

Treatment patterns and outcomes with luspatercept in patients with lower-risk myelodysplastic syndromes: A retrospective US cohort analysis

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Anemia is the most common cytopenia associated with lower-risk myelodysplastic syndromes (LR-MDS), resulting in between 50% and 90% of patients requiring red blood cell (RBC) transfusions.^{1,2} However, severe anemia and transfusion dependency have been associated with shorter overall survival.³ The real-world clinical benefit of available treatments for myelodysplastic syndromes (MDS) ranks among the lowest of all hematologic malignancies, especially when compared with findings from clinical trials,^{4,5} potentially in part due to the variability between trial participants and the general patient populations.^{6,7} Luspatercept is a first-in-class erythroid maturation agent and recombinant transforming growth factor β superfamily ligand-binding fusion protein that works to restore erythropoiesis by increasing the number and improving the quality of mature RBCs.⁸ Based on the results from the MEDALIST trial (NCT02631070)⁹ and the recent COMMANDS trial (NCT03682536),¹⁰ luspatercept is approved by the US Food and Drug Administration (FDA) for the treatment of anemia with or without prior erythropoiesis-stimulating agent (ESA) use in adult patients with very low- to intermediate-risk MDS who may require regular RBC transfusions.^{11,12} In this study, we collected real-world data from patients with LR-MDS treated with luspatercept in the United States and analyzed treatment patterns and clinical outcomes.

In this retrospective medical chart review, we used de-identified, patient-level data abstracted from patients' electronic medical records into an electronic case report form by physicians recruited from the Cardinal Health Oncology Provider Extended Network (OPEN), a community of >800 private practice and

hospital-based oncologists/hematologists across the United States; and all study procedures were conducted in accordance with the Declaration of Helsinki. Eligible patients were ≥ 18 years of age at initiation of luspatercept treatment for LR-MDS, were diagnosed with LR-MDS (International Prognostic Scoring System [IPSS] score of Low or Intermediate-1 risk and/or a Revised IPSS [IPSS-R] score of Very low, Low, or Intermediate risk) confirmed by bone marrow biopsy on or after January 1, 2015, and had ≥ 12 weeks of luspatercept treatment (unless the patient died <12 weeks following initiation). Data were collected between May 31, 2022 and July 12, 2022. The primary outcome was the achievement of transfusion independence (TI) or maintenance of non-transfusion dependent (NTD) status for ≥ 8 weeks during the first 24 weeks (weeks 1–24) of luspatercept treatment. Key secondary outcomes were achievement of modified hematologic improvement-erythroid (mHI-E, defined as a reduction in RBC and/or platelet sessions of ≥ 4 sessions in a ≥ 8 -week period in patients with a baseline transfusion burden [TB] of ≥ 4 RBC and/or platelet sessions, or as an increase in hemoglobin level of ≥ 1.5 g/dL in a ≥ 8 -week period in patients with a baseline TB of <4 RBC and/or platelet sessions) and reduction in TB from baseline (defined as the 8 weeks prior to luspatercept initiation) during weeks 1–24 of luspatercept treatment. TB at baseline was based on the number of transfusion sessions (any units of RBCs and/or platelets received in a single day) and was categorized as: 0 sessions = NTD; 1–3 sessions = low TB (LTB); 4–5 sessions = moderate TB (MTB); and ≥ 6 = high TB (HTB). TB during luspatercept treatment was defined based on the lowest number of transfusion sessions during any rolling/consecutive

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American Society of Clinical Oncology (Mukherjee S, et al. *J Clin Oncol*. 2023;41[suppl 16]: abstract 7057), the 28th Congress of the European Hematology Association (Mukherjee S, et al. *HemaSphere*. 2023; 7[suppl 3]:1349–1350), and the 11th Annual Meeting of the Society of Hematologic Oncology (Mukherjee S, et al. *Clin Lymphoma Myeloma Leuk*. 2023;23[suppl 1]:S352–S353).

