#### **RESEARCH ARTICLE**

## Epilepsia®

## **Epilepsy center characteristics and geographic region influence presurgical testing in the United States**

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## **Abstract**

**Objective:** Persons with drug-resistant epilepsy may benefit from epilepsy surgery and should undergo presurgical testing to determine potential candidacy and appropriate intervention. Institutional expertise can influence use and availability of evaluations and epilepsy surgery candidacy. This census survey study aims to examine the influence of geographic region and other center characteristics on presurgical testing for medically intractable epilepsy.

**Methods:** We analyzed annual report and supplemental survey data reported in 2020 from 206 adult epilepsy center directors and 136 pediatric epilepsy center directors in the United States. Test utilization data were compiled with annual center volumes, available resources, and US Census regional data. We used Wilcoxon rank-sum, Kruskal–Wallis, and chi-squared tests for univariate

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analysis of procedure utilization. Multivariable modeling was also performed to assign odds ratios (ORs) of significant variables.

**Results:** The response rate was 100% with individual element missingness  $\langle 11\%$ across 342 observations undergoing univariate analysis. A total of 278 complete observations were included in the multivariable models, and significant regional differences were present. For instance, compared to centers in the South, those in the Midwest used neuropsychological testing  $OR = 2.87,95\%$  confidence interval  $|CI| = 1.2-6.86$ ;  $p = .018$ ) and fluorodeoxyglucose-positron emission tomography  $(OR = 2.74, 95\% CI = 1.14-6.61; p = .025)$  more commonly. For centers in the Northeast (OR = .46, 95% CI = .23–.93; *p* = .031) and West (OR = .41, 95% CI = .19–.87; *p* = .022), odds of performing single-photon emission computerized tomography were lower by nearly 50% compared to those in the South. Center accreditation level, demographics, volume, and resources were also associated with varying individual testing rates.

**Significance:** Presurgical testing for drug-resistant epilepsy is influenced by US geographic region and other center characteristics. These findings have potential implications for comparing outcomes between US epilepsy centers and may inject disparities in access to surgical treatment.

#### **KEYWORDS**

drug-resistant epilepsy (DRE), epilepsy monitoring unit (EMU), epilepsy surgery

## **1** | **INTRODUCTION**

Epilepsy affects nearly 3.5 million persons in the United States.<sup>[1](#page-10-0)</sup> Approximately 30% of individuals develop drugresistant epilepsy (DRE), defined by refractory seizures despite appropriate treatment with two antiseizure medications[.2](#page-10-1) DRE is associated with increased morbidity and mortality, decreased quality of life, and increased health care utilization among all persons with epilepsy.<sup>3,4</sup>

Epilepsy surgery is an effective treatment. For focal onset DRE, resective surgery is superior to medical man-agement for treatment of seizures and may be curative.<sup>[5,6](#page-10-3)</sup> Recent surgical advances including stereotactic laser interstitial thermal therapy and neuromodulation have expanded the population of eligible patients. All patients with DRE should be evaluated at a comprehensive epilepsy center for consideration of epilepsy surgery or other specialized services to improve seizure control and maximize likelihood of seizure freedom.<sup>7-9</sup>

Surgical candidacy is assessed through specialized presurgical evaluations to define the likelihood of seizure freedom or palliation more clearly. In addition to clinical assessment, multimodal testing is needed to evaluate electrophysiology, brain structure, and function. Long-term monitoring (LTM) with video-electroencephalography

#### **Key Points**

- The objective was to determine epilepsy center characteristics associated with increased odds of having a specific presurgical test performed
- The study design was a census survey of all center directors at NAEC-accredited epilepsy centers performed in 2020 with 100% response rate
- US epilepsy center characteristics, including location, are associated with variations in presurgical testing
- These findings may contribute to disparities in access to surgical treatment and could impact surgical outcomes

(EEG) for seizure capture, high-resolution structural brain magnetic resonance imaging (MRI), and neuropsychological testing are currently standard of care investigations in children and adults.<sup>10-14</sup>

In recent years, advances in imaging modalities, EEG capabilities, and surgical techniques have diversified evaluation and treatment approaches. Despite increasing numbers of available tests, the quality of evidence for their use in presurgical evaluations remains low.<sup>15-17</sup> This knowledge gap contributes to significant variability in practice, the scope and impact of which is incompletely understood.

The vast majority of presurgical evaluations in the United States are performed at epilepsy centers accredited by the National Association of Epilepsy Centers (NAEC)[.18](#page-10-7) On an annual basis, the NAEC collects data from approximately 260 accredited epilepsy centers on the size and scope of epilepsy monitoring unit (EMU), personnel, diagnostic testing, surgeries, and other services. We designed and disseminated a supplemental survey further examining testing and treatment practices pertaining to epilepsy surgery. This study details reported variability in diagnostic testing across NAEC member centers and describes center features associated with specific test utilization patterns.

## **2** | **MATERIALS AND METHODS**

We analyzed data obtained from the 2019 annual report<sup>[18](#page-10-7)</sup> and a supplemental epilepsy surgery practice survey (Appendix [S1](#page-11-0)) from all Level 3 and Level 4 NAEC epilepsy centers. The 2019 annual reports were collated to the corresponding centers' supplemental census survey to avoid duplication of data collection. All reported data reflect pre-COVID-19 pandemic practice. Importantly, for combined adult/pediatric centers, one survey was sent to the adult director and another was sent to the pediatric director.

To combine data from the annual survey and the supplemental survey, data from combined adult/pediatric center annual surveys were divided based on age category (age  $\langle$  19 years and  $\geq$  19 years) and linked to the supplemental survey from that demographic center director ("pediatric combined" or "adult combined").

## **2.1** | **Statistical analysis**

Survey responses were described using frequency (percentage of nonmissing totals) for categorical variables and median (interquartile range) for continuous variables. Standard procedures with one-inflated distributions were first dichotomized with two categories: 100% or <100%. Wilcoxon rank-sum, Kruskal–Wallis, and chi-squared tests were used to compare procedure utilization between accreditation levels (Level 3 vs. 4) or center demographics (adult combined vs. adult-only vs. pediatric combined vs. pediatric-only).

For each of the 15 evaluation procedures, separate regression models were built to evaluate associations

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between center characteristics and utilization, defined as reported practice percentage. Continuous variables with wide ranges were scaled by 10 or 100 units so that model estimates were easier to interpret. Potential model covariates included accreditation level, center and center director demographics, institution type (academic, private practice, or teaching affiliate), US Census Bureau geographic region (South, Midwest, Northeast, or West), number of epileptologists with ≥2 years of fellowship, number of EMU beds, number of annual EMU admissions (in hundreds), waiting days for routine EMU admissions (in tens), waiting days for epilepsy specialist appointments (in tens), waiting days for surgeon referrals/appointments (in tens), offering resective or ablative surgery and surgical intracranial electrodes (yes/no), intracranial surgery and monitoring rates (per 100EMU admissions), percent of resections with electrocorticography (ECOG), use of image postprocessing (IPP; yes/no), data analysis support (yes/no), image-guided robotics (yes/no), and frequency of multidisciplinary epilepsy patient management conference (MEPMC; no formal meeting, as needed, or weekly).

We then performed multivariable analysis. Because utilization was expressed in percentages bounded between and including 0 and 100%, a transformation was utilized before model fitting to shift outcomes inward from the two extreme values of 0 or 100%. Utilization outcomes were transformed by the mathematical equation,  $(y * [n-1] + .5) / n$ , where *y* was the percentage and *n* was the sample size. A logit function was further applied to the transformed outcomes to achieve continuous and unbounded dependent variables. We fit linear regression models starting with all potential covariates, then we used a backward stepwise algorithm based on Akaike information criterion to eliminate nonsignificant predictors. Finally, model estimates were exponentiated to present them as odds ratios (ORs) on the original scale. Probability values < .05 were considered statistically significant. All statistical analyses were conducted in R version 4.0 (R Core Team).

## **2.2** | **Standard protocol approvals**

The ethical standards committee at Nationwide Children's Hospital determined this study to be exempt from institutional review board approval.

