ACR Open Rheumatology
Vol. 4, No. 9, September 2022, pp 825–831
DOI 10.1002/acr2.11485

American College of Rheumatology
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Investigation of Inactive Disease States Among Patients With Juvenile Idiopathic Arthritis in the Childhood Arthritis and Rheumatology Research Alliance Registry

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Objective. Inactive disease is the treatment goal for juvenile idiopathic arthritis (JIA), but there are multiple measures for disease activity. The objective was to compare individuals with JIA who meet different definitions for inactive disease.

Methods. Disease activity measures were determined at the 1-year follow-up visit for all patients with JIA enrolled in a North American multicenter registry from 2015 to 2019, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. Patient and disease characteristics between those who met only one composite definition of inactive disease were compared by χ^2 for categorical variables and Wilcoxon rank sum for continuous variables. The Spearman correlation coefficient was calculated for simple disease measures.

Results. Among all 2904 patients with JIA enrolled in the CARRA Registry with 1-year visit data, 1984 (68%) had no active joints, 1485 (51%) had a physician global score of 0, 1366 (47%) had a patient/parent global score of 0, 1293 (45%) met the American College of Rheumatology provisional criteria for clinical inactive disease (ACR CID), and 1325 (46%) had a clinical Juvenile Arthritis Disease Activity Score (cJADAS10) of 1 or less. Almost half (47%) did not meet either composite definition of inactive disease, and 38% met both ACR CID and cJADAS10 of 1 or less.

Conclusion. In a multicenter cohort of patients with JIA in North America, a large proportion of patients had inactive disease by single or composite measures after 1 year of observation in the Registry. There was significant overlap between patients who met ACR CID criteria and those who had a cJADAS10 of 1 or less. Additional studies are needed to evaluate the reasons for discordance in inactive disease measures.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is an inflammatory disease beginning in childhood that typically requires ongoing monitoring and treatment to minimize adverse outcomes in the short and long term. The stated goal of treatment in JIA is inactive disease (1–3) generally defined as a lack of evidence for inflammation in the joints, the eyes, and other extra-articular sites (4,5). Given the lack of disease activity specific biomarkers for JIA, disease activity is usually measured in clinical practice by single measures like active joint count (AJC) or composite disease activity scores, a combination of patient- and physician-reported clinical factors (6). Treatment recommendations (7,8) and treatment strategy recommendations (1) both use a measure of disease activity to determine a plan of care for each patient; however, recent treat to target (T2T) recommendations strongly suggest the use of a composite score to capture multiple aspects of the disease, preferably a continuous measure that can be determined at the point of care (1).

There are several definitions for clinical inactive disease by composite disease activity measures, including the American College of Rheumatology provisional criteria for clinical inactive disease (ACR CID) (9), the Juvenile Arthritis Disease Activity Score (JADAS) (10), and the clinical JADAS (cJADAS), the cJADAS10 includes a maximum AJC of 10 (11). The ACR CID is a binary measure that requires several conditions to meet the definition of inactive disease. The factors included in ACR CID are no joints with active arthritis, physician's global assessment of disease activity score (PGA) of best possible on the scale used, no active features of systemic JIA, no active uveitis, a duration of morning

This work was supported by the Rheumatology Research Foundation Norman B Gaylis, MD Clinical Research Award (to Dr. Mannion).

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Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr2.11485&file=acr211485-sup-0001-Disclosureform.pdf.

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Submitted for publication March 24, 2022; accepted in revised form June 15, 2022.

stiffness of 15 minutes or less, and no elevated laboratory measure of inflammation (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) attributable to JIA (9). The cJADAS10 is the sum of the PGA (0-10 visual analog scale [VAS]), the parent/patient global assessment of overall well-being on a 0-10 VAS (PtGE), and the AJC (11); the JADAS includes a normalized ESR in the total sum (10).

Because these scores can be measured during each clinical encounter, they are ideal for repeated measurement that would be used in a T2T protocol. Current T2T guidelines for JIA suggest a target of inactive disease but decline to suggest one composite measure over another (1). Although the composite measures are designed to identify inactive disease, different components are used to determine disease activity status. It is unclear whether the measures will identify the same group of patients or whether one measure will result in more favorable short- and long-term outcomes and thus should be prioritized for use during clinical assessments. In an inception cohort of patients with JIA in the UK, of the patients meeting at least one definition of inactive disease, only 44% met both the ACR CID and the cJADAS10 definition of inactive disease (12).

