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RESEARCH ARTICLE

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Generalizability of nociception level as a measure of intraoperative nociceptive stimulation: A retrospective analysis

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Abstract

Background: Nociception-guided intraoperative opioid administration might help reduce postoperative pain. A commonly used and validated nociception monitor system is nociception level (NOL), which provides the nociception index, ranging from 0 to 100, with 0 representing no nociception and 100 representing extreme nociception. We tested the hypothesis that NOL responses are similar in men and women given remifentanil and fentanyl, across various types of anesthesia, as a function of American Society of Anesthesiologists physical status designations, and over a range of ages and body morphologies.

Methods: We conducted a retrospective cohort analysis of trial data from eight prospective NOL validation studies. Among 522 noncardiac surgical patients enrolled in these studies, 447 were included in our analysis. We assessed NOL responses to various noxious and non-noxious stimuli.

Results: The average NOL in response to 315 noxious stimuli was 47 ± 15 (95% CI = 45–49). The average NOL in response to 361 non-noxious stimuli was 10 ± 12 (95% CI = 9–11). NOL responses were similar in men and women, in patients given remifentanil and fentanyl, across various types of anesthesia, as a function of American Society of Anesthesiologists physical status designations, and over a range of ages and body morphologies.

Conclusion: Nociception level appears to provide accurate estimates of intraoperative nociception over a broad range of patients and anesthetic conditions.

KEYWORDS
analgesia, fentanyl, monitoring, nociception, pain, PMD-200

Editorial Comment

Estimation of the level of nociception is now possible during general anesthesia. In this reanalysis of data from eight studies, the authors assessed the nociception level index for events that were classified as either nociceptive or non-nociceptive. It was found that there was a large difference in the nociception level index for these two types of events, and this was consistent

across a number of characteristics such as age, sex, body mass index, and type of anesthesia. Not all events could, however, be classified. Readers can note competing interests for some co-authors.

1 | INTRODUCTION

Anesthesia allows patients to tolerate surgical procedures that would otherwise inflict unbearable pain, provoke extreme physiologic exacerbations, and result in unpleasant memories. Nociception is defined as the neural process of detection, transduction, and transmission of noxious stimuli.[1] There is a general consensus that noxious stimuli should be managed during general anesthesia to prevent excessive sympathetic nervous system activation. Excessive noxious stimulation may also activate pain pathways that might augment postoperative pain and potentiate intraoperative recall.[2]

The challenge, of course, is that general anesthesia precludes facile evaluation of stimuli that would normally provoke pain, which by definition is a conscious response. There are now several devices that estimate nociception during general anesthesia including the Surgical Pleth Index, pupillary reflexes, galvanic skin responses, and heart-rate variability.[3–6] A commonly used and well validated system is the PMD-200 monitor with Nociception Level (NOL) technology (Medasense Biometrics Ltd. Ramat Gan, Israel). The NOL index is based on a combination of nociception related physiological variables including heart rate, heart rate variability, photo-plethysmographic waveforms, skin conductance, and their time derivative.[7] Based on a random forest model, the device generates the NOL index, displayed as a scale from 0 to 100 with 0 representing no nociception and 100 representing extreme nociception.[7–9]

The NOL index responds consistently to various levels of noxious stimulation[9–11] with higher sensitivity and specificity than other nociceptive measures.[8,10] A reasonable question is whether NOL responses are consistent across various patient and anesthetic characteristics; that is, the extent to which NOL responses are generalizable. To address this pertinent question, we re-evaluated eight studies in which NOL responses to non-noxious and various noxious stimuli were prospectively recorded. Specifically, we tested the hypothesis that NOL responses are similar in men and women, in patients given remifentanil and fentanyl, across various types of anesthesia, as a function of American Society of Anesthesiologists (ASA) physical status designations, and over a range of ages and body morphologies.

2 | METHODS

As of January 2021 when our analysis began, there were 12 studies of NOL monitoring with a total of 592 patients that were published or known to Medasense, of which 8 were included reflecting 522 patients or 88% of patients known to date. Three studies were excluded due to lack of data sharing agreement; one was excluded because it did not annotate surgical stimulation.

We analyzed NOL recordings from adults who had elective surgical procedures (general, gynecological, and urological) with permission of the investigators of eight prospective studies conducted between August 2016 and December 2020 (Table 1, Supplemental Table 1). All eight studies were individually approved by the relevant Institutional Review Boards, and all patients enrolled signed written informed consents (Supplemental Table 2). Not all results have been published, but data were shared with the manufacturer in a compliant manner and with permission for the current use.[9,12–15] We considered all 522 patients who met enrollment criteria for the underlying studies. We excluded patients whose recordings were missing annotations including demographic characteristics or were otherwise incomplete, leaving 447 for analysis (Table 1).

Subgroups were classified as a function of age (18–65 years old, over 65 years old), sex (female, male), body mass index (BMI) (normal,

TABLE 1 Patients who participated in the eight included studies.

