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Incorporating mpMRI biopsy data into established pre-RP nomograms: potential impact of an increasingly common clinical scenario

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Abstract

Background: We examine the practical application of multiparametric MRI (mpMRI) prostate biopsy data using established pre-RP nomograms and its potential implications on RP intraoperative decision-making. We hypothesize that current nomograms are suboptimal in predicting outcomes with mpMRI targeted biopsy (TBx) data.

Materials and methods: Patients who underwent mpMRI-based TBx prior to RP were assessed using the MSKCC and Briganti nomograms with the following iterations: (1) Targeted (T) (targeted only), (2) Targeted and Systematic (TS) and (3) Targeted Augmented (TA) (targeted core data; assumed negative systematic cores for 12 total cores). Nomogram outcomes, lymph node involvement (LNI), extracapsular extension (ECE), organ-confined disease (OCD), seminal vesicle invasion (SVI), were compared across iterations. Clinically significant impact on management was defined as a change in LNI risk above or below 2% (Δ2) or 5% (Δ5).

Results: A total of 217 men met inclusion criteria. Overall, the TA iteration had more conservative nomogram outcomes than the T. Moreover, TA better predicted RP pathology for all four outcomes when compared with the T. In the entire cohort, Δ2 and Δ5 were 16.6–25.8% and 20.3–39.2%, respectively. In the subset of 190 patients with targeted and systematic cores, TA was a better approximation of TS outcomes than T in 71% (MSKCC) and 82% (Briganti) of patients.

Conclusion: In established pre-RP nomograms, mpMRI-based TBx often yield variable and discordant results when compared with systematic biopsies. Future nomograms must better incorporate mpMRI TBx core data. In the interim, augmenting TBx data may serve to bridge the gap.

Keywords: Briganti, mpMRI, targeted biopsy, MSKCC, nomogram, radical prostatectomy

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Introduction

Radical prostatectomy (RP) remains a standard of care therapy for clinically localized prostate cancer (PCa).[1] However, the role of pelvic lymph node dissection (PLND) at the time of RP remains controversial, as its oncologic benefit remains unclear.[2–4] Moreover, significant variability exists among international guidelines regarding indications for PLND at the time of RP. The National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines recommend performing PLND for patients with ⩾2% and ⩾5% risk of pathological node positive (pN+) disease, respectively, whereas the American Urological Association (AUA) provides no

specific recommendations and suggests, based on expert opinion, that PLND be performed in patients with unfavorable intermediate- or high-risk disease.[5–7]

Nevertheless, pre-RP nomograms have been designed to predict risk of lymph node involvement (LNI), which in turn informs a surgeon's decision to perform PLND.[8,9] These nomograms were historically constructed to estimate LNI based on systematic 12-core prostate biopsies (PBx). With the introduction of multiparametric magnetic resonance imaging (mpMRI), cognitive or fusion targeted biopsies (TBx) have become increasingly prevalent, sometimes in the absence of traditional systematic biopsies (SBx). Current nomograms may not be applicable to men presenting with TBx core data.[10,11]

Herein, we aimed to examine the practical application of mpMRI TBx data using established pre-RP nomograms and its potential implications on RP perioperative decision-making. We hypothesize that current pre-RP nomograms may be suboptimal in estimating the risk of LNI for men diagnosed with PCa *via* mpMRI TBx. Furthermore, we developed a novel method to 'augment' mpMRI TBx cores to improve nomogram outcome predictions to better identify appropriate candidates for PLND.

Methods

Following institutional review board approval (ref. #18D.597), retrospective chart review of a prospectively maintained RP database was conducted at Thomas Jefferson University (TJU) and the University of Toronto (UT). All men with positive mpMRI TBx with available biopsy pathology from 2015 to 2018 were included. Positive mpMRI was inclusive of any lesions with a PI-RADS (Prostate Imaging–Reporting and Data System) score of 3–5. Standard PLND was completed in all men undergoing RP at TJU while standard PLND was completed selectively in men with ⩾2–5% risk of LNI at UT (surgeon preference). PBx pathology reports were abstracted for date of procedure, technique (targeted or both targeted and systematic), and Gleason score (total and core level data). RP pathology synoptic reports were abstracted for date of procedure, completion of LND, T-stage, N-stage, final Gleason score, surgical margin status, extracapsular extension (ECE), and seminal vesicle invasion (SVI). Organ confined disease (OCD) was defined as ⩽pT2N0 on RP pathology. Age, race, clinical stage, and preoperative prostate-specific antigen (PSA) were also documented for all patients.