We sought to classify the disease activity status of patients with JIA in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. The objective of this analysis was to determine the frequency of patients with JIA who met any definition for inactive disease in the CARRA Registry, compare the agreement between different definitions of inactive disease, and compare patient characteristics of individuals who meet one but not both composite definitions for inactive disease.

PATIENTS AND METHODS

We used a prevalent cohort of participants from the CARRA Registry. The CARRA Registry collects clinical data at least every 6 months on all enrolled individuals with rheumatic disease from more than 70 pediatric rheumatology clinics in the United States and Canada (13). Participants are enrolled in the Registry anytime on or after diagnosis and after parents and/or guardians provide written informed consent and patients aged 7-18 years provide assent for data collection and research analysis. The analysis included 1-year follow-up visit data from the start of the Registry in July 2015 through December 2019.

Clinical disease activity measures collected at each Registry visit include PGA on a 21-point (0.5 increment) scale from 0 to 10, patient/parent global assessment of overall well-being (PtGE) on an 11-point scale from 0 to 10, pain intensity in last 7 days on an 11-point scale from 0 to 10, AJC (numeric free text, no maximum), duration of morning stiffness (categorical: none, ≤15 minutes, 16-60 minutes, and >60 minutes), childhood health assessment questionnaire (CHAQ), presence of systemic symptoms in the last 2 weeks, ESR value, provider determined abnormal ESR because of JIA, and presence of active uveitis (if diagnosed with uveitis). Uveitis was determined to be inactive in individuals who had a diagnosis of uveitis in the Registry and on the most recent recorded ophthalmology examination had no cells reported in the anterior chamber. Uveitis diagnosis and history is collected by the pediatric rheumatology site and reported if ever present prior to the index visit. Individuals met the definition for ACR CID if the PGA was 0, the AJC was 0, they had 15 minutes or less of morning stiffness, they did not have active systemic symptoms, they did not have active uveitis, and the ESR was not abnormal because of JIA (9). The cJADAS10 is the sum of the PGA, the PtGE, and the AJC with a maximum count of 10 for a total score of 0 to 30. Individuals who had a cJADAS10 of 1 or less met the cJADAS10 definition for inactive disease (11). PGA, PtGE, pain, AJC, and CHAQ were individually considered simple disease activity measures, and ACR CID and cJADAS10 were considered composite disease activity measures.

For this analysis, we included individuals diagnosed with JIA who had at least 12 months of observable time after enrollment and completion of the 1-year follow-up visit to maximize the opportunity for patients to achieve inactive disease. We reported the demographic and disease characteristics at the 1-year visit for all patients regardless of disease duration. Individuals were excluded if they had incomplete PGA, PtGE, AJC, morning stiffness, or uveitis activity (if participant had a diagnosis of uveitis in the Registry) measures at the 1-year visit. The patient and disease characteristics between those who met one composite definition of inactive disease, but not the other, were compared by χ^2 for categorical variables and Wilcoxon rank sum for continuous variables. The Spearman correlation coefficient was calculated between simple disease activity measures: PGA and PtGE, PGA and AJC, PtGE and AJC, PGA and pain, and PtGE and pain at the 1-year visit for all patients. To assess for the effects of longer disease assessment experience, we performed a sensitivity analysis using only participants who were enrolled within 60 days of diagnosis. The University of Alabama at Birmingham Institutional Review Board (IRB) approved this analysis, protocol IRB-170112004. Participants provided informed, written consent for participation in research activity including publication upon enrollment into the CARRA Registry. We used SAS version 9.4 for analysis and considered a *P* value of less than 0.05 as significant.

RESULTS

The CARRA Registry contained 2904 patients with JIA who had complete disease activity data at the 1-year postenrollment visit. Almost three fourths (72%) of the patients were female, 82% were White, and the median age at the 1-year visit was 11 years (interquartile range [IQR] 7-15 years) (Table 1). Most of the patients had polyarticular JIA (pJIA) or oligoarticular JIA (oJIA) (rheumatoid factor [RF] negative pJIA 1057 [36%]; RF positive pJIA 230 [8%]; oJIA 840 [29%]). Only 6% (168) of individuals had a diagnosis of uveitis ever recorded by the 1-year postenrollment visit.