Study	Participated	Excluded by criteria	Excluded for missing annotations (stimuli/ medication/demographics)	Missing/faulty records (raw data)	Included
#1 Meijer et al.[9]	80	0	4	6	70
#2 Meijer et al.[12]	50	0	3	4	43
#3 Fuica et al.[14]	95	10	0	4	81
#4 Farhang et al. (*unpublished*)	61	0	3	19	39
#5 Renaud-Roy et al.[15]	60	1	2	3	54
#6 Espitalier et al.[13]	70	4	1	1	64
#7 Richebe et al. (*unpublished*)	80	5	0	1	74
#8 Ruetzler et al. (*unpublished*)	26	0	3	1	22
Total	522	20	16	39	447

TABLE 2 Events included in the analysis.

Stimulus intensity	Total events	Excluded for opioids	Used for study	Noxious/non-noxious
Severe (intubation)	353	71	282	Total noxious events: 315
Moderate–severe (incision\trocar)	398	365	33	
Moderate (insufflation)	117	117	0	Total non-noxious events: 361
Minor (e.g., stitching)	64	40	24	
Non-noxious (e.g., cleaning)	339	2	337	
Total	1271	595	676	

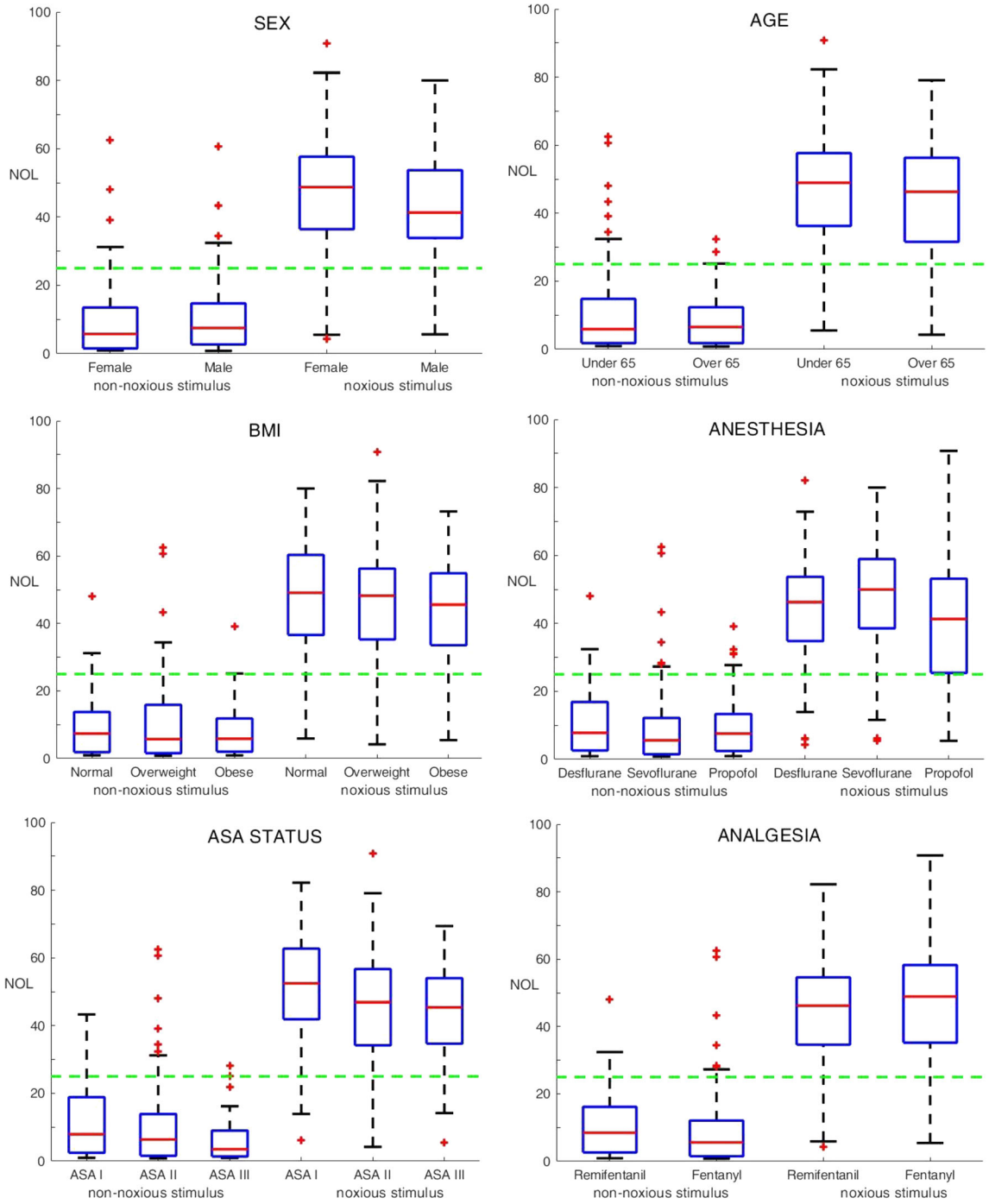

FIGURE 1 Subgroup analyses.