## **3** | **RESULTS**

## **3.1** | **Exploratory characteristics**

The supplemental survey response rate was 100%, although the survey was not always complete. A total of 342

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<span id="page-3-0"></span>**TABLE 1** Exploratory characteristics,  $N = 342$ 



Abbreviations: IPP, image postprocessing; MEPMC, multidisciplinary epilepsy patient management conference.

observations were included, with 206 (60%) respondents reporting as adult EMU directors. Level 4 EMU centers accounted for 274 (80%) of observations, and 211 (62%) were categorized as academic/university type institutions. Epilepsy center demographics and characteristics are summarized in Table [1](#page-3-0). Degree of missingness for all variables was <11% (Table [2](#page-3-1)).

## **3.2** | **Testing differences**

Percent utilization of diagnostic tests for presurgical evaluation varied between Level 3 and Level 4 centers, as summarized in Table [3](#page-4-0). LTM EEG for seizure capture and brain MRI were utilized in 100% of evaluations for the vast majority of centers and are presented as percent of centers

#### <span id="page-3-1"></span>**TABLE 2** Data missingness,  $N = 342^a$



<span id="page-3-2"></span>Abbreviations: EMU, epilepsy monitoring unit; IPP, image postprocessing; MEPMC, multidisciplinary epilepsy patient management conference. aStatistics presented: number of missing observations.

with 100% utilization. Neuropsychological testing and interictal brain fluorodeoxyglucose–positron emission tomography (FDG-PET) use varied significantly between centers (presented as median and interquartile range), as did less ubiquitous test modalities.

Similarly, testing practices varied between epilepsy center population types (Table [4\)](#page-5-0). FDG-PET, single-photon emission computerized tomography (SPECT), functional MRI (fMRI), EEG source imaging (ESI), genetic testing, and social work evaluation had higher median utilization percentages in pediatric-only centers, whereas neuropsychological testing and psychiatric evaluation had lower percentage utilization in pediatric populations.

## **3.3** | **Center characteristics associated with diagnostic test utilization**

A total of 278 complete observations were included in the multivariable model examining center characteristics associated with testing frequencies (Table [S1](#page-11-0)). Summaries of statistically significant findings are detailed in Table [5](#page-6-0) (more common evaluations) and Table [6](#page-8-0) (less common evaluations).

The most common tests were brain MRI, LTM EEG for seizure capture, neuropsychological testing, and FDG-PET. Lower MRI utilization was associated with a greater number of epileptologists with ≥2 years of fellowship training ( $OR = .93, 95\%$  confidence interval  $[CI] = .87-.99$ ;  $p = .031$ ). LTM EEG for seizure capture was more commonly utilized at centers with MEPMC weekly meetings (OR = 15, 95% CI = 4.3–52.1; *p*< .001) or MEPMC meetings

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as needed (OR = 8.39, 95% CI = 2.27–31.0; *p* = .0020) compared to no formal meetings. Neuropsychological testing was more commonly utilized by centers in the Midwest (compared to the South;  $OR = 2.87$ , 95%  $CI = 1.2 - 6.86$ ;  $p = .018$ ), those capable of resective or ablative surgery (OR = 15.7, 95% CI = 1.99–124; *p* = .009), and those with weekly MEPMC (compared to no MEPMC;  $OR = 54.4$ , 95% CI =  $6.79-435$ ;  $p = <.001$ ).

FDG-PET and SPECT utilization varied by location and population. Compared to those in the South, Midwest centers (OR = 2.74, 95% CI = 1.14–6.61; *p* = .025) utilized PET more often; whereas pediatric center directors reported decreased FDG-PET use (OR = .24, 95% CI = .09–.67;  $p = .007$ ). SPECT was more commonly used in the South than at centers in the Northeast ( $OR = .46, 95\%$  $CI = .23-.93$ ;  $p = .031$ ) or West (OR = .41, 95% CI = .19–  $.87; p = .022$ ).