Two nomograms were utilized in this study: the Kattan Memorial Sloan Kettering Cancer Center (MSKCC) nomogram and the 2012 Briganti nomogram.[8,9] Each patient was individually assessed with both nomograms using the following iterations: (1) 'Targeted' (T), utilizing TBx core data only; (2) 'Targeted and Systematic' (TS), utilizing all available PBx core data; and (3) 'Targeted Augmented' (TA), utilizing TBx core data alone while assuming negative remaining PBx cores for a total of 12 cores (Figure 1). Nomogram outputs were abstracted for each patient: LNI (Briganti) and OCD, ECE, LNI, SVI (MSKCC).

Mean ± standard deviation (SD) nomogram outcomes were compared between the T and TA iterations. Paired Student's t test was utilized to calculate statistical differences between the two iterations. All statistical tests were two-tailed and a p value <0.05 was considered statistically significant. RP pathology was used to validate nomogram outcomes. Clinically significant impact on management was defined as a change in risk above or below 2% (Δ2) or 5% (Δ5), based on current guidelines recommendations, that may impact decision to complete PLND.[5,6]

Results

Patients demographics

A total of 217 men met inclusion criteria. Of the 159 men from UT, 90 (56.6%) underwent PLND, while all 58 men from the TJU cohort underwent standard PLND. Table 1 highlights key demographic data and preoperative parameters for the entire cohort and individual institutions. Of the 190 patients who underwent both TBx and SBx, 16 patients (8.4%) had discordant pathology: all 16 demonstrated Gleason score upgrading on SBx cores when compared with TBx.

Nomogram and RP outcomes

In Table 2, the MSKCC and Briganti nomogram risk outcomes were compared between the

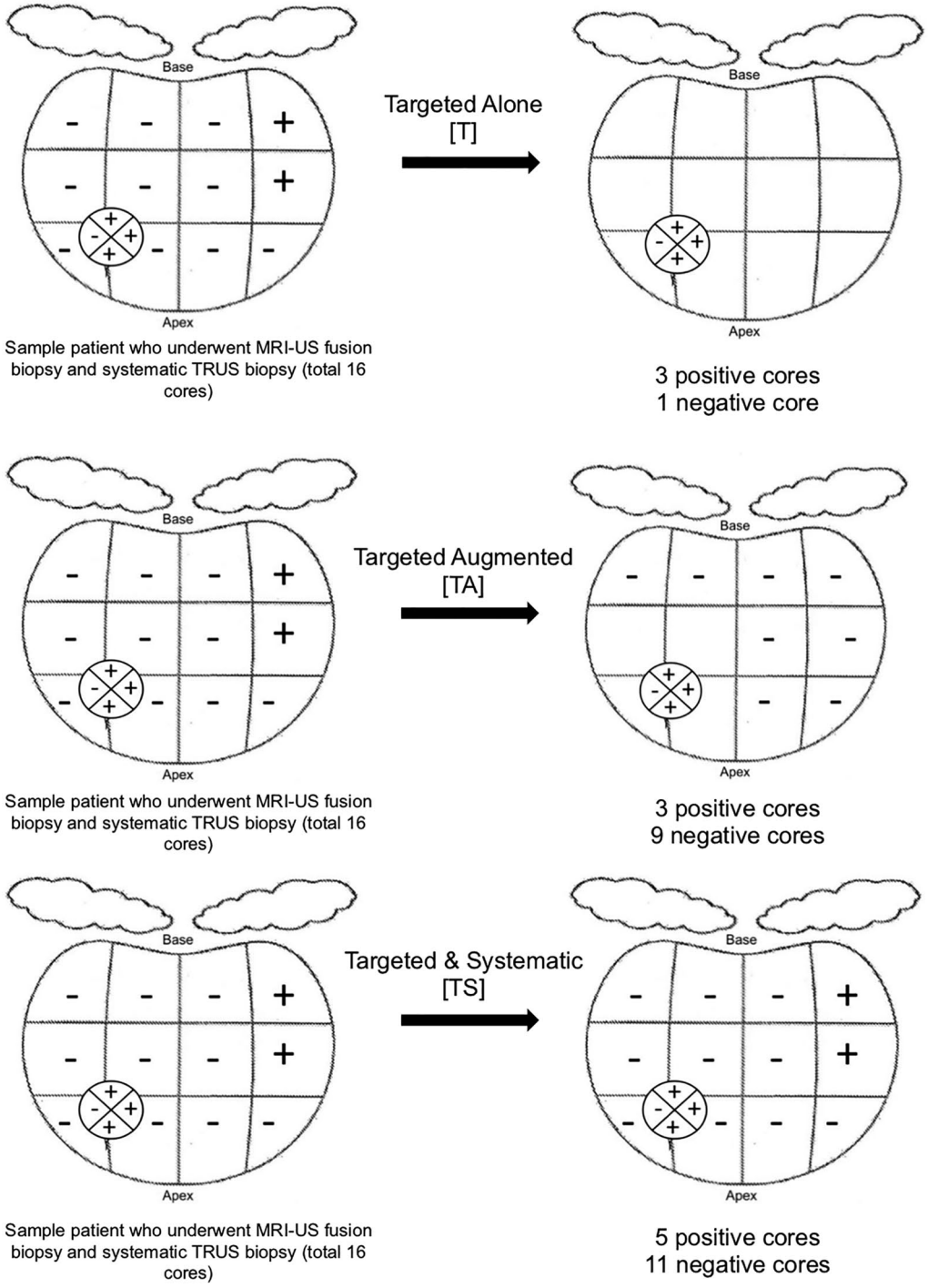

Figure 1. A sample patient who underwent MRI-US fusion targeted biopsy in addition to a 12-core systematic biopsy (total 16 cores) is depicted on the left. He had 2/12 cores positive on systematic biopsy and 3/4 cores positive on targeted biopsy. Biopsy core data was assessed according to the three iterations as depicted on the right.

T and TA iterations. Comparison of nomogram outcomes for individual cohorts are depicted in Supplementary Table 1A and 1B. On average, the TA iteration had more conservative nomogram predictions than the T iteration for all outcomes. These differences were statistically significant at $p < 0.001$ in both nomograms at both institutions.

Table 1. Patient demographics.

	Entire cohort	TJU cohort	UT cohort	*p* value
Total number, *n* (%)	217 (100.0)	58 (26.7)	159 (73.3)	–
Age, years (mean ± SD)	62.4 ± 6.5	61.5 ± 6.1	62.7 ± 6.7	0.230
PSA, ng/ml (mean ± SD)	8.6 ± 7.7	10.9 ± 10.7	7.7 ± 6.1	0.007
Clinical T stage, *n* (%)				<0.001
cT1	138 (63.6)	50 (86.2)	88 (55.3)	
cT2	77 (35.5)	7 (12.1)	70 (44.0)	
cT3	2 (0.9)	1 (1.7)	1 (0.6)	
Prostate biopsy technique, *n* (%)				0.572
Targeted only	27 (12.4)	6 (10.3)	21 (13.2)	
Targeted and Systematic	190 (87.6)	52 (89.7)	138 (86.8)	
Prostate biopsy grade group, *n* (%)				0.137
Grade group 1	50 (23.0)	8 (13.8)	42 (26.4)	
Grade group 2	89 (41.0)	24 (41.4)	65 (40.9)	
Grade group 3	45 (20.7)	13 (22.4)	32 (20.1)	
Grade group 4	22 (10.1)	10 (17.2)	12 (7.5)	
Grade group 5	11 (5.1)	3 (5.2)	8 (5.0)	

PSA, prostate-specific antigen; TJU, Thomas Jefferson University; UT, University of Toronto.

