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ORIGINAL ARTICLE

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Differential outcomes for frontal versus posterior demyelination in childhood cerebral adrenoleukodystrophy

Ashish O. Gupta[1] | **David R. Nascene**[2] | **Ryan Shanley**[3] | **Daniel L. Kenney-Jung**[4] | **Julie B. Eisengart**[1] | **Troy C. Lund**[1] | **Paul J. Orchard**[1] | **Elizabeth I. Pierpont**[1]

[1]Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota, USA

[2]Department of Radiology, University of Minnesota, Minneapolis, Minnesota, USA

[3]Bioinformatics and Biostatistics Core, University of Minnesota, Minneapolis, Minnesota, USA

[4]Department of Neurology, University of Minnesota, Minneapolis, Minnesota, USA

Correspondence
Elizabeth I. Pierpont, Department of Pediatrics, University of Minnesota, Division of Clinical Behavioral Neuroscience, 2450 Riverside Avenue, RPB Suite 550, Minneapolis, MN, 55454, USA.
Email: pier0053@umn.edu

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Abstract

In the most common variant of childhood cerebral adrenoleukodystrophy (cALD), demyelinating brain lesions are distributed predominately in parieto-occipital white matter. Less frequently, lesions first develop in frontal white matter. This matched cohort study examined whether outcomes after standard treatment with hematopoietic cell transplantation (HCT) differ in patients with early stage frontal lesions as compared to parieto-occipital lesions. Retrospective chart review identified seven pediatric patients with frontal cALD lesions and MRI severity score < 10 who underwent a single HCT at our center between 1990 and 2019. Concurrent MRI, neurocognitive and psychiatric outcomes at last comprehensive follow-up (mean 1.2 years; range 0.5-2.1 years) were compared with a group of seven boys with the parieto-occipital variant matched on pre-HCT MRI severity score. Both groups showed similar rates of transplant complications and radiographic disease advancement. Neurocognitive outcomes were broadly similar, with more frequent working memory deficits among individuals with frontal lesions. Psychiatric problems (hyperactivity, aggression, and atypical behavior) were considerably more common and severe among patients with frontal lesions. Aligned with the critical role of the frontal lobes in emotional and behavioral regulation, functional disruption of self-regulation skills is widely observed among patients with frontal lesions. Comprehensive care for cALD should address needs for psychiatric care and management.

KEYWORDS

adrenoleukodystrophy, cerebral, cognition, MRI, psychiatric, stem cell transplantation

1 | INTRODUCTION

Childhood cerebral adrenoleukodystrophy (cALD) is a rare X-linked, progressive demyelinating disorder affecting young boys. Hematopoietic cell transplantation (HCT) is the current standard of care to halt cALD progression with an overall survival of ~80%.[1] Even when HCT occurs early in the disease course, individuals with cALD commonly experience neurocognitive deficits and/or psychiatric disturbance following treatment.[2] Pre-treatment MRI severity and

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TABLE 1 Study cohort characteristics

Demographics	Frontal ($N = 7$)	Parieto-occipital ($N = 7$)
Baseline variables	Mean (SD); range	Mean (SD); range
Age at transplant (years)	11.8 (2.5); 9-16	7.5 (1.6); 5-10
Pre-HCT Loes MRI severity score	5.6 (1.7); 3-8	5.5 (2.0); 3-9
Race	*N*	*N*
White/Caucasian	6	6
Black/African American	1	0
Asian	0	1
Transplant variables		
Conditioning		
fTBI/Cy/ATG	4	0
Bu/Cy ± Alemtuzumab or ATG	2	7
Bu/Flu	1	0
Graft source		
Bone marrow	5	2
Sibling	2	1
Unrelated	3	1
UCB	2	5
HLA matching		
6/6	5	5
5/6	2[a]	1
4/6	0	1
GVHD prophylaxis		
CSA/Pred	4	2
CSA/MMF	3	4
CSA/Mtx	0	1
Engraftment	Median (range)	Median (range)
Neutrophil (days)	14 (9-45)	16 (11-35)
Platelets (days)	49 (23-217)	42 (28-71)
aGvHD	*N*	*N*
Grade 1–2	2	3
Grade 3–4	1	0
cGvHD	0	1
Graft failure	2[b]	0
5-year survival, Alive	7[c]	7
Follow-up evaluation	Mean (SD); range	Mean (SD); range
Years since HCT	1.2 (0.6); 0.5–2.1	1.2 (0.5); 0.8-2.1
Loes MRI severity score	7.0 (2.9); 4–10	8.4 (4.0); 4-16
Psychiatric medication	*N*	*N*
Stimulant medication	6	1
Other ADHD medication	1	0
Sleep medication	2	0