overweight, obese), ASA physical status (ASA I, II, III), anesthesia drugs (propofol, sevoflurane, desflurane), and opioid (fentanyl, remifentanil). As suggested in the manufacturer's user manual, we used a NOL threshold of 25 (on a 0–100 scale) to define positive responses to noxious or non-noxious stimulation. Specifically, we expected NOL values less than 25 in response to defined periods of non-noxious stimulation, and NOL values exceeding 25 in response to defined noxious stimulation. We considered five periods during surgery: a non-noxious period (e.g., before skin incision), minor stimuli (e.g., urethral catheterization), moderate stimuli (insufflation, small incision), moderate-to-severe stimuli (e.g., first incision, trocar insertion), and severe stimulation (laryngoscopy and intubation). The timepoints were analyzed per patient to quantify the intraoperative response to noxious and non-noxious stimuli during the surgical procedure. The post-stimulus reaction was defined as the average of the non-continuous 30 seconds with the highest NOL values within a 3-min window post stimulus.

Analgesic medications obviously blunt responses to nociceptive stimuli and should therefore reduce the NOL response to stimulation. The definition of an appropriate characterization of stimuli must therefore consider stimulation intensity in context of analgesic level. We used the Combined Index of Stimulus and Analgesia (CISA) score to grade the combination of the stimulus level and the analgesia level.[7] The CISA score is a linear combination of the stimulus intensity and the effect of analgesic drugs. The stimulus intensity level was defined by experts as a discrete ordinal number between 0 and 10 that represents the intensity of the surgical event. The effect of analgesic drugs was defined according to effect-site concentrations of opioids (scaled by a normalization factor). The effect of the site concentration of opioids was continuously calculated based on annotated infusion rates, boluses, and the pharmacokinetics models of Minto et al[16] and Schafer et al[17] as appropriate for the opioid used in the study. The type and timing of stimuli, and administration of opioids were continuously annotated during surgeries and processed following the surgeries to compute the CISA score. The CISA score set the "ground truth" of expected nociceptive level for our analysis and was performed offline. NOL value, in contrast, represent instantaneous output of the measurement system.

We defined nociceptive events as having a CISA score exceeding 4.9 on the 0–10 scale (the threshold above which we consider CISA as definitely nociceptive): This is equivalent to a severe stimulus with analgesia effect-site concentration up to 3.3 ng/mL. Non-nociceptive events were defined by CISA scores <2.5 (the threshold below which we consider CISA as definitely non-nociceptive): This is equivalent to non-noxious stimulus, minor stimulus with an opioid concentration of at least 1.5 ng/mL, or moderate stimulus with opioid concentration of at least 4.5 ng/mL.

2.1 | Statistical analysis

Differences between noxious and non-noxious stimuli were assessed with box plots, histograms, and receiver operating characteristics

TABLE 3 Median and mean NOL value across subgroups in response of noxious versus non-noxious stimuli.

Subgroup	Non-noxious median (25%–75%)	Non-noxious mean (Std)	Noxious median (25%–75%)	Noxious mean (Std)
Gender				
Female	6 (2–15)	10 (12)	50 (40–58)	48 (15)
Male	8 (2–13)	10 (10)	44 (34–56)	44 (15)
Age				
Under 65	6 (2–16)	10 (11)	49 (39–58)	47 (15)
Over 65	6 (2–12)	10 (13)	47 (35–57)	45 (15)
BMI				
Normal, 18–25 kg/m^2	8 (2–16)	11 (13)	49 (41–59)	48 (14)
Overweight, 25–30 kg/m^2	6 (1–15)	10 (11)	47 (35–56)	45 (17)
Obese, >30 kg/m^2	6 (2–12)	9 (10)	49 (37–57)	47 (14)
Anesthesia				
Desflurane	6 (3–17)	11 (10)	46 (35–54)	44 (16)
Sevoflurane	6 (2–15)	11 (14)	53 (44–61)	51 (14)
Propofol	6 (2–12)	8 (8)	43 (31–52)	43 (14)
ASA physical status				
I	8 (2–19)	12 (11)	52 (39–62)	50 (16)
II	7 (2–14)	10 (12)	47 (38–57)	46 (15)
III	4 (1–9)	7 (9)	47 (35–56)	45 (15)
Analgesia				
Remifentanil	5 (3–12)	10 (9)	44 (36–53)	44 (14)
Fentanyl	6 (2–14)	11 (13)	50 (42–60)	50 (15)

(ROC) curves of the NOL response based on NOL >25 for noxious stimuli and ≤25 for non-noxious and opioid-blunted stimuli. The whiskers for the boxplots were set at ±2.7 standard deviations representing 99.3% coverage for normal distribution, 95% CI for the means were estimated from the means and standard errors (SEs), using the formula: lower limit = mean − ($z_{1-\alpha} \times$ SE) and the upper limