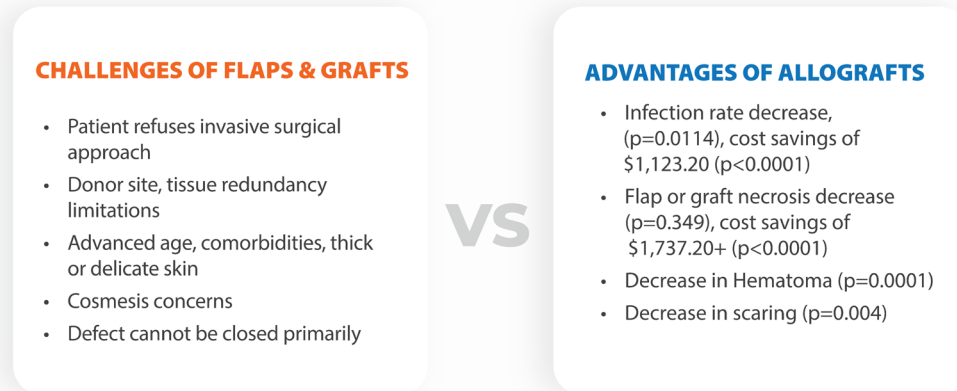
finger in a 76-year-old White male are shown (Figure 3). DHACM was applied every one to two weeks from the date of the Mohs surgery to re-epithelialization. Closure occurred in 7 to 16 weeks for the presented cases without complications.

**FIGURE 3.** (A) Eighty-five-year-old White male underwent MMS on the right superior crus of antihelix resulting in a 3.3 cm x 3.0 cm x 0.3 cm defect. The patient has a history of hypertension and prostate cancer. (B) Complete re-epithelialization of the defect at 16 weeks. (C) Seventy-four-year-old White female who smokes 1 pack of cigarettes per day underwent MMS on the right superior lateral eyelid. The post-MMS defect was surrounded by atrophic skin and measured 3.4 cm x 2.0 cm x 0.2 cm. (D) Complete re-epithelialization of the defect 9 weeks later. (E) Seventy-six-year-old White male with a history of coronary artery disease and a splenectomy, underwent MMS at the second web space by the left index finger. The post-MMS defect was surrounded by atrophic skin and measured 3.9 cm x 3.6 cm x 0.2 cm. (F) Complete re-epithelialization of the defect approximately 7 weeks later.





**FIGURE 4.** Factors impacting the decision to use an allograft in preference to an autograft. Autologous tissue grafts and flaps are the predominant approaches for repairing Mohs-related defects.



\*Patient complications and wound characteristics should contribute to the decision process since alternatives are needed in high-risk reconstructions as suggested. \*Subset of patients affected will vary. Not likely to exceed 10%. These data were based on 429 patient records which met inclusion criteria from approximately 4,400 records over 5 years with a DHACM allograft utilization of approximately 7%.

## DISCUSSION

Our primary finding is that purchasing a placental allograft accounts for an average of 76.4% (\$2,442.70) of the total reconstruction cost or \$692.20 per cm<sup>2</sup> of defect treated (\$2,422.70 / 3.5 average defect cm<sup>2</sup>). Subjects treated with dHACM, avoided significant costly postoperative complications and ancillary procedures, while SOC patients incurred greater costs secondary to increased resource utilization (direct treatment of adverse sequelae, outpatient visits, aesthetic services) which offset the per-patient cumulative cost averages (\$3,171.36 vs \$2,342.86,  $P<0.0001$ ). This trend was observed for the high-risk group and overall group (Table 2). A significantly longer length of care was identified in the autologous tissue group compared to allografts ( $48.3 \pm 69.4$  days vs  $33.3 \pm 35.2$  days,  $P=0.0031$ ), suggesting that additional time was required to successfully discharge these patients. dHACM patients also underwent fewer scar revisions (0.7% vs 7.0%,  $P=0.0044$ ) or other adjunct cosmetic procedures commonly used to address appearance. Regression modeling identified autologous flap/graft necrosis and infection as the greatest impacts on total cost. A significant predictive relationship between cost and a history of previous Mohs with reconstruction at the study index site suggests donor site tissue quality may impact the success of autologous tissue-based reconstructions.