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TABLE 1 Demographics, disease, clinical, and treatment characteristics of patients with LR-MDS treated with luspatercept.

| Characteristic | All patients, N = 253 |
|---|-----------------------|
| Age, years, median (range) | |
| At diagnosis | 71.6 (49.2-95.5) |
| At luspatercept initiation | 73.3 (51.1-96.7) |
| Sex, n (%) | |
| Male | 133 (52.6) |
| Female | 120 (47.4) |
| Race, n (%) | |
| White | 180 (71.1) |
| Asian | 8 (3.2) |
| Black/African American | 57 (22.5) |
| Native Hawaiian or Other Pacific Islander | 1 (0.4) |
| American Indian or Alaska Native | 3 (1.2) |
| Unknown | 4 (1.6) |
| Ethnicity, n (%) | |
| Hispanic/Latino/Latina | 35 (13.8) |
| Non-Hispanic/non-Latino/non-Latina | 215 (85.0) |
| Unknown | 3 (1.2) |
| Insurance/payer at data collection, n (%) | |
| Medicare | 194 (76.7) |
| Medicaid | 7 (2.8) |
| Commercial | 44 (17.4) |
| Military | 3 (1.2) |
| Self-pay | 0 (0.0) |
| Unknown | 5 (2.0) |
| US region of residence, n (%) ^a | |
| Northeast | 48 (19.0) |
| Midwest | 63 (24.9) |
| South | 97 (38.3) |
| West | 45 (17.8) |
| ECOG-PS status at luspatercept initiation, n (%) ^b | |
| 0/1 | 167 (66.0) |
| 2+ | 86 (34.0) |
| Mutations identified at any time, n (%) | |
| SF3B1 | |
| Mutation detected | 107 (42.3) |
| No mutation detected | 129 (51.0) |
| Unknown | 17 (6.7) |
| TET2 | |
| Mutation detected | 21 (8.3) |
| No mutation detected | 167 (66.0) |
| Unknown | 65 (25.7) |
| ASXL1 | |
| Mutation detected | 15 (5.9) |
| No mutation detected | 192 (75.9) |

TABLE 1 (Continued)

| Characteristic | All patients, N = 253 |
|---|-----------------------|
| Unknown | 46 (18.2) |
| DNMT3A | |
| Mutation detected | 20 (7.9) |
| No mutation detected | 171 (67.6) |
| Unknown | 62 (24.5) |
| RUNX1 | |
| Mutation detected | 5 (2.0) |
| No mutation detected | 199 (78.7) |
| Unknown | 49 (19.4) |
| TP53 | |
| Mutation detected | 11 (4.3) |
| No mutation detected | 185 (73.1) |
| Unknown | 57 (22.5) |
| Cytogenetic abnormalities at any time, n (%) | |
| -7/del(7q) | |
| Positive | 10 (4.0) |
| Negative | 241 (95.3) |
| Unknown | 2 (0.8) |
| del(5q) | |
| Positive | 16 (6.3) |
| Negative | 235 (92.9) |
| Unknown | 2 (0.8) |
| Complex karyotype | |
| Positive | 14 (5.5) |
| Negative | 234 (92.5) |
| Unknown | 5 (2.0) |
| Most recent cytogenetic category prior to initiation of luspatercept, n (%) | |
| Very good: -Y, del(11q) | 8 (3.2) |
| Good: normal, del(5q), del(12p), del(20q), double including del(5q) | 186 (73.5) |
| Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones | 35 (13.8) |
| Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q) | 1 (0.4) |
| Very poor: complex, >3 abnormalities | 7 (2.8) |
| Unknown | 16 (6.3) |
| Select comorbidities ^c at luspatercept initiation, n (%) | |
| Select comorbidities | |
| Cardiovascular disease | 101 (39.9) |
| Cerebrovascular disease | 35 (13.8) |
| Chronic pulmonary disease | 45 (17.8) |
| Diabetes | 96 (37.9) |
| Renal disease | 23 (9.1) |
| Patients with ≥1 select comorbidity | 192 (75.9) |
| Patients with ≥2 select comorbidities | 86 (34.0) |

TABLE 1 (Continued)

| Characteristic | All patients, N = 253 |
|---|-----------------------|
| Pre-luspatercept TB (8 weeks prior), n (%) | |
| NTD ^d | 21 (8.3) |
| LTB ^e | 208 (82.2) |
| MTB ^f | 24 (9.5) |
| HTB ^g | 0 (0) |
| Duration of follow-up, months | |
| Mean (SD) | 8.2 (5.9) |
| Median (range) | 5.7 (2.1–34.5) |
| Hematologic parameters at luspatercept initiation | |
| Hemoglobin, g/dL | |
| Number of patients with results | 253 |
| Mean (SD) | 7.9 (0.9) |
| Median (range) | 7.9 (5.9–10.5) |
| ANC, per μL | |
| Number of patients with results | 213 |
| Mean (SD) | 2388.3 (1473.6) |
| Median (range) | 2000 (400–9300) |
| Platelet count, $\times 10^9/\text{L}$ | |
| Number of patients with results | 252 |
| Mean (SD) | 180.3 (111.3) |
| Median (range) | 156.5 (19.0–670.0) |
| Duration of luspatercept treatment, months | |
| Median (95% CI) | 10.8 (9.2–13.3) |
| Treatments received before luspatercept, n (%) | |
| 0 | 3 (1.2) |
| 1 | 219 (86.6) |
| 2 | 24 (9.5) |
| 3 | 7 (2.8) |
| Prior ESA use, n (%) | |
| Yes | 220 (87.0) |
| No | 33 (13.0) |
| Luspatercept dose/frequency at initiation, n (%) | |
| 1 mg/kg every 3 weeks | 253 (100) |
| 1.75 mg/kg every 3 weeks | 0 (0) |
| Dose escalations, n (%) | |
| 0 | 155 (61.3) |
| 1 | 49 (19.4) |
| 2 | 47 (18.6) |
| ≥ 3 | 2 (0.8) |
| Dose reductions, n (%) | |
| 0 | 237 (93.7) |
| 1 | 14 (5.5) |
| 2 | 2 (0.8) |
| ≥ 3 | 0 (0.0) |
| Dose holds/interruptions | |
| 0 | 233 (92.1) |

TABLE 1 (Continued)

| Characteristic | All patients, N = 253 |
|---|-----------------------|
| 1 | 13 (5.1) |
| 2 | 3 (1.2) |
| ≥ 3 | 4 (1.6) |
| Status of luspatercept treatment, n (%) | |
| Still on luspatercept | 169 (66.8) |
| Discontinued luspatercept | 84 (33.2) |
| Primary rationale for discontinuation | |
| Worsening of disease (new onset or worsening transfusion requirement) | 5 (2.0) |
| Worsening of disease (progression to higher-risk MDS) | 21 (8.3) |
| Lack of hematologic improvement (based on hemoglobin levels) | 26 (10.3) |
| Toxicity/adverse event | 1 (0.4) |
| Patient choice | 3 (1.2) |
| Death | 26 (10.3) |
| Other | 2 (0.8) |
| Dose/frequency at discontinuation | |
| 0.6 mg/kg every 3 weeks | 1 (0.4) |
| 1 mg/kg every 3 weeks | 40 (15.8) |
| 1.33 mg/kg every 3 weeks | 16 (6.3) |
| 1.75 mg/kg every 3 weeks | 27 (10.7) |

Note: Percentages may not total 100 due to rounding.

Abbreviations: ANC, absolute neutrophil count; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; ESA, erythropoiesis-stimulating agent; HTB, high transfusion burden; LR-MDS, lower-risk myelodysplastic syndromes; LTB, low transfusion burden; MTB, moderate transfusion burden; NTD, non-transfusion dependent; RBC, red blood cell; SD, standard deviation; TB, transfusion burden; US, United States.

^aNortheast: CT, DE, MA, MD, ME, NH, NJ, NY, PA, RI, VT; Midwest: IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI; South: AL, AR, DC, FL, GA, KY, LA, MS, NC, OK, SC, TN, TX, VA, WV; West: AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY.

^bECOG-PS: 0 = fully active, no restriction; 1 = restricted in strenuous physical activities, fully ambulatory, and able to carry out light work; 2 = capable of all self-care but unable to carry out any work activities, up and about >50% of waking hours; 3 = capable of only limited self-care, confined to bed or chair >50% of waking hours; 4 = completely disabled, could not carry out any self-care, totally confined to bed or chair.

^cSelect comorbidities include cardiovascular disease (any patient indicated as having cardiovascular disease, congestive heart failure, or myocardial infarction), cerebrovascular disease, chronic pulmonary disease, diabetes, and renal disease.