In only 21 (9.7%) cases, the TA iteration had worse LNI outcomes than the T iteration. Two of these patients had a higher percentage of positive cores on the TA iteration as they both had more than 12 targeted cores sampled on the initial biopsy. For the remaining 19 cases, we noted that all patients had 100% positive core involvement on their targeted cores alone, and only their MSKCC nomogram outcomes were affected.

Table 2 also depicts the comparison of nomogram outcomes with final RP pathology. Risk of LNI was calculated in all patients who underwent PLND while ECE, SVI, and OCD was calculated for all patients regardless of whether PLND was performed. Comparison for nomogram and RP outcomes for individual institutions are depicted in Supplementary Table 1A and 1B. When compared with RP pathology, the TA iteration was a better approximation than the T iteration for LNI, ECE, SVI, and OCD in both nomograms.

Clinically significant impact on management

Table 3 represents patients whose risk of LNI crossed the 2% (Δ2) or 5% (Δ5) threshold across iterations. When comparing TA and T iterations, 16.6–25.8% met Δ2 criteria and 20.3–39.2% met Δ5 criteria in the entire cohort. Of the 124 patients that underwent either Δ2/5 with the Briganti nomogram, 17 (13.7%) of them underwent both Δ2 and Δ5: 6 (35.0%) from the TJU cohort and 11 (65.0%) from the UT cohort. No patients underwent both Δ2 and Δ5 with the MSKCC nomogram.

Utilizing the TS iteration as an internal validation

Finally, as an internal validation, in a subset of patients who underwent both SBx and TBx ($n = 190$), we compared their TA and T outcomes to their TS outcomes for LNI risk. This data is depicted in Table 4. In both nomograms, the TA iteration was a better approximation to

Table 2. Comparison of nomogram outcomes between T and TA iterations and with pathology outcomes.

Pre-RP nomogram outcomes, mean (SD)	MSKCC (T)	MSKCC (TA)	Mean difference (SEL-ORIG)	Briganti (T)	Briganti (TA)	Mean difference (SEL-ORIG)	RP pathology outcomes
LNI*	11.40 (10.62)	8.00 (8.61)	−3.40	18.18 (17.29)	6.38 (9.83)	−11.80	6.04†
ECE	59.61 (11.85)	53.10 (13.75)	−6.52	–	–	–	42.40†
SVI	9.73 (9.28)	5.67 (7.04)	−4.06	–	–	–	7.37†
OCD	38.64 (12.51)	45.38 (14.62)	6.75	–	–	–	54.84†

*Risk of LNI only includes patients who underwent PLND during RP ($n = 148$).
†TA is better than T in predicting RP pathology.
ECE, extracapsular extension; LNI, lymph node involvement; OCD, organ-confined disease; RP, radical prostatectomy; SD, standard deviation; SVI, seminal vesicle invasion; T, Targeted; TA, Targeted Augmented.

Table 3. Clinically significant impact on management between T and TA iteration.

	MSKCC, *n* (%)	Briganti, *n* (%)	MSKCC, *n* (%)	Briganti, *n* (%)	MSKCC, *n* (%)	Briganti, *n* (%)
Entire cohort	**T Bx only ($n = 27$)**		**T+S Bx ($n = 190$)**		**All Bx ($n = 217$)**	
Δ2	3 (11.11)	3 (11.11)	33 (17.37)	53 (27.89)	36 (16.59)	56 (25.81)
Δ5	4 (14.81)	9 (33.33)	40 (21.05)	76 (40.00)	44 (20.28)	85 (39.17)
TJU cohort	**T Bx only ($n = 6$)**		**T+S Bx ($n = 52$)**		**All Bx ($n = 58$)**	
Δ2	1 (16.67)	1 (16.67)	4 (7.69)	18 (34.62)	5 (8.62)	19 (32.76)
Δ5	1 (16.67)	2 (33.33)	14 (26.92)	20 (38.46)	15 (25.86)	22 (37.93)
UT cohort	**T Bx only ($n = 21$)**		**T+S Bx ($n = 138$)**		**All Bx ($n = 159$)**	
Δ2	2 (9.52)	2 (9.52)	29 (21,01)	35 (25.36)	31 (19.50)	37 (23.27)
Δ5	3 (14.29)	7 (33.33)	26 (18.84)	56 (40.58)	29 (18.24)	63 (39.62)

Bx, biopsy; T, Targeted; TJU, Thomas Jefferson University; T+S, Targeted and Systematic; UT, University of Toronto.

the patient's TS outcomes than the T iteration in 71–82% of cases.

