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# Impact of Race, Gender, and Socioeconomic Status on Symptom Severity at Time of Urologic Referral

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#### Abstract

**Background and Objectives** The Dysfunctional Voiding and Incontinence Scoring System (DVISS) is a validated tool to evaluate lower urinary tract dysfunction (LUTD) severity in children. DVISS provides a quantitative score (0–35) including a quality-of-life measure, with higher values indicating more/worse symptoms. Clinically, variability exists in symptom severity when patients present to pediatric urology with LUTD. We hypothesized that symptom severity at consultation varied based on race, gender, and/or socioeconomic status.

**Methods** All urology encounters at a single institution with completed modified DVISS scores 6/2015–3/2018 were reviewed. Initial visits for patients 5–21 years old with non-neurogenic LUTD were included. Patients with neurologic disorders or genitourinary tract anomalies were excluded. Wilcoxon rank sum tests compared scores between White and Black patients and between male and female patients. Multiple regression models examined relationships among race, gender, estimated median household income, and insurance payor type. All statistics were performed using Stata 15.

**Results** In total, 4086 initial patient visits for non-neurogenic LUTD were identified. Median DVISS scores were higher in Black (10) versus White (8) patients (p < 0.001). Symptom severity was higher in females (9) versus males (8) (p < 0.001). When estimated median income and insurance payer types were introduced into a multiple regression model, race, gender, and insurance payer type were significantly associated with symptom severity at presentation.

**Conclusions** Race, gender, and socioeconomic status significantly impact LUTS severity at the time of urologic consultation. Future studies are needed to clarify the etiologies of these disparities and to determine their clinical significance.

**Keywords** Dysfunctional voiding  $\cdot$  Lower urinary tract dysfunction  $\cdot$  Pediatric urology  $\cdot$  Racial disparities  $\cdot$  Gender disparities  $\cdot$  Socioeconomic disparities

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#### Abbreviations

LUTD	Lower urinary tract dysfunction
LUTS	Lower urinary tract symptoms
DVISS	Dysfunctional Voiding and Incontinence Scor-
	ing System
ICD	International Classification of Diseases
CHIP	Children's Health Insurance Program
NINDS	National Institute of Neurological Disorders and
	Stroke
IAT	Implicit Associations Test

### Introduction

Lower urinary tract dysfunction (LUTD), bladder and bowel dysfunction, and dysfunctional elimination syndrome all describe functional disorders of the lower urinary tract without clear neurologic or anatomic etiologies. These disorders may include overactive bladder, voiding postponement, underactive bladder, dysfunctional voiding, primary bladder neck dysfunction, giggle incontinence, vaginal reflux, urinary frequency, and enuresis [1–3]. LUTD is the most common reason for referral to the pediatric urologists and studies across ethnicities estimate the prevalence rate to be as high as 17–22% among school aged children [4, 5].

Several symptom questionnaires have been developed to better quantify symptom severity in pediatric patients with lower urinary tract symptoms (LUTS) [6, 7]. Since 2006, our pediatric urology division has used a slight modification of the Dysfunctional Voiding and Incontinence Scoring System (DVISS) for all pediatric patients with LUTD [8, 9]. The DVISS is a validated tool to evaluate lower urinary tract and bowel symptoms in children, which includes a quality of life or degree of bother question. A quantitative score (0–35) is provided with higher values indicating more/worse symptoms and a score of greater than 8.5 was shown to have a 90% sensitivity and specificity for diagnosis bowel and bladder dysfunction in boys and girls [8]. This 14-question questionnaire has been found to have high diagnostic accuracy when compared to physician assessment of bladder and bowel dysfunction as well as excellent internal reliability [7, 10]. A slight modification of the DVISS has been previously published with the minor change of adding infrequent voiding as an option for the question on urination frequency (Fig. 1) [9]. The use of this instrument assists pediatric urologists in determining the severity of a patient's symptoms at the time of presentation and allows physicians to better assess for improvement over time.

Patients with bladder and bowel dysfunction are often referred to a pediatric urologist to confirm the absence of a neurologic or anatomic cause of these symptoms and to assist with management of these disorders. Significant variability exists in the severity of symptoms with which patients present to pediatric urology with these disorders. Presumably, this variability may be related to the family's perception of whether these symptoms are problematic, cultural expectations of when children should be continent, the comfort of primary care clinicians with caring for these

Fig. 1 Modified DVISS Questionnaire [8, 9]

Does your child wet during the	No Sometimes		1-2 times/day	Always		
day?				3	5	
How wet is your child during the	Not Dar		Damp Pants		Pants soaked	
day?	0	Underw		3	5	
	-	1		-		
Does your child wet during the	No 1-2 nights/week		week	3-5 nights/weel	c 6-7 nights/week	
night?	0	1	3		5	
How wet is your child during the		Not	Dam	p sheet/Pull-up	Sheets/Pull-up	
night?		0	1		soaked	
					4	
How many times does your child	Less	than 4/day	5	5-7 per day	More than 7/day	
urinate?		1		0	1	
My child strains during urination		No		Yes	Not sure	
		0		4	0	
My child feels pain during	No			Yes	Not sure	
urination	0		1		0	
My child starts and stops the	No		Yes		Not sure	
flow of urine when he or she is		0		2	0	
peeing						
My child needs to go back and	No		Yes		Not sure	
pee again (or wets) soon after		0		2	0	
finishing peeing						
My child has a sudden feeling of		No		Yes	Not sure	
having to urinate immediately		0	1		0	
My child holds by squatting or	No		Yes		Not sure	
crossing his/her legs		0		2	0	
My child wets on the way to the		No		Yes	Not sure	
toilet		0		2	0	
My child has a bowel movement		No		Yes	Not sure	
every day		1		0	0	
If your child experiences any of	No	Sometin	nes	Yes, affects	Seriously	
the symptoms mentioned above,	0 1		2		affects	
does it affect his/her family,					3	
social, or school life?						

issues, and their perception of whether or not the presenting symptoms are severe enough to merit urologic consultation.

Studies throughout the medical literature have shown the impact of race, gender, and socioeconomic status on health care access and utilization [11–17]. These disparities often lead to differences that can significantly impact healthcare expenditure and patient outcomes, including quality of life [18]. This study sought to determine whether the symptom severity in patients with bladder and bowel dysfunction at the time of presentation to a pediatric urologist varies depending on the patient's race, gender, and/or socioeconomic status. We hypothesized that female gender, African-American race, and lower socioeconomic status would be associated with higher DVISS scores at time of initial presentation to a pediatric urologist.

#### **Patients and Methods**

All urology encounters at a single institution with a completed modified DVISS score (Fig. 1) between June 2015 and March 2018 were reviewed. Only the first visit for each patient was included in this analysis. All International Classification of Diseases (ICD)-9 and ICD-10 diagnosis codes that had been associated with these visits were obtained. Only visits with a primary ICD-9 and ICD-10 diagnosis code related to LUTD (e.g., urgency, incontinence, frequency, constipation) were included (listed in Table 1). Any patients with diagnosis codes related to neurologic disorders (e.g., spina bifida), genitourinary tract anomalies, or complex medical syndromes that have been associated with LUTD were excluded (listed in Table 2).

Race, gender, zip code, and insurance payer type (selfpay, financial assistance/Medicaid/Children's Health Insurance Program (CHIP), private/military, and international) were extracted from the electronic medical record for each patient. Limited numbers of patients who selfidentified as races other than White or Black precluded our ability to include them in our analysis when comparing DVISS scores among racial groups. Data from the 2013–2017 American Community Survey was used to determine median household income by zip code (as provided by the US Census Bureau through the American FactFinder website). International patients (n = 16) were excluded from our analyses.

Wilcoxon rank sum tests were used to compare modified DVISS scores between White and Black patients as well as between male and female patients. Multiple regression models were used to determine how race, gender, estimated median household income, and insurance payer type affected LUTS severity at the time of presentation to urology. Statistical analyses were performed with Stata 15 (StataCorp, College Station, TX).

#### Results

A modified DVISS score was available for a total of 11,758 pediatric urology visits between June 2015 and March 2018. A total of 5645 of these visits had a primary diagnosis code related to LUTD. From these visits, 4226 unique patients were identified. In total, 140 patients had neurologic, genitourinary, or syndromal disorders that excluded them from the final analysis, leaving a total of 4086 patients with an initial visit for non-neurogenic LUTD (Fig. 2). Population characteristics can be found in Table 3.

When symptom severity scores were compared between Black or African-American patients and White patients, the median modified DVISS scores were 10 (IQR 7-15) for Black or African-American patients and 8 (IQR 4-13) for White patients (p < 0.001). When gender differences were examined, the median DVISS scores were found to be 9 (IOR 4-14) for females and 8 (IOR 4-13) for males (p < 0.001). The bother score (as determined by the last question in the questionnaire) was significantly higher in females than in males (p = 0.004). There was no significant difference in bother score between Black or African-American and White patients (p = 0.072). Multiple regression was used to examine how race, gender, and estimated household income by zip code affect symptom severity at the time of initial presentation to urology. The addition of estimated median household income did not eliminate the significant impact of race and gender on LUTS severity at the time of initial visit with urology. In this model, Black or African-American patients would present with DVISS scores 1.59 points higher than White patients (p < 0.001). Female patients would have scores 0.58 points higher than male patients (p = 0.006). Additionally, a \$10,000 increase in estimated income was associated with a 0.1 point decrease in symptom severity score (p=0.015) (Table 4). Upon adding insurance payer type to the model, race, gender, and insurance payer type all had significant relationships with symptom severity at the time of initial presentation to a urologist. However, the effects of estimated income on symptom severity were no longer found to be significant (p=0.591). In this model, even after factoring in income status, Black or African-American patients presented with DVISS scores 1.0 point higher than White patients (p < 0.001), females presented with scores 0.6 points higher than males (p = 0.004), and financial assistance/Medicaid/CHIP patients presented with DVISS scores 1.0 points higher than self-pay patients (p < 0.001) and 1.8 points higher than private or military insurance patients (p < 0.001) (Table 5).

Table 1 ICD-9 and ICD-10 codes related to LUTD

ICD-9/ICD-10 code	Description
560.32	Fecal impaction
597.89	Other urethritis
616.1	Vaginitis and vulvovaginitis
625.6	Stress incontinence, female
625.8	Other specified symptoms associated with female genital organs
625.9	Unspecified symptoms associated with female genital organs
698.1	Pruritus of genitalia
787.6	Incontinence of feces
788.1	Dysuria
788.2	Retention of urine
788.3	Urinary incontinence
788.41	Urinary frequency
788.43	Nocturia
788.61	Splitting of urinary stream
788.62	Slowing of urinary stream
788.63	Urgency of urination
788.64	Urinary hesitancy
788.65	Straining on urination
788.69	Other abnormal urination
788.91	Functional urinary incontinence
788.99	Other symptoms involving urinary system
F98.0	Enuresis not due to a substance or known physiological condition
F98.1	Encopresis not due to a substance or known physiological condition
K56.41	Fecal impaction
K59.00	Constipation, unspecified
K59.01	Slow transit constipation
K59.02	Outlet dysfunction constipation
K59.04	Chronic idiopathic constipation
K59.09	Other constipation
N32.81	Overactive bladder
N34.2	Other urethritis
N39.3	Stress incontinence (female) (male)
N49.41	Urge incontinence
N39.42	Incontinence without sensory awareness
N39.43	Post-void dribbling
N39.44	Nocturnal enuresis
N39.45	Continuous leakage
N39.46	Mixed incontinence
N39.490	Overflow incontinence
N39.492	Postural (urinary) incontinence
N39.498	Other specified urinary incontinence
N76.0	Acute vaginitis
R10.2	Pelvic and perineal pain
R15.1	Fecal smearing
R15.9	Full incontinence of feces
R19.7	Diarrhea, unspecified
R30.0	Dysuria
R32	Unspecific urinary incontinence
R33.9	Retention of urine, unspecified
R35.0	Frequency of micturition
R35.1	Nocturia

ICD-9/ICD-10 code	Description
R35.8	Other polyuria
R39.11	Hesitancy of micturition
R39.12	Poor urinary stream
R39.13	Splitting of urinary stream
R39.14	Feeling of incomplete bladder emptying
R39.15	Urgency of urination
R39.16	Straining to void
R39.19	Other difficulties with micturition
R39.81	Functional urinary incontinence
R39.82	Chronic bladder pain

#### Discussion

Table 1 (continued

Race, gender, and socioeconomic status all appear to be independently associated with symptom severity in children presenting for the first time to a pediatric urology with a complaint of LUTD. Racial disparities in triage and referrals for higher level of care have been noted in many studies across various medical fields [14-17]. One study examining emergency department waiting times in acute stroke patients revealed significantly longer waiting times for Black patients when compared to White patients. Black patients were also more likely to wait longer than the National Institute of Neurological Disorders and Stroke (NINDS) recommended 10 min to see an emergency physician from the time of presentation [15]. These observed racial disparities raise the question of whether or not unconscious bias may play a role in perceived severity of patient symptoms when the decision needs to be made regarding how urgently the individual needs to be seen for further evaluation.