Table 1. Comparison of clinical characteristics at baseline by inactive disease definition at 1-year visit (N = 2904), *P* value for comparison between ACR CID only and cJADAS10 ID only

Characteristic	All patients, N = 2904	ACR CID only n = 202 (7%)	cJADAS10 ID only n = 234 (8%)	Both ACR and cJADAS10 ID n = 1091 (38%)	Not in inactive disease n = 1377 (47%)	*P* value comparing ACR CID only and cJADAS10 ID only
Sex (female)	2091 (72%)	149 (74%)	165 (71%)	769 (70%)	1008 (73%)	0.5
Race, n (%)						
White	2389 (82)	177 (88)	181 (77)	928 (85)	1103 (80)	0.008
Black	142 (5)	9 (5)	13 (6)	37 (3)	83 (6)	0.8
Asian	118 (4)	3 (2)	14 (6)	51 (5)	50 (4)	0.03
Hispanic	282 (10)	11 (5)	24 (10)	84 (8)	163 (12)	0.1
Age (y), median (IQR)	11 (7-15)	12 (8-14)	11 (7-14)	10 (6-14)	12 (9-15)	0.6
ILAR subtype, n (%)						0.6
Systemic	250 (9)	18 (9)	30 (13)	119 (11)	83 (6)	
Oligo	840 (29)	62 (31)	64 (27)	366 (34)	348 (25)	
RF+ poly	230 (8)	18 (9)	19 (8)	60 (5)	133 (10)	
RF− poly	1057 (36)	68 (34)	79 (34)	396 (36)	514 (37)	
ERA	264 (9)	15 (7%)	19 (8)	70 (6%)	160 (12)	
Psoriatic	205 (7)	17 (8)	14 (6)	61 (6)	113 (8)	
Undifferentiated	58 (2)	4 (2)	9 (4)	19 (2)	26 (2)	
Active joint count, median (IQR)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)	1 (0-3)	0.04
Limited joint count, median (IQR)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)	1 (0-2)	0.04
CHAQ, median (IQR)	0 (0-0.38)	0.25 (0-0.5)	0 (0-0.1)	0 (0-0)	0.25 (0-0.75)	<0.0001
Pain, median (IQR)	0 (0-0)	0 (0-2)	0 (0-0)	0 (0-0)	0 (0-2)	0.002
PGA, median (IQR)	0 (0-1.5)	0 (0-0)	0.5 (0-1)	0 (0-0)	2 (1-3)	<0.0001
PtGE, median (IQR)	1 (0-3)	3 (2-5)	0 (0-0)	0 (0-0)	2 (1-4)	<0.0001
cJADAS10, median (IQR)	2 (0-5.5)	3 (2-5)	0.5 (0-1)	0 (0-0)	5.5 (3-9)	<0.0001
Abnormal ESR attributed to JIA, n (%)	102 (4%)	0	12 (5%)	0	90 (7%)	0.003
Abnormal CRP attributed to JIA, n (%)	75 (3%)	0	5 (2%)	5 (0.5%)	65 (5%)	0.1
History of uveitis, n (%)	168 (6%)	5 (3%)	21 (9%)	75 (7%)	67 (5%)	0.008
Morning stiffness (row percentages), n (%)						<0.0001
None	2053 (71)	160 (8)	165 (8)	1039 (51)	689 (34)	
≤15 min	336 (12)	42 (13)	15 (4)	52 (15)	227 (68)	
16-60 min	273 (9)	0	25 (9)	0	248 (91)	
>60 min	125 (4)	0	4 (3)	0	121 (97)	

Abbreviations: ACR CID, American College of Rheumatology provisional criteria for Clinical Inactive Disease; AJC, active joint count; CHAQ, Childhood Health Assessment Questionnaire; CRP, C-reactive protein; cJADAS10, clinical Juvenile Disease Activity Score maximum 10 AJC; cJADAS10 ID, cJADAS10 Inactive Disease; ERA, enthesitis related arthritis; ESR, erythrocyte sedimentation rate; ILAR, International League of Associations for Rheumatology; IQR, interquartile range; JIA, juvenile idiopathic arthritis; Oligo, oligoarticular; PGA, physician global assessment; poly, polyarticular; PtGE, patient/parent global assessment of overall well-being; RF, rheumatoid factor.