^dNTD defined as 0 RBC sessions and/or platelet sessions during weeks 1–8 prior to luspatercept initiation.

^eLTB defined as 1–3 RBC sessions and/or platelet sessions during weeks 1–8 prior to luspatercept initiation.

^fMTB defined as 4–5 RBC sessions and/or platelet sessions during weeks 1–8 prior to luspatercept initiation.

^gHTB defined as ≥ 6 RBC sessions and/or platelet sessions during weeks 1–8 prior to luspatercept initiation. A transfusion session was defined as receiving any units of RBCs and/or platelets in a single day (e.g., if a patient received transfusions over 2 days, that would be 2 sessions).

8-week period and was categorized as: 0 sessions = TI; 1–3 sessions = LTB; 4–5 sessions = MTB; and ≥ 6 sessions = HTB. Achievement of mHI-E during weeks 1–24 of luspatercept treatment was calculated in patients who were transfusion dependent (TD) prior to luspatercept initiation and who had received

luspatercept treatment for ≥ 24 weeks during study follow-up. Full materials and methods can be found in the Online Supporting Information Content.

Twenty-four participating physicians abstracted data from the medical charts of 253 eligible patients; median duration of follow-up was 5.7 months (range, 2.1–34.5). Table 1 shows the demographics, disease, clinical, and treatment characteristics of the study cohort. Among all patients, 86.6% ($n = 219$) had received 1 line of treatment and 12.3% ($n = 31$) had received 2 or 3 lines of treatment prior to luspatercept initiation. The most frequently used therapy prior to luspatercept was ESAs (87.0%, $n = 220$). All patients (100%, $n = 253$) initiated luspatercept at the recommended starting dose of 1 mg/kg every 3 weeks. The median duration of treatment was 10.8 months (95% confidence interval, 9.2–13.3 months) (Supporting Information: Figure S1). Most patients (61.3%, $n = 155$) had no dose escalations, 93.7% ($n = 237$) had no dose reductions, and 92.1% ($n = 233$) had no dose holds or interruptions. During study follow-up, 33.2% of the patients ($n = 84$) discontinued luspatercept; most ($n = 57$) discontinued at less than the maximum recommended dose of 1.75 mg/kg every 3 weeks and 40 patients discontinued luspatercept at the dose of 1 mg/kg every 3 weeks (Table 1). Treatment sequencing is shown in Supporting Information: Figure S2.

Most patients (87.4%, $n = 221$) achieved TI or maintained NTD status for ≥ 8 weeks during weeks 1–24 of luspatercept treatment. Of 21 patients who were NTD at baseline, 4.8% ($n = 1$) became TD,

whereas the rest maintained NTD status for ≥ 8 weeks (Figure 1A). Of 89 patients who were TD at baseline and received luspatercept for ≥ 24 weeks, 64.0% ($n = 57$) achieved mHI-E during weeks 1–24 of luspatercept treatment (Figure 1B). Among all patients, median hemoglobin level generally increased during weeks 1–24 of luspatercept treatment (Figure 1C). Platelet and absolute neutrophil levels at diagnosis, luspatercept treatment initiation, and during weeks 1–24 of luspatercept treatment are shown in Supporting Information: Figure S3. Of the 232 patients who were TD at baseline, 90.9% ($n = 211$) experienced a reduction in TB. Among the 208 patients who had LTB at baseline, 89.9% ($n = 187$) achieved TI for ≥ 8 weeks, and 10.1% ($n = 21$) maintained LTB for ≥ 8 weeks (Figure 1D). Of the 24 patients who had MTB at baseline, 58.3% ($n = 14$) and 41.7% ($n = 10$) achieved TI and LTB for ≥ 8 weeks, respectively (Figure 1E). A sensitivity analysis varying the TB definition reference thresholds for MTB and HTB at baseline and during luspatercept treatment showed the same results with no numerical differences in rates of TB at baseline (Table 1) or during weeks 1–24 of luspatercept treatment (Figure 1).

Of the 107 patients with an *SF3B1* mutation, 84.1% ($n = 90$) achieved TI or maintained NTD status for ≥ 8 weeks during weeks 1–24 of luspatercept treatment. mHI-E was achieved in 68.6% ($n/N = 24/35$) of patients with *SF3B1* mutation who were TD at baseline and who received luspatercept for ≥ 24 weeks. Of the 15 patients with *SF3B1* mutations who were NTD at

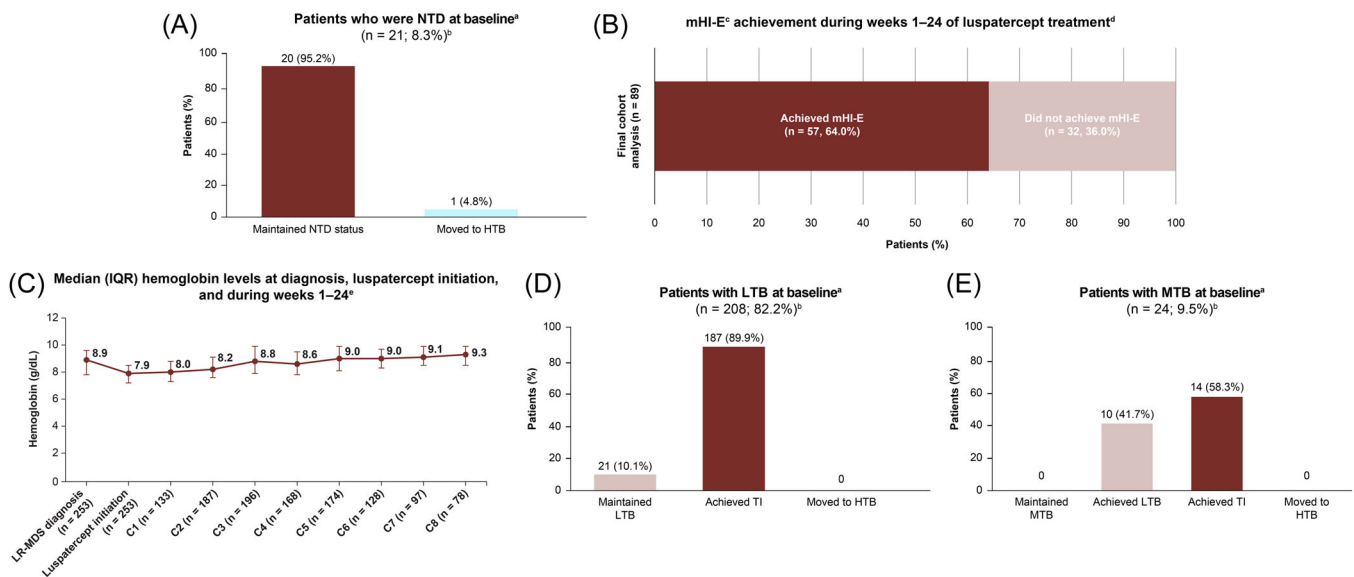


FIGURE 1 TB and modified hematologic improvement-erythroid (mHI-E) achievement during weeks 1–24 of luspatercept treatment and median (IQR) hemoglobin levels at diagnosis, luspatercept initiation, and during weeks 1–24. (A) Patients who were NTD at baseline^a; (B) mHI-E^c achievement during weeks 1–24 of luspatercept treatment^d; (C) Median (IQR) hemoglobin levels at diagnosis, luspatercept initiation, and during weeks 1–24^e; (D) Patients with LTB at baseline^a; (E) Patients with MTB at baseline^a. ^aBaseline TB was assessed during the 8 weeks prior to luspatercept initiation. ^bTB during luspatercept treatment was based on the lowest TB during any rolling/consecutive 8-week period post luspatercept initiation and categorized as follows: TI: 0 RBC sessions and/or platelet sessions during any 8-week period post luspatercept initiation; LTB: 1–3 RBC sessions and/or platelet sessions during any 8-week period post luspatercept initiation; MTB: 4–5 RBC sessions and/or platelet sessions during any 8-week period post luspatercept initiation; HTB: ≥ 6 RBC sessions and/or platelet sessions during any 8-week period post luspatercept initiation. A transfusion session was defined as receiving any units of RBCs and/or platelets in a single day (e.g., if a patient received transfusions over 2 days, that would be 2 sessions). ^cA reduction in RBC sessions and/or platelet sessions of ≥ 4 sessions over a period of 8 weeks in patients with a baseline TB of ≥ 4 RBC sessions and/or platelet sessions or as an increase in the hemoglobin level of ≥ 1.5 g/dL over a period of 8 weeks in patients with a baseline TB of < 4 RBC sessions and/or platelet sessions. ^dmHI-E was calculated for patients who were TD at baseline and who had received luspatercept treatment for ≥ 24 weeks during study follow-up. ^eC1 = weeks 1–3; C2 = weeks 4–6; C3 = weeks 7–9; C4 = weeks 10–12; C5 = weeks 13–15; C6 = weeks 16–18; C7 = weeks 19–21; C8 = weeks 22–24. C, cycle; HTB, high transfusion burden; IQR, interquartile range; LR-MDS, lower-risk myelodysplastic syndromes; LTB, low transfusion burden; mHI-E, modified hematologic improvement-erythroid; MTB, moderate transfusion burden; NTD, non-transfusion dependent; RBC, red blood cell; TB, transfusion burden; TD, transfusion dependent; TI, transfusion independence.