(Continues)

TABLE 1 (Continued)

Demographics	Frontal ($N = 7$)	Parieto-occipital ($N = 7$)
Neurocognitive impairment[d]		
Verbal reasoning	3	2
Visual reasoning	2	0
Working memory	4	0
Processing speed	2	3

Abbreviations: aGvHD, acute graft vs host disease; ATG, anti-thymocyte globulin; Bu, busulfan; cGvHD, chronic graft vs host disease; CSA, cyclosporine; Cy, cyclophosphamide; fTBI, fractional total body irradiation; Flu, fludarabine; HCT, hematopoietic cell transplant; HLA, human leukocyte antigen; MMF, mycophenolate mofetil; Mtx, methotrexate; MRI, magnetic resonance imaging; UCB, Umbilical cord blood.

[a]One patient received double UCB both 5/6 matching.

[b]One patient met the criteria for primary graft failure (absence of neutrophil engraftment by day 42 post-HCT) but subsequently engrafted. The second patient had secondary graft failure with an autologous recovery at day 276 post-HCT. Both patients are alive and neither underwent a second HCT.

[c]One patient died 9.7 years after HCT due to cardiorespiratory arrest secondary to disease progression.

[d]Neurocognitive impairment is defined as a score of <70 on Wechsler IQ scales.

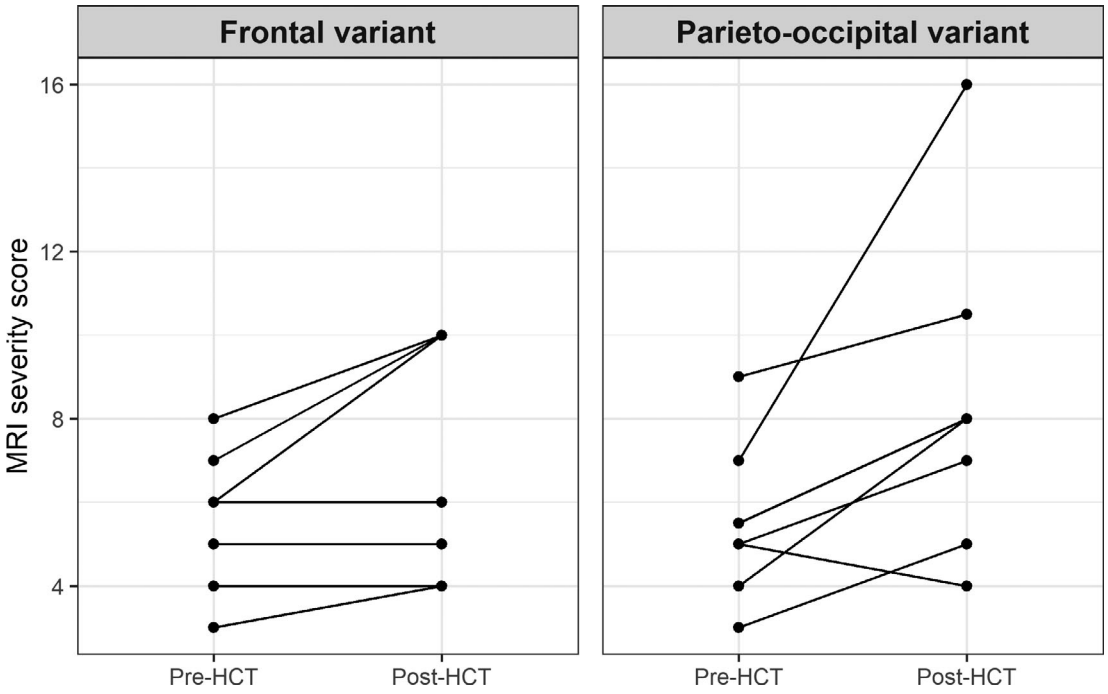

FIGURE 1 Loes MRI severity scores were obtained prior to treatment and at a mean of 1.2 years after hematopoietic stem cell transplantation. Connected lines represent the change in scores for individual patients with frontal or parietal-occipital demyelinating lesions