In the Journal of General Internal Medicine, Chapman and colleagues discuss physician susceptibility to implicit bias. Physician training tends to emphasize group level information such as population risk facts, and the uncertainties and time pressures surrounding the diagnostic process can lead to a reliance on stereotypes for efficiency in decision-making. Additionally, a physician's vast knowledge of scientific data can create a strong belief in one's own personal objectivity, which can ironically lead to bias in decision-making [19]. This potential for implicit bias within clinical practice was demonstrated in a study performed in Boston, MA, where researchers examined the role of unconscious bias among physicians when making thrombolysis recommendations for Black and White patients with acute coronary syndromes. An internet-based tool with a clinical vignette of a patient presenting to the emergency department with an acute coronary syndrome in addition to a questionnaire measuring explicit (conscious) bias and three Implicit Association Tests (IATs) were sent to internal medicine and emergency medicine residents across four academic medical centers. The IATs revealed implicit stereotypes of Black Americans as less cooperative when compared to White Americans. As these implicit biases increased, physicians' likelihood of treating White patients and not treating Black patients with thrombolysis also went up [20].

Pediatric patients are not protected from the effects of implicit bias. Multiple studies reveal the impact of race and ethnicity on treatment of pain in pediatric patients. The treatment of pain due to fractures, abdominal pain, and appendicitis in minority children has been shown to involve less pain medication, which may suggest variability in the threshold to treat moderate to severe pain based on race and ethnicity [21–23]. In fact, Raphael and Oyeku discuss the importance of addressing these implicit biases that clearly color the care of our vulnerable patients in their recent commentary in *Pediatrics* [24].

In this study, it is possible that the differences seen between Black and White patients at the time of presentation to pediatric urology were related to differences in cultural expectations related to toileting or cultural perceptions with regard to when a bothersome urinary symptom warrants a specialist's evaluation. However, we cannot rule out the possibility that implicit bias may play a role in the decision to consult a specialist.

Gender or sex disparities have also been noted in the medical literature with regard to how subjective complaints are interpreted by health care providers. In the pediatric population, the parents' and/or providers' perceptions of whether a child is exaggerating or minimizing their symptoms could directly affect the decision to seek higher levels of care. In a study examining health care providers' judgments of trustworthiness among chronic pain patients, female patients were estimated to have less pain and be more likely to exaggerate their pain when compared to male patients [25]. Resultantly, female patients were less likely to be recommended analgesics and more likely to be recommended psychological treatment [25]. Therefore, the higher symptom severity scores seen in girls with LUTD at the time of presentation to pediatric urology may be reflective of how their subjective symptoms are being perceived by parents, caregivers, and primary care providers as being exaggerated.

Table 2ICD-9 and ICD-10 codes for neurologic,<br/>genitourinary, or syndromal<br/>diagnoses excluded from the<br/>dataset