Discussion

The addition of mpMRI as a diagnostic tool has allowed for better sampling and detection of clinically significant PCa. mpMRI fusion TBx have become increasingly utilized in the diagnosis and surveillance of PCa. With multiple prospective studies now demonstrating its ability to better identify clinically significant PCa and limit identification of low-risk PCa,[12–14] mpMRI fusion biopsies are now recommended by international guidelines in the setting of repeat biopsies and active surveillance.[5,6,15,16] Indeed, the recent multicenter randomized controlled PRECISION trial demonstrated the superiority of mpMRI TBx over TRUS SBx in detecting PCa in biopsy-naïve men.[13] Systematic reviews by Wu and Valerio also report the efficacy of mpMRI TBx over SBx.[17,18] However, while the optimism for TBx is high, it should be noted that SBx still identifies clinically significant PCa missed by TBx and mpMRI fusion biopsy outcomes are highly variable based on institution.[12,19] As such, at this time, the general consensus is that TBx should be done in conjunction with SBx to maximize diagnostic yield.[20]

Table 4. Approximation of TA and T iteration to the TS.

		MSKCC, *n* (%)	Briganti, *n* (%)
Entire cohort (*n* = 190)	**TA closer to TS**	135 (71.1)	156 (82.1)
	T closer to TS	34 (17.9)	18 (9.5)
	No difference	21 (11.1)	16 (8.4)
TJU cohort (*n* = 52)	**TA closer to TS**	25 (48.1)	35 (67.3)
	T closer to TS	21 (40.4)	16 (30.8)
	No difference	6 (11.5)	1 (1.9)
UT cohort (*n* = 138)	**TA closer to TS**	110 (79.7)	121 (87.7)
	T closer to TS	13 (9.4)	2 (1.5)
	No difference	15 (10.9)	15 (10.9)

T, Targeted; TA, Targeted Augmented; TJU, Thomas Jefferson University; T+S, Targeted and Systematic; UT, University of Toronto.

With mpMRI serving as such an important biomarker for clinically significant PCa, there exists an urgent need to integrate mpMRI data into pre-RP risk tools to improve patient stratification during initial risk assessment.[21,22] A recent study by Briganti and colleagues aimed to address this need by developing a novel nomogram that considers relevant mpMRI data and clinical parameters.[23] These additional variables include clinical staging (OCD, ECE, SVI) on mpMRI, maximum lesion diameter and Gleason Grade Group on TBx. With an area under the receiver operating characteristic curve (AUC) of 0.84, their nomogram demonstrated a higher net benefit compared with the 2012 Briganti, 2017 Briganti, and MSKCC models, which are currently available models developed using standard biopsies alone.[8,9,24] However, these results have yet to be validated.

As clinicians often use preoperative nomograms to complement their decision making to perform PLND during RP, practical utilization of these established pre-RP nomograms may be problematic, especially in men presenting with only TBx cores. Therefore, we sought an intuitive way to incorporate targeted cores into current pre-RP nomograms when systematic cores are absent. As the number of TBx to a single region of interest ranges between 2 and 4,[16,25] we developed a model to augment TBx core data to facilitate use of established pre-RP nomograms. This augmentation is done by utilizing only the available targeted core data while assuming negative remaining biopsy cores for a total of 12 cores (Figure 1).

In our study, the predicted risk of LNI for TBx data after augmentation for the entire cohort (regardless of PLND) decreased by 2.85% and 10.44% using the MSKCC and Briganti nomograms, respectively (data not shown). More importantly, nomogram predictions after augmentation of TBx data appears to be a closer approximation of the actual risk of LNI based on patients' RP pathology (Table 2). Furthermore, with the MSKCC nomogram, utility of the TA iteration also better predicts ECE, OCD, and SVI.