Some variables predicted differential utilization of less common evaluations. Wada testing was utilized at centers with a lower EMU admission volume (OR = .89, 95% CI  $=$  .80–1.00;  $p = .047$ ) and a lower intracranial monitoring rate (OR = .92, 95% CI = .86–.98;  $p = .006$ ), in addition to other features. Among the other test modalities, genetic testing had the greatest OR with pediatric center directors  $(OR = 16, 95\% \text{ CI} = 8.64 - 29.8; p = <.001)$ . Conversely, the most negative association was psychiatric consultations and centers offering surgery with intracranial electrodes

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Abbreviations: EEG, electroencephalography; ESI, EEG source imaging; FDG-PET, fluorodeoxyglucose–positron emission tomography; fMRI, functional MRI; HD-EEG, high-definition EEG; LTM, long-term monitoring; MEG/MSI, magnetoencephalography/magnetic source imaging; MRI, magnetic resonance imaging; SPECT, single-photon emission computerized tomography; TMS, transcranial magnetic stimulation.

<span id="page-4-1"></span>a Statistics presented: *n* (%) or median (interquartile range).

<span id="page-4-2"></span>b Statistical tests performed: chi-squared test of independence, Wilcoxon rank-sum test, ESI EEG source imaging.

<span id="page-4-3"></span> $\degree p < .05$ .

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#### <span id="page-5-0"></span>**TABLE 4** Diagnostic test utilization by center director demographics



Abbreviations: EEG, electroencephalography; ESI, EEG source imaging; FDG-PET, fluorodeoxyglucose–positron emission tomography; fMRI, functional MRI; HD-EEG, high-definition EEG; LTM, long-term monitoring; MEG/MSI, magnetoencephalography/magnetic source imaging; MRI, magnetic resonance imaging; SPECT, single-photon emission computerized tomography; TMS, transcranial magnetic stimulation.

ESI  $0(0-15)$   $0(0-5)$   $0(0-11)$   $4(0-19)$   $0.044$ <sup>c</sup> Genetic testing  $10 (5-10)$   $5 (0-10)$   $50 (25-75)$   $70 (30-80)$   $$0.01$ <sup>c</sup>$ TMS  $0 (0-0)$   $0 (0-0)$   $0 (0-0)$   $0 (0-0)$   $0 (0-1)$   $0.001$ <sup>c</sup> Neuropsychological Testing 100 (90–100) 95 (75–100) 90 (50–100) 90 (75–100) 00 (75–100) 00 14<sup>c</sup> Social Work Evaluation 25 (10-55) 30 (10-80) 30 (10-90) 72 (16-100) 0.012<sup>c</sup> Psychiatric Evaluation 25 (10-50) 25 (10-50) 26 (10-50) 26 (10-30) 15 (10-30) 034<sup>c</sup> Psychological Evaluation 25 (15–50) 20 (5–50) 25 (10–50) 22 (10–58) .5

<span id="page-5-1"></span>a Statistics presented: *n* (%) or median (interquartile range).

<span id="page-5-3"></span><span id="page-5-2"></span>b Statistical tests performed: chi-squared test of independence, Kruskal–Wallis test, ESI EEG source imaging.  $\degree p < .05$ .

 $(OR = .19, 95\% \text{ CI} = .04 - .82; p = .027)$ . Additional independent factors associated with increased utilization are summarized in Table [5.](#page-6-0)

## **4** | **DISCUSSION**

This is the first study to evaluate the impact of epilepsy center characteristics on presurgical testing for DRE. Previous studies and systematic reviews have not conclusively characterized the diagnostic accuracy, costeffectiveness, or prognostic implications of many available tests.<sup>[15–17,19–22](#page-10-6)</sup> This knowledge gap is in part due to a lack of multicenter studies directly comparing modalities, difficulty establishing study periods over time with rapidly developing diagnostic and therapeutic techniques and diverse protocols, and cultural biases to testing.<sup>16,23,24</sup> We identified practice variability across centers that could contribute to disparities in epilepsy surgery access and potentially impact outcomes. $^{20}$  As a step forward in addressing these questions, we describe the variability of presurgical evaluation across epilepsy centers in the United States.