baseline, 6.7% ($n = 1$) became TD and 93.3% ($n = 14$) maintained NTD status for ≥ 8 weeks. Of the 92 patients with *SF3B1* mutations who were TD at baseline, 88.0% ($n = 81$) experienced a reduction in TB.

Among the 33 patients who did not receive ESA therapy prior to luspatercept initiation (the ESA-naive subgroup), 90.9% ($n = 30$) of the patients received ≥ 1 line of therapy, most frequently granulocyte-macrophage colony-stimulating factor ($n = 20$). At baseline, 81.8% ($n = 27$) of ESA-naive patients had LTB, 15.2% ($n = 5$) had MTB, and 1 patient was NTD. Of the 32 ESA-naive patients who were TD at baseline, almost all (96.9%) achieved TI ≥ 8 weeks during luspatercept treatment, and 93.8% achieved TI ≥ 12 weeks (Supporting Information: Figure S4). Of the 6 ESA-naive patients who were evaluable for mHI-E, 83.3% ($n = 5$) achieved mHI-E during weeks 1–24 of luspatercept treatment. Most patients among the ESA-naive subgroup (93.9%, $n = 31$) were still receiving luspatercept treatment at the time of data collection; 1 (3.0%) patient discontinued due to lack of hematologic improvement and 1 (3.0%) patient discontinued due to normalization of hemoglobin based on physician discretion.

In this nationwide, retrospective study we observed high rates of TI and mHI-E achievement, and TB reduction in patients with LR-MDS who received luspatercept. The rate of TI achievement with luspatercept was higher among patients with LTB (89.9%) than patients with MTB (58.3%) at baseline, and 90.9% of patients who were TD at baseline experienced a reduction in TB during weeks 1–24 of luspatercept treatment. Only 10.3% ($n/N = 26/253$) of the patients who discontinued luspatercept were receiving the highest dose of luspatercept at discontinuation, suggesting a potential need for education and evaluation with operational workflows in clinical practice to ensure that luspatercept dose titration practices align with recommendations in US prescribing information¹² to optimize response/TI achievement. Therapeutic benefit was also seen in the ESA-naive subgroup ($n = 33$). These results align, albeit in a smaller number of patients, with the phase 3 COMMANDS trial, which evaluated first-line use of luspatercept in ESA-naive patients with LR-MDS.¹⁰ In conclusion, our findings confirm that luspatercept treatment helps promote achievement of TI and reduction in TB among patients with LTB and MTB at baseline. These data extend evidence from the MEDALIST trial⁹ and COMMANDS trial¹⁰ in support of the continued, robust clinical benefit of luspatercept in patients with LR-MDS who are TD.

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AUTHOR CONTRIBUTIONS

Sudipto Mukherjee, Cherrise Brown-Bickerstaff, Adeola Y. Makinde, and Ali McBride designed the study and were involved in the acquisition, analysis, and interpretation of the data. JaLyna Laney was involved in the acquisition, analysis, and interpretation of the data. Angelica Falkenstein, Emily Bland, Marné Garretson, and David Huggar were involved in the analysis and interpretation of the data.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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