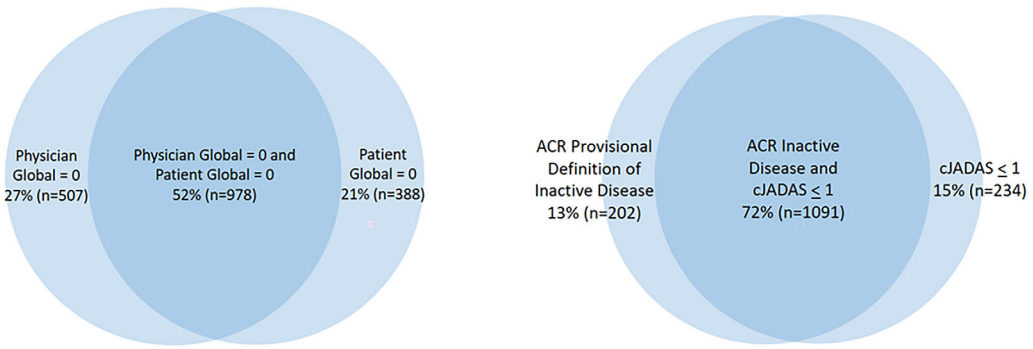

Figure 1. **(A)** Venn diagram of simple disease activity measure overlap: PGA of 0 and Pea of 0. **(B)** Venn diagram of composite disease activity measure overlap: ACR provisional definition of inactive disease and a cJADAS10 of one or less. ACR, American College of Rheumatology; cJADAS10, clinical Juvenile Arthritis Disease Activity Score; PGA, physician global assessment; pea, patient/parent global assessment of well-being.

Table 2. Percentile distribution of PtGE scores when PGA is 0, AJC is 0, or ACR CID criteria are met and percentile distribution of PGA scores when PtGE is 0 or AJC is 0

	5th percentile	25th percentile	50th percentile	75th percentile	95th percentile
PtGE					
When PGA = 0	0	0	0	1	5
When AJC = 0	0	0	0	2	6
When ACR CID criteria are met	0	0	0	1	4
PGA					
When PtGE = 0	0	0	0	0.5	2
When AJC = 0	0	0	0	0.5	2

Abbreviations: ACR CID, American College of Rheumatology provisional criteria for Clinical Inactive Disease; AJC, active joint count; PGA, physician global assessment; PtGE, patient/parent global assessment of overall well-being.

At the 1-year postenrollment visit, the cohort had a median AJC of 0 (IQR 0-1), median pain score of 0 (IQR 0-0), median CHAQ of 0 (IQR 0-0.38), and a median cJADAS10 of 2 (0-5.5) (Table 1). Among all 2904 individuals with JIA at the 1-year visit, 68% had 0 active joints, 47% had a PtGE of 0, 51% had a PGA of 0, 45% met the ACR provisional definition for CID, and 46% had a cJADAS10 of 1 or less.

Among individuals who had a PGA of 0 (1485; 51%) or a PtGE of 0 (1366; 47%), 52% (978) had both (Figure 1). The correlation between physician score and patient or parent score was moderate ($R = 0.46$, $P < 0.001$). We reported the percentile distributions of PtGE or PGA when other measures for inactive disease were met (Table 2). The fifth, twenty-fifth, and fiftieth percentiles were all 0, but the PtGE seventy-fifth and ninety-fifth percentile scores were higher than the PGA seventy-fifth and ninety-fifth percentile scores. Among patients with a PGA of 0, at least 25% of patients had a PtGE of 1 or more, and at least 5% had parent global of 5 or more (Table 2). The highest correlation among simple disease activity measures was between PGA and AJC ($R = 0.75$, $P < 0.001$), and the lowest correlation was between PGA and pain ($R = 0.20$, $P < 0.001$) (Table 3).

At the 1-year visit, 1377 (47%) patients with JIA did not meet the ACR CID or cJADAS10 definition for inactive disease, and 1091 (38%) met both. There was significant overlap (72%) among those individuals who met a composite definition for inactive disease (Figure 1). Among those who met either the ACR CID (n = 202) or the cJADAS10 (n = 234) definition of inactive disease, but not the other at the 1-year visit, there was no significant difference between groups for gender, age, International League of Associations for Rheumatology (ILAR) subtype, or CRP (Table 1). There were statistical differences in AJC, limited joint count, CHAQ, and pain with minimal absolute differences. There were more White individuals in the ACR CID–only group and more Asian individuals in the cJADAS10–only group. There were more individuals with uveitis in the cJADAS10–only group compared with ACR CID, although absolute numbers were small. The PtGE was significantly higher in the ACR CID group compared with the cJADAS10 group, and the PGA was 0 for all ACR CID group because of the score criteria and calculations.

There were 577 patients enrolled within 60 days of JIA diagnosis with a completed 12-month visit. Among these patients enrolled at diagnosis, by the 1-year visit 65% (n = 373) had no active joints, 46% (n = 268) had a PtGE of 0, 51% (n = 292) had a PGA of 0, 47% (n = 272) met the ACR CID criteria, and 43% (n = 246) had a cJADAS10 of 1 or less. Of the patients with JIA who met either the ACR CID or cJADAS10 CID (n = 297), most met both definitions (n = 221; 74%) with 17% (n = 51) meeting only the ACR CID criteria and 8% (n = 25) meeting only the cJADAS10 CID criteria.

Table 3. Correlation between simple measures of disease activity by Spearman's correlation coefficient (all P values <0.0001)

Measures	Spearman's correlation coefficient (r)
PGA and PtGE	0.46
PtGE and AJC	0.37
PGA and AJC	0.75
PtGE and pain	0.44
PGA and pain	0.20
PtGE and CHAQ	0.54
PGA and CHAQ	0.35

Abbreviations: AJC, active joint count; CHAQ, childhood health assessment questionnaire; PGA, physician global assessment; PtGE, parent/patient global assessment of overall well-being.

DISCUSSION

Measuring disease activity is critical to assessing the effectiveness of treatment and disease severity in chronic illness like JIA and is recommended as part of T2T practices. We found that in a prevalent cohort of individuals with at least 1 year of disease duration, 68% had no joints with active arthritis, 44% met ACR CID, and 46% had a cJADAS10 of 1 or less. These frequencies remained consistent if the analysis was limited to patients enrolled at diagnosis. The proportion of patients in the CARRA Registry who have inactive disease are similar to other studies reporting 47% to 68% inactive disease at 1 year (5,12). Although a systematic review of remission rates in patients with JIA found 13 different sets of criteria used over 17 studies, among those that reported

ACR preliminary criteria for clinically inactive disease, the frequency of inactive disease ranged from 33% at 6 months to 67% at 8 years (4). Although a large proportion of individuals with JIA can achieve inactive disease, they do not always satisfy inactive disease criteria by parallel measures.

Disease activity can be measured in different ways, using simple measures or composite measures that combine different aspects or perspectives of disease, and it is unclear whether one measure will more correctly identify patients with inactive disease or lead to better outcomes in the future. ACR CID is composed of measures that are determined by the provider, without a patient score (9). The cJADAS10 is calculated with equal weight between provider opinion, patient or parent opinion, and the provider-determined AJC on examination (11). One difference between these composite measures is the required absence of specific disease activity criteria in ACR CID compared with the allowance of a cJADAS10 of 1 from the PGA, the PtGE, or AJC. Another important difference is the integration of patient score. Aspects of disease beyond physiologic immune dysregulation, including pain, fatigue, stress, and medication side effects, can affect patient score of disease activity, and there is concern that a higher patient-reported score may not indicate a need for treatment intensification (6). The overlap between scores of 0 on physician global and parent global was higher in our cohort (52%) compared with the UK cohort (35%) (12), although the correlation between scores was moderate (R = 0.46). The strongest correlation was between PGA and AJC, R = 0.75 ($P < 0.0001$), which is understandable given the importance of disease manifestations to clinician determination of disease activity (4,5). PGA and PtGE are scored using different scales (21-point and 11-point, respectively), which may affect the absolute matching, but correlation is independent of scale.

It is unclear how well these composite scores agree in a large population of patients with JIA. In a UK inception cohort, 44% of patients had an overlap of ACR preliminary CID and cJADAS10 criteria (12), which is lower than the overlap of 72% in this study. This could be related to the difference between the UK population compared with the North American population, or new diagnosis and prevalent cases, although the proportion of individuals who met both criteria was 74% among newly diagnosed patients in our cohort. The ACR CID used in our study includes morning stiffness, whereas the ACR preliminary CID criteria does not. The inclusion of morning stiffness may inform the PtGE and in this case lead to better agreement between ACR CID and cJADAS10. Because these measures may identify different groups of patients, one measure may lead to improved future outcomes. In a cohort of patients with pJIA and patients with oJIA, achieving a cJADAS10 of 1 or less or ACR preliminary criteria for inactive disease status was associated with decreased risk of limited range of motion in the subsequent 5 years, but only a cJADAS10 of 1 or less was associated with better functional and health-related quality of life status (14). This suggests that including the PtGE in research protocols for treatment decisions will impact long-term outcomes that contain patient-reported outcomes like pain and fatigue. But it is unclear how much the PtGE affects the development of joint damage or chronic inflammation and how well clinicians can impact the aspects of PtGE that are external to JIA (6).

The ACR CID (9) is binary for achievement of inactive disease compared with the continuous integer measure of the cJADAS10 (11). This measurement difference may make the cJADAS10 more useful for monitoring over time, as in a T2T strategy. A single clinic in the United States implemented a T2T quality improvement initiative using the electronic medical record to standardize disease activity measurement using the cJADAS10, disease activity target review, and clinical decision support algorithm for treatment escalation for patients with pJIA in a routine clinical setting (15). During the 8-month intervention, they demonstrated attestation of the disease activity target in 77% of visits and use of the treatment algorithm in 45% of visits. In both early and established disease, there was a reduction in median disease activity scores (15).

Additional studies are needed to determine the outcomes following achievement of inactive disease by one or both of these composite scores in a North American population. We included all subtypes of JIA and did not limit to oJIA or pJIA, even though the inactive disease measures have only been validated for those subtypes (9,11). Future studies will assess differences in longer-term outcomes for patients who achieve CID by specific measures.

In a large, multicenter cohort from North America, half of the prevalent patients with JIA met one or more criteria for inactive disease 1 year after enrollment in the Registry, and 74% met both cJADAS10 and ACR CID criteria.

ACKNOWLEDGMENTS

This work could not have been accomplished without the aid of the following organizations: The National Institutes of Health's National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the Arthritis Foundation. We would also like to thank all participants and hospital sites that recruited patients for the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. The authors thank the following CARRA Registry site principal investigators, sub-investigators, and research coordinators:

N. Abel, K. Abulaban, A. Adams, M. Adams, R. Agbayani, J. Aiello, S. Akoghlanian, C. Alejandro, E. Allenspach, R. Alperin, M. Alpizar, G. Amarilyo, W. Ambler, E. Anderson, S. Ardoin, S. Armendariz, E. Baker, I. Balboni, S. Balevic, L. Ballenger, S. Ballinger, N. Balmuri, F. Barbar-Smiley, L. Barillas-Arias, M. Basiaga, K. Baszis, M. Becker, H. Bell-Brunson, E. Beltz, H. Benham, S. Benseler, W. Bernal, T. Beukelman, T. Bigley, B. Binstadt, C. Black, M. Blakley, J. Bohnsack, J. Boland, A. Boneparth, S. Bowman, C. Bracaglia, E. Brooks, M. Brothers, A. Brown, H. Brunner, M. Buckley, M. Buckley, H. Bukulmez, D. Bullock, B. Cameron, S. Canna, L. Cannon, P. Carper, V. Cartwright, E. Cassidy, L. Cerracchio, E. Chalom, J. Chang, A. Chang-Hoftman, V. Chauhan, P. Chira, T. Chinn, K. Chundru, H. Clairman, D. Co, A. Confair, H. Conlon, R. Connor, A. Cooper,

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Mannion had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Mannion, Xie, Beukelman.

Acquisition of data. Mannion, Xie, Beukelman.

Analysis and interpretation of data. Mannion, Xie, Beukelman.

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