Unlike the Briganti nomogram, biopsy core data is not required when estimating RP outcomes using the MSKCC nomogram.[8,9] In cases where PBx data is absent, nomogram outcomes, after utilizing remaining preoperative parameters, are predicted based on the average value of the represented cohort within the database. As such, this may account for the reason why 19 patients had worse LNI outcomes predicted by the TA iteration than the T iteration. Indeed, these actually reflect a systematic error in the MSKCC nomogram, as patients with 100% positive core involvement revert to nomogram outcomes that ignore core involvement altogether. Therefore, in these patients, these nomogram outcomes could not be interpreted accurately as the assumptions made

by the nomogram may not necessarily reflect the patient's true outcome.

The consistent differences in nomogram outcomes between the T and TA iterations question the application of pre-RP nomograms in patients who only undergo TBx. It also brings to the forefront whether PLND performed on these patients are justified. Aside from incurring higher costs and increased operative time, PLND completion may also increase complication risks. PLND at the time of RP is associated with pelvic lymphocele formation in 2–9% of patients.[26] Other potential complications include lymphedema, venous thromboembolism, and injury to the ureter or surrounding neurovasculature.[27] From our results, 17–39% of patients who underwent PLND at the time of RP did not actually meet criteria for PLND based on current guideline recommendations after utility of the TA iteration.[5,6]

Despite the increased diagnostic yield of mpMRI fusion TBx, most patients still undergo SBx in addition to TBx. In our study, the TS iteration, which incorporates all available core data, most accurately reflects the true LNI risk in this patient population. When comparing TA or T with TS, we found that consideration of targeted cores only revealed suboptimal risk predictions, further justifying the need to consider systematic or augmented cores in preoperative risk nomograms. Although the PROMIS trial reported mpMRI TBx having a higher sensitivity and negative predictive value than standard TRUS biopsies for detecting clinically significant PCa, its low specificity (41%) indicates that mpMRI is not a perfect discriminatory test.[12] Moreover, results from the recently published ASIST trial demonstrated that mpMRI fusion TBx did not increase upgrading rates when compared with SBx alone, that both SBx and TBx missed significant cancer at almost equal rates, and that there are significant differences in TBx outcomes based on institution and level of expertise. The authors also suggested that patients with higher risk of disease should undergo SBx regardless of mpMRI findings.[19] These studies further support the increasing evidence that SBx should be continued in addition to TBx.

We acknowledge that the study is not without its limitations. First, our study design was retrospective in nature with its inherent limitations. No central pathology review of PBx or RP pathology was utilized, though all were read and interpreted by experienced genitourinary pathologists. We also acknowledge that our concept of augmenting TBx data with negative systematic cores for a total of 12 cores may be flawed. First, the number of targeted cores obtained from each region of interest may vary, thereby affecting the percentage of 12 cores attributed to TBx and SBx. In addition, as PCa is known to be a multifocal disease, presuming negative cores in the remainder of the prostate may artificially improve a patient's risk profile; yet, patients only receiving TBx inherently have the risk of missed clinically significant PCa anyway. Finally, both nomograms utilized in our study were developed using distinctly different patient cohorts (different era of treatment, variable surgeon preferences, and techniques with regards to degree of lymph node dissection, etc.), which may impact nomogram accuracy.

Ultimately, however, the goal of this study was to highlight the drastic misrepresentation of disease burden in men who undergo TBx alone and the need for new nomograms that account for mpMRI TBx. In the interim, utilization of an augmented nomogram may help provide guidance for surgical planning.

Conclusion

As mpMRI fusion biopsies become more commonplace in the diagnosis and management of PCa, there must be better incorporation of fusion biopsy data into future nomograms. TBx data, used in isolation in current nomograms, significantly overestimate final pathology outcomes and cannot be used reliably. Augmentation with negative systematic cores may serve as a bridge in the interim to help guide surgical planning.

Author contribution

JYL was responsible for data curation, formal analysis, and writing (original, review, and editing). JOHC, HG, ET, and ST were responsible for data curation and writing (review and editing). EJT, CDL, LGG, and NEF were responsible for resources and supervision, writing (review and editing). TC was responsible for conceptualization, resources, supervision, and writing (review and editing).

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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