ICD-9/ICD-10 code	Description
323.82	Other causes of myelitis
336.9	Spinal cord disease, unspecified
596.54	Neurogenic bladder, unspecified
596.55	Detrusor sphincter dyssynergia
741	Spina bifida
741.02	Spina bifida with hydrocephalus – dorsal (thoracic) region
741.03	Spina bifida with hydrocephalus – lumbar region
741.9	Spina bifida; without mention of hydrocephalus
742.3	Congenital hydrocephalus
742.59	Other spinal cord anomaly
756.17	Spina bifida occulta
759.5	Tuberous sclerosis
G04.89	Other myelitis
G06.1	Intraspinal abscess and granuloma
G37.3	Acute transverse myelitis in demyelinating disease of central nervous system
G80.1	Spastic diplegic cerebral palsy
G80.8	Other cerebral palsy
G80.9	Cerebral palsy, unspecified
G82.20	Paraplegia, unspecified
G95.9	Disease of spinal cord, unspecified
K59.2	Other neurogenic bowel
Q05.1	Thoracic spina bifida with hydrocephalus
Q05.4	Unspecified spina bifida with hydrocephalus
Q07.00	Arnold-Chiari syndrome without spina bifida or hydrocephalus
N31.2	Other flaccid neuropathic bladder
N31.9	Neuromuscular dysfunction of bladder, unspecified
Q04.0	Congenital malformations of corpus callosum
Q05.2	Lumbar spina bifida with hydrocephalus
Q05.3	Sacral spina bifida with hydrocephalus
Q05.7	Lumbar spina bifida without hydrocephalus
Q05.9	Spina bifida, unspecified
Q06.8	Other specified congenital malformations of spinal cord
Q76.0	Spina bifida occulta
Q76.49	Other congenital malformations of spine, not associated with scoliosis
Q85.1	Tuberous sclerosis
S14.109D	Unspecified injury at unspecified level of cervical spinal cord
S24.101A	Unspecified injury at T1 level of thoracic spinal cord
594.1	Other bladder calculus
N21.0	Calculus in bladder
N21.1	Calculus in urethra
239.4	Bladder neoplasm, unspecified
C67.9	Malignant neoplasm of bladder, unspecified
D41.4	Neoplasm of uncertain behavior of bladder
D49.4	Neoplasm of unspecified behavior of bladder
866.02	Kidney laceration closed
959.14	Other injury external genitalia
S31.41XA	Laceration without foreign body of vagina and vulva
\$37.021A	Major contusion of right kidney
\$37.32XA	Contusion of urethra
S37.33XA	Laceration of urethra
598.1	Traumatic urethral stricture
598.2	Postoperative urethral stricture
598.8 598.9	Other urethral stricture
598.9	Urethral stricture, unspecified

Table 2 (continued)

ICD-9/ICD-10 code	Description
N35.011	Post-traumatic bulbous urethral stricture
N35.013	Post-traumatic anterior urethral stricture
N35.014	Post-traumatic urethral stricture, male, unspecified
N35.8	Other urethral stricture
N35.9	Urethral stricture, unspecified
Q64.32	Congenital stricture of urethra
752.61	Hypospadias
Q54.0	Hypospadias, balanic
Q54.1	Hypospadias, penile
Q54.2	Hypospadias, penoscrotal
Q54.3	Hypospadias, perineal
Q54.8	Other hypospadias
752.62	Epispadias
Q64.0	Epispadias
Q64.10	Exstrophy of urinary bladder, unspecified
599	Other disorders of urethra and urinary tract
619	Fistula involving female genital tract
619.1	Digestive-genital tract fistula, female
N36.0	Urethral fistula
N36.44	Muscular disorders of urethra
N36.8	Other specified disorders of urethra
N82.3	Fistula of vagina to large intestine
Q64.2	Congenital posterior urethral valves
Q64.74	Double urethra
Q62.32	Cecoureterocele
L90.0	Lichen sclerosus et atrophicus
756.71	Prune belly syndrome
Q79.4	Prune belly syndrome
Q93.81	Velo-cardio-facial syndrome
D82.1	DiGeorge syndrome
E72.01	Cystinuria
E88.40	Mitochondrial metabolism disorder, unspecified

Alternatively, cultural expectations regarding the prevalence and therefore "normalcy" of LUTS among girls may lead to higher thresholds for referral. The difference in DVISS scores at the time of presentation to urology may also be related to pathophysiologic differences in how symptoms present in girls versus boys and a resultant tendency for LUTD to initially present with higher severity in girls.

Estimated median household income by zip code was initially found to significantly affect severity scores when examined alongside race and gender. However, once insurance status was included in the analysis, this effect was lost. This loss of significance may be related to the fact that income levels even within the same zip code can be vastly variable. Future research using census tract data could potentially show that estimated income remains significant when the data obtained has a higher level of accuracy. Based on the available data, it appears that income levels may only be relevant due to their relationship with insurance type as those with lower financial means may need