neurocognitive status are well-established predictors of treatment response,[3-5] but examination of the impact of the lesion location on outcomes has been limited by small sample sizes. Typically, lesions first develop in the splenium of corpus callosum with subsequent expansion into parieto-occipital white matter (POWM). In about 15-17% of cases, cALD emerges in the genu of corpus callosum expanding to frontal white matter (FWM).[6,7] The FWM variant has been suggested to be an unfavorable risk factor for disease progression after treatment.[4,6] Given the possibility of differential treatment response and the vastly different functions supported by the frontal vs posterior regions of the brain, this matched case series investigated the impact of lesion location on treatment response and neuropsychological outcomes.

2 | METHODS

Ethics approval for this retrospective analysis was obtained from the University of Minnesota Institutional Review Board. Brain MRIs from pre-treatment evaluations were reviewed for all 158 patients who underwent HCT at our center between January 1, 1990 and December 31, 2019.

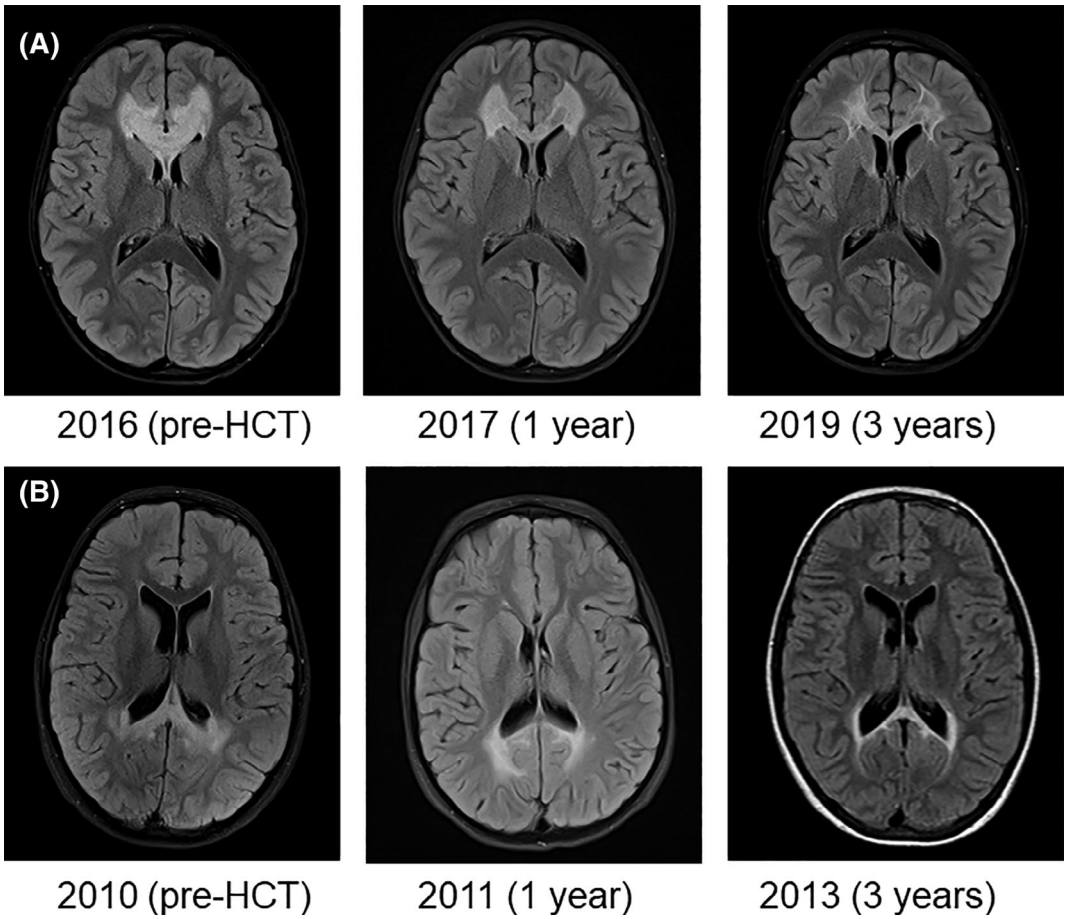

FIGURE 2 Longitudinal T2 FLAIR axial images for two patients with cerebral ALD lesions affecting (A) frontal white matter and (B) parietal-occipital white matter. MRIs for both patients received the same Loes MRI severity score of 4 at the time of HCT

Demyelination pattern and MRI severity were determined using the Loes scale.[8] The following inclusion criteria were applied to identify the FWM cohort: under age 18 years at the time of HCT; Loes score < 10; FWM demyelination without POWM disease; treated with a single allogeneic HCT. The seven patients meeting these inclusion criteria were matched to seven patients with POWM disease based on closest possible pre-HCT Loes score and lack of FWM involvement. A flow chart describing study selection is available in DATA S1.

Demographic data and transplant variables are presented in Table 1. HCT followed previously described institutional procedures; neutrophil and platelet engraftment, graft-vs-host disease and graft failure were determined based on reported HCT criteria.[9] Follow-up MRI severity scores, neurocognitive testing and psychiatric scores from the most recent comprehensive clinical evaluation were obtained from chart review (mean 1.2 years post-HCT, range 0.5-2.1 years). To analyze comparable data for each matched FWM-POWM pair, scores were used from the most recent visits in which data were available for both patients at the same time point (±3 months). Consistent with published methods,[10] verbal reasoning, visual reasoning, working memory, and processing speed were measured with the Wechsler intelligence scales. Psychiatric symptoms were assessed via caregiver ratings on clinical scales of the Behavior Assessment Scale for Children (BASC), a well-validated measure of pediatric psychopathology. Severe impairment was defined by neurocognitive and psychiatric scores ≥2 SDs from the normative mean. A decline of >7.5 points on a Wechsler scale was used to identify a minimum clinically important difference from pre- to post-HCT.[11] Clinical progress notes were reviewed to obtain additional detailed information about psychiatric concerns and psychoactive medications prescribed. Statistical analysis focused on descriptive statistics with confidence intervals and Kaplan-Meier calculations for overall survival. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Written informed consent to participate in clinical outcomes research was obtained from parents/guardians of patients included in this study.

3 | RESULTS

The 5-year overall survival was 100% in both groups, with a similar rate of transplant-related complications including graft-vs-host disease (Table 1). One late death was observed in the FWM cohort at 9.6 years post-HCT due to cardiorespiratory arrest secondary to disease progression. Post-HCT change in Loes MRI severity scores during the study period, illustrated in Figure 1, did not differ reliably in the POWM as compared to the FWM group (mean difference: 1.4, 95% CI: −1.6, 4.4). Figure 2 displays representative MRI images from two patients with FWM or POWM lesions, with pre-HCT images and follow up out to 3 years after treatment. Neurocognitive outcomes were also broadly similar (Figure 3). In both groups, 5/7 boys (71%) exhibited clinically meaningful decline in ≥1 neurocognitive domain from pre-HCT to follow-up. Development of severe impairment in working memory, which requires significant focus and attention to retain information for brief periods, was more frequent in the boys with FWM (4/7) as compared to POWM (0/7) lesions.

Clinical psychiatric concerns were more evident at follow up in the FWM group. Stimulant medication was prescribed to 6/7 (86%) FWM patients to address concerns with poor attention, impulse control and/or behavior regulation, as compared to 1/7 (14%) POWM patients. All four FWM patients with available caregiver ratings exhibited severe hyperactivity, and 3/4 demonstrated severely atypical behavior (eg, acting out of touch with reality, confused or disorganized speech, bizarre behaviors), whereas none of the POWM patients showed severe psychiatric symptoms (Figure 4). Neuropsychological evaluation reports provided evidence of severe behavioral problems for the three FWM patients without available caregiver ratings. One patient with FWM disease (age 11) was unable to remain seated for more than a few seconds during neuropsychological assessment. His clinical notes described poor social boundaries, near-constant talking, tangential speech, and destructive behaviors (eg, bending puzzle pieces, ripping pages out of test books), consistent with parent and teacher interview data indicating severe behavioral problems. Inattention, irritability and

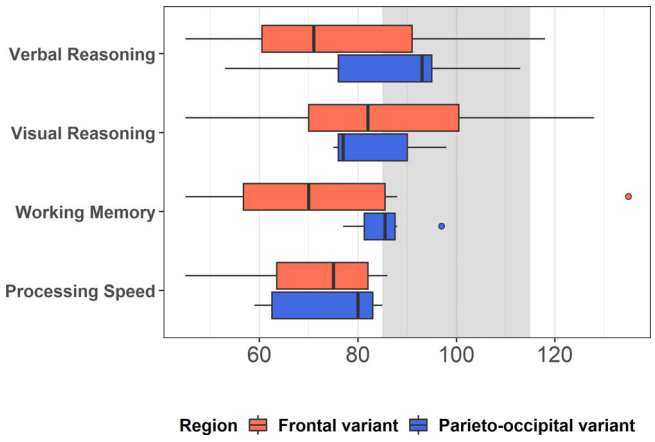

FIGURE 3 Neurocognitive outcomes of patients with frontal and parietal-occipital demyelination variant of cerebral ALD after hematopoietic stem cell transplantation. Wechsler IQ scales have a normative mean of 100 ± 15. Gray shading depicts scores in the average range. Boxplots represent the interquartile range for each outcome with a vertical line at the median. Outliers are denoted with dots, and the remaining range of each outcome is shown with horizontal lines

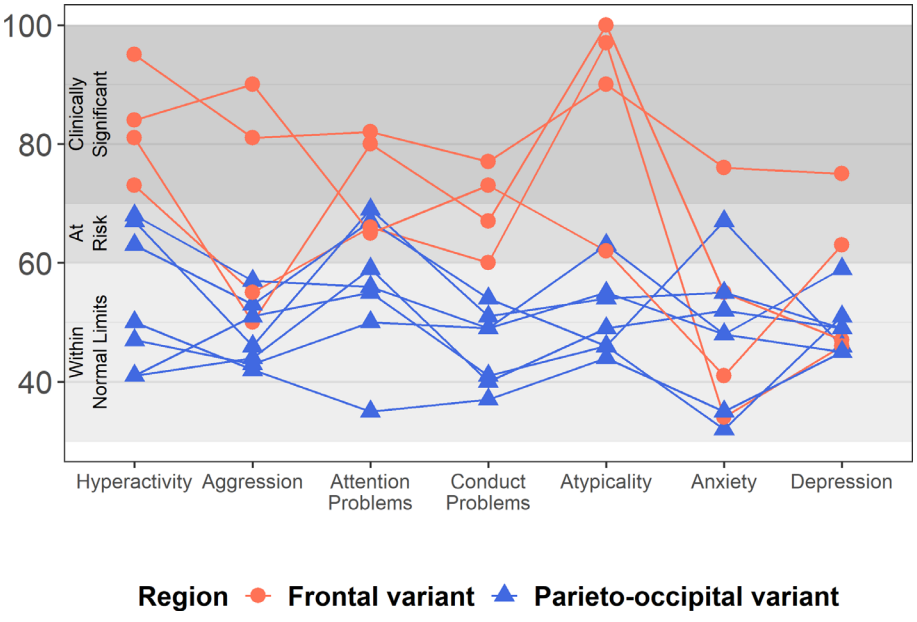

FIGURE 4 Caregiver ratings of psychiatric symptoms following hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy. T-scores on clinical scales of the Behavior Assessment System for Children (BASC) have a normative mean of 50 ± 10. Higher scores indicate more severe symptoms. Connected markers depict scores for individual patients

behavioral outbursts were noted for another patient (age 11), and the third patient (age 17) exhibited physically aggressive and oppositional behaviors with family members.

4 | DISCUSSION

This investigation revealed greater risk for severe psychiatric and working memory impairment when demyelinating cALD lesions were located in FWM, a critical brain region for regulation of thoughts, emotions and behavior. As compared to patients with the more common POWM variant of cALD, boys with FWM lesions were more likely to develop inattentive, hyperactive, aggressive and severely atypical behaviors, and to require medication to treat psychiatric symptoms. These results highlight the importance of comprehensive post-HCT care to address the behavioral health manifestations of cALD. Such severe psychiatric concerns exert wide-ranging effects on academic performance, task completion, social relationships, and day-to-day function.

Although pronounced psychiatric impairment was more widely observed in the FWM cohort, the current study failed to replicate a previous report suggesting greater risk for progression of cALD among FWM patients as compared to POWM patients. Kühl and colleagues reported a higher risk for fatal disease progression among patients with FWM lesions when Loes score was ≥ 4 ($n = 4$); below this threshold, outcomes were more favorable ($n = 2$).[4] While the study by Kühl et al. involved a longer follow-up period, the changes among those patients who progressed occurred within a time frame comparable to the present study. With a case-matching design, our investigation found that post-HCT advancement of MRI severity scores was no greater in the FWM group than the POWM group. Although 6/7 patients (86%) in our cohort had pre-HCT scores between 4 and 9, just one FWM patient (pre-HCT score of 6) died of eventual disease progression. Our finding of more comparable HCT survival and MRI progression in the FWM and POWM cohorts when MRI severity score < 10 is consistent with an earlier study by Loes et al. showing equivalent rates of disease progression in non-transplanted patients with FWM and POWM lesions.[6] Taken together with recent studies, our findings suggest that over-reliance on MRI severity "cutoff" scores to aid in prediction of favorable vs unfavorable outcomes may oversimplify the factors contributing to treatment response in this complex demyelinating disease. MRI severity, the neurocognitive status of a patient at the time of HCT, treatment-related variables, and the location of the lesion may all impact the likelihood of neurological and neuropsychological morbidities in the years following treatment.[4,5,12]

This retrospective study spanned over three decades with different conditioning regimens, GVH prophylaxis and potential neurotoxicity, which could have adversely affected neurocognitive function. Since moderate reduction in memory is a potential neurocognitive side effect of total body irradiation (TBI),[13,14] use of fractionated TBI conditioning could have contributed to neurocognitive deficits in two of the four patients with FWM lesions who experienced severe working memory impairment. Nevertheless, effects of treatment regimens are unlikely to explain the range of symptoms observed in our cALD patients. Psychiatric disturbance involving hyperactivity and severely atypical behavior is not commonly reported among survivors of HCT,[15] implicating a more direct association with FWM demyelinating lesions.

The results of this investigation provide evidence that along with MRI severity and neurocognitive status at the time of treatment, lesion location should be considered among risk factors for neurocognitive and psychiatric morbidities. Whether HCT remains the standard of care for early cALD or is replaced by emerging gene therapy approaches,[16] identification of prognostic factors that facilitate comprehensive care are critical. Care models should address the need for psychiatric resources for children and families, with recognition of differential risk based on lesion location.

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CONFLICT OF INTEREST

Ashish Gupta, Ryan Shanley, Daniel Kenney-Jung, and Elizabeth Pierpont declare that they have no conflict of interest. David Nascene consults with Biogen and WorldCare Clinical. Julie Eisengart served as an advisory board member for bluebird bio. Troy Lund and Paul Orchard receive research support from bluebird bio. Guarantor: Elizabeth I. Pierpont.

AUTHOR CONTRIBUTIONS

Ashish Gupta: study concept and design, data acquisition, analysis, and interpretation of data, and drafting and revising the manuscript. **David Nascene**: MRI interpretation and scoring and revising the manuscript for important intellectual content. **Ryan Shanley**: analysis and interpretation of data, drafting figures, and drafting

and revising the manuscript. **Daniel Kenney-Jung**: data acquisition, interpretation of data, and revising the manuscript for important intellectual content. **Julie Eisengart**: data acquisition, interpretation of data, and drafting and revising the manuscript. **Troy Lund**: data acquisition, interpretation of data, and revising the manuscript for important intellectual content. **Paul Orchard**: data acquisition, interpretation of data, and revising the manuscript for important intellectual content. **Elizabeth Pierpont**: study concept and design, data acquisition, analysis and interpretation of data, drafting/revising the manuscript and study supervision. **Elizabeth Pierpont**: responsibility for the work and the conduct of the research, has access to the data, and controlled the decision to publish.

ETHICS APPROVAL

This study was approved by the University of Minnesota Institutional Review Board under the following protocol: STUDY00002247.

ORCID

Elizabeth I. Pierpont https://orcid.org/0000-0001-7555-8613

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SUPPORTING INFORMATION

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