Best use cases for dHACM include: defects greater than 3.0 cm in a moderate to high-risk functionally and cosmetically sensitive area such as the superior crus of antihelix (3A, 3B), particularly when imbibition is inadequate for a full-thickness skin graft to survive, and when the wound exhibits exposed cartilage which must be protected as it is an avascular entity. Patients who smoke (3C, D) also have an increased risk of flap or graft failure due to hypoxia with the potential for an ensuing

cascade of necrosis, inflammation, infection risk, pain, scar tissue formation, impaired cosmesis, and function impairment which can affect both the Primary and Secondary donor site defects, prolonging wound care. Although not analyzed in this study, dHACM may be beneficial when 1) side-to-side repair is not feasible, 2) there is limited tissue redundancy adjacent to the wound (low flap feasibility), 3) where secondary intention is a sub-optimal option, 4) or when patients with significant comorbidities demonstrate other risks for post-MMS complications (Figure 4).

An allograft may be warranted at highly dynamic locations that are heavily utilized and traumatized such as the hands and digits (Figure 3E, 3F), where development of vessels to supply an autograft is challenged. The additional potential for adhesions at the exposed tendon at the base of this wound may warrant an allograft. Lastly, healing via secondary intention would create difficulty in daily dressing changes and wound cleaning for this patient to perform one-handed if a caregiver is not available.

While autologous skin reconstruction remains the gold standard of treatment, as the patient population ages, we believe there will be a growing need for non-surgical reconstructive options.<sup>21</sup> An elderly population will mean greater frailty and risk of recurrent resections and reconstructions limiting donor sites. Expectations of a good aesthetic outcome, timely closure, and a straightforward recovery remain important to an aging individual (Figure 3A-F).<sup>22,23</sup>

Economic literature on regenerative biomaterials is primarily in chronic wound management, traumatic wound reconstruction, or burn injury.<sup>23</sup> The cost-benefit evidence is especially favorable for Medicare-aged patients with diabetic foot ulcers.<sup>24,25</sup>

Management with these advanced therapies is often associated with lowering overall medical costs through reduced utilization of resources and healthcare services.<sup>24,26</sup> In the current study dHACM accounts for an average of 76.4% of total reconstruction costs; however, 98.3% ((\$15.87/\$940.66) – 1) of downstream costs (complications) were averted for an overall reduction in cumulative costs. This cost savings is greatest in high-risk patients who would have more post-repair sequelae with an autologous graft (-\$409.55, ICER is dominant). Patients of high- or moderate-risk areas would save an average of \$96.29 (ICER is dominant). Our data suggests that in elderly patients with wounds that cannot be closed primarily, dHACM appears to be a useful alternative to standard skin grafting and skin flaps with minimal financial tradeoff.

### Study Limitations

This is not a randomized, controlled prospective study and thus causative correlations should not be implied but rather form the basis of testable hypotheses. Male gender was 78%. US research has shown that the incidence of basal cell carcinoma, the most frequent NMSC, has an incidence of 469 more cases per 100,000 person-years for men than women (a 1.46-fold increase).<sup>27</sup> However, women were reported to be more sensitive to issues of cosmesis (odds ratio 2.84,  $P=0.009$ ).<sup>17</sup> Future studies should evaluate how gender impacts patient satisfaction. Our study based the effectiveness on the incidence of at least one adverse post-repair event when in reality, patients can experience more than one complication or outcome.

### DISCLOSURES

DM and RAF are clinical researchers for MIMEDX Group, Inc. BH is a consultant to MIMEDX Group, Inc. The other authors, their immediate families, or any foundation with which they are affiliated have no conflicts of interest relevant to the subject matter of this manuscript.

**Funding:** Third-party data analysis was supported in part by the company, MIMEDX Group, Inc. through a clinical research agreement.

### ACKNOWLEDGMENT

We would like to thank Georgina M. Michael for her thoughtful data review and medical writing.

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