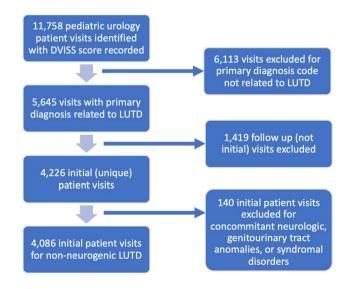


Fig. 2 Study flowchart

 Table 3
 Population characteristics

	Ν	Percent- age of total
Race		
White	2369	58.0%
Black	770	18.8%
Asian	78	1.9%
Indian	12	0.3%
Native Hawaiian or Other Pacific Islander	8	0.2%
American Indian or Alaska Native	4	0.1%
Other	830	20.3%
Refused	15	0.4%
Gender		
Female	2089	51.1%
Male	1997	48.9%
Insurance type		
Uninsured/self-pay	1881	46.0%
Financial assistance/Medicaid/CHIP	1353	33.1%
Private/military	836	20.5%
International	16	0.4%

to rely on insurance plans available through state or federally funded programs such as Medicaid and CHIP. Patients who have not been able to obtain one of these plans also turn to financial assistance programs through the hospital. Patients with financial assistance plans, Medicaid, or CHIP tend to present with more severe LUTS when compared to self-pay patients and when compared to patients with private or military insurance. This difference may be related to differing thresholds regarding when a problem is considered severe enough to seek specialty care related to ease of access through various insurance plans. It is also possible that referrals and insurance authorizations take more time to process among patients with financial assistance or state/federally funded programs, leading to a delay in arrival to a pediatric urology clinic.

This study has several limitations including its retrospective design and use of diagnosis codes to query the electronic medical record. Incorrect diagnoses and patients

 Table 4
 Multiple regression model examining relationships among

 DVISS score and race, gender, and estimated household income

	Coefficient	95% confidence interval	<i>p</i> -value
Race	1.59	1.03–2.14	< 0.001
Gender	0.58	0.16-1.00	0.006
Median household income (×\$1000) by zipcode	-0.01	-0.02 to $-0.17$	0.015

 Table 5
 Multiple regression model examining relationships among

 DVISS score and race, gender, estimated household income, and
 insurance payer type. Self-pay and private/military insurance both

 were compared to financial assistance/Medicaid/CHIP
 Financial assistance/Medicaid/CHIP

	Coefficient	95% confidence interval	<i>p</i> -value
Race	1.033	0.463-1.604	< 0.001
Gender	-0.600	-1.012 to -0.189	0.004
Median household income (×\$1000) by zipcode	-0.002	-0.010-0.006	0.591
Self-pay	-1.88	-2.406 to -1.366	< 0.001
Private/military insur- ance	-1.80	-2.415 to -1.178	< 0.001

ultimately diagnosed with a neurogenic or anatomic anomaly may also have been included inadvertently. Use of zip code for income estimation is also limited as discussed above. Ultimately, the difference in DVISS scores among these various populations was 2 points or less. While these differences were noted to be statistically significant, the clinical significance of these score differences is less clear. The optimal DVISS score cutoff to distinguish children with voiding abnormalities from those who are normal has been previously reported to be 8.5; however, the clinical meaningful difference in score has not been previously reported.<sup>8</sup> While there is concern that these differences in symptom severity at the time of presentation may translate to longer time to resolution or higher levels of patient distress, future studies are needed to clarify how these differences may or may not impact the course of the disease. Additionally, our study was conducted at a free-standing children's hospital with a large referral population including patients seeking second and third opinions. Therefore, it is unclear how generalizable our results are.

#### Conclusions

Race, gender, and socioeconomic status all significantly impact the severity of LUTS in patients who are initially seen by pediatric urology. While socioeconomic status clearly appears to play an important role in this patient population's access to pediatric urology, it does not negate the role of race and gender as demonstrated by our model. Future studies are needed to clarify the reasons behind why these disparities exist and to determine the clinical significance of these findings. Additionally, these findings may merit the initiation of quality improvement and/or community outreach projects to enhance the availability of resources to potentially at-risk populations. Author Contribution Joan Ko conceptualized and designed the study, acquired the data, analyzed and interpreted the data, drafted the manuscript, and revised the manuscript critically for important intellectual content. Christopher Corbett acquired the data and revised the manuscript critically for important intellectual content. Jason Van Batavia conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. Amanda Berry, Stephen Zderic, Dana Weiss, and Chris Long contributed to conception and design of the study, and revision of the article. Katherine Fischer revised the manuscript critically for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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#### Declarations

**Ethics Approval** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Children's Hospital of Philadelphia Institutional Review Board.

Conflict of Interest The authors declare no competing interests.

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