Testing often occurs in a stepwise approach. Inpatient LTM EEG, high-resolution structural brain MRI, and neuropsychological testing are well-established components

of standard assessment for persons with DRE. $10-14}$  This survey of all NAEC-accredited Level 3 and 4 epilepsy centers confirms high utilization of standard investigations. On univariable testing, Level 4 centers utilized a greater array of test modalities. These findings are expected, considering the differences between Level 3 and Level 4 epilepsy centers.[17](#page-10-10) NAEC designates center level based on local resources, with Level 4 centers serving as regional or national referral sites with expertise in specialized neuroimaging, intracranial EEG, and more complex sur-gical techniques.<sup>[9](#page-10-11)</sup> Similarly, pediatric epilepsy surgery encompasses a distinct subset of considerations and challenges, often requiring evaluation in highly specialized centers.[12,13](#page-10-12)

Core test utilization differed between geographic regions after correcting for other characteristics, and these variations may influence outcomes. Centers in the South reported decreased neuropsychology utilization compared to those in the Midwest. The regional influence of neuropsychology evaluation is important, as this is considered a central component of presurgical evaluation by many working groups, including the International League Against Epilepsy.<sup>25</sup> More broadly, neuropsychological evaluation is also a helpful tool for all stages of epilepsyrelated care, and is essential for detecting adverse cogni-tive and/or behavioral impairment after epilepsy surgery.<sup>[26](#page-11-2)</sup>



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Note: Estimates presented are odds ratios with 95% confidence intervals. *Note*: Estimates presented are odds ratios with 95% confidence intervals.

Abbreviations: EEG, electroencephalography; EMU, epilepsy monitoring unit; FDG-PET, fluorodeoxyglucose–positron emission tomography; IPP, image postprocessing; LTM, long-term monitoring; MEPMC, Abbreviations: EEG, electroencephalography; EMU, epilepsy monitoring unit; FDG-PET, fluorodeoxyglucose–position emission tomography; IPP, image postprocessing; LTM, long-term monitoring; MEPMC, multidisciplinary epilepsy patient management conference; MRI, magnetic resonance imaging. multidisciplinary epilepsy patient management conference; MRI, magnetic resonance imaging.

<span id="page-7-0"></span> $^{a}p$  < .05.

The lower utilization in the South may be secondary to a greater burden of epilepsy with fewer resources in this region.<sup>27,28</sup> The impact of differential utilization of neuropsychological testing remains unknown and requires further investigation.

Ancillary tests are often employed when the epilepto genic zone is not identified on structural imaging, data are discordant, or eloquent cortex mapping is needed to in form surgical planning.<sup>23,29,30</sup> Furthermore, epilepsy surgery in children requires a distinct testing approach, given considerations of brain development, neuroplasticity, and pediatric-specific epilepsy syndromes.[24](#page-11-5) Our data reveal a close association between center characteristics and use of these test modalities.

Functional testing includes imaging with FDG-PET and SPECT as well as fMRI, functional magnetoenceph alography/magnetic source imaging (MEG/MSI), and Wada, which require multidisciplinary expertise and are not available at all centers. Furthermore, there are no definitive studies reporting superior outcomes between modalities. Respondents reported median percentages of cases using FDG-PET, SPECT, fMRI, and Wada as 60%, 10%, 25%, and 10%, respectively (Table [S1\)](#page-11-0). As expected, Level 4 centers reported increased utilization of PET, SPECT, fMRI, and Wada, which is reflective of the NAEC accreditation levels and increased surgical complexity at Level 4 centers. Another shared characteristic linked to increased use of PET, fMRI, and SPECT was IPP, likely re lated to the benefit of more advanced analysis to improve their sensitivity and specificity for identifying the epilep togenic zone or functional tissue.

Several variations in ancillary testing were novel, in cluding a striking regional influence on the use of FDG-PET and SPECT. FDG-PET was utilized more often in the Midwest compared to the South, whereas SPECT was utilized more commonly in the South compared to the Northeast and West. Given their clinical similarities to help localize seizure focus, PET and SPECT have been directly compared in previous studies, with varied con clusions. A 2016 meta-analysis concluded PET may be valuable in MRI-negative temporal lobe epilepsy, but the prognostic implication of SPECT is unclear.<sup>16</sup> It has also been postulated that use of PET versus SPECT is often de pendent on facility resources and experience.<sup>31</sup> The geographic influences in our model may support this notion of experience through an influence of training institution and eventual practice location. The effects on outcomes remain uncertain.

Volume of procedure types and center director demo graphics were also linked to test utilization. Adult center directors and those with lower intracranial monitoring rates reported greater use of FDG-PET and Wada. This finding may reflect that centers with a higher proportion



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of temporal lobectomies in adults utilize more FDG-PET and Wada. Centers with more resections accompanied by intraoperative ECOG reported greater SPECT and fMRI use, which may be due to a higher proportion of extratemporal resections.

MEG/MSI, high-definition EEG (HD-EEG), and ESI combine spatial and temporal data for localizing epileptiform activity. Among all respondents, MEG/MSI was utilized in a median of 5% of presurgical evaluations, whereas ESI and HD-EEG were utilized in fewer cases. MEG/MSI was utilized more often in higher volume centers and those utilizing image-guided robotics, whereas HD-EEG was more commonly utilized in private practice centers. Similar to MEG/MSI, ESI was utilized by centers with image-guided robotics, but also correlated with combined adult and pediatric centers as well as higher percentage of resections with intraoperative ECOG. These tests remain rarely utilized among US epilepsy centers, likely limiting significant effects on outcomes within the US health care system.

Psychological comorbidities are common in persons with epilepsy, $32$  and social determinants of health are key drivers of quality of life in epilepsy. $33$  Despite this, a minority of presurgical patients received psychiatric, psychological, and social work evaluations. These findings are particularly striking in light of NAEC recognition of these as essential services at specialized epilepsy centers,<sup>[9](#page-10-11)</sup> and attestation by the responding directors that these services can be provided at their center. We again noted regional influences, with Midwest centers utilizing social work more than centers in the South. This may reflect a critical geographic disparity in resources and should be further explored. $34$  Psychiatric consultations were utilized less in pediatric populations and at Level 3 centers, likely reflecting disparities in available resources.

The census survey instruments had a 100% response rate, with a low range of missingness, which was likely due to their requirement for NAEC accreditation. However, the findings are limited primarily by how data were acquired through the NAEC accreditation annual report and supplemental epilepsy surgery survey. Medical directors were asked to estimate the percentage of presurgical patients who had each diagnostic test over the past year, rather than provide actual percentages for each test, raising concern for recall bias. Although NAEC member centers do not provide the entirety of epilepsy care in the United States, they likely represent most of the special-ized evaluations and procedures for those with DRE.<sup>[18](#page-10-7)</sup> Therefore, our analysis likely reflects accurate data regarding the current state of diagnostic testing for epilepsy care in the United States.

## **5** | **CONCLUSIONS**

Our study is the first to identify effects of epilepsy center characteristics on presurgical testing, which may contribute to disparities in epilepsy surgery access. $35$  These findings provide a critical foundation to better examine outcomes for persons with DRE and highlight the difficulty in developing standardized testing algorithms. Future studies linking presurgical testing variation and patient outcomes are urgently needed to better identify disparities and improve care.

## **AUTHOR CONTRIBUTIONS**

Stephanie M. Ahrens: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. Kristen H. Arredondo: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. Anto I. Bagic: Drafting/ revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. Shasha Bai: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; additional contributions: performed biostatistical analysis. Kevin E. Chapman: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. Michael A. Ciliberto: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design. Dave F. Clarke: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. Mariah Eisner: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; additional contributions: performed biostatistical analysis. Nathan B. Fountain: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. Jay R. Gavvala: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design. M. Scott Perry: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design. Kyle C. Rossi: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design. Lily C. Wong-Kisiel: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design. Susan T. Herman: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. Adam P. Ostendorf: Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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## **CONFLICT OF INTEREST**

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## <span id="page-11-0"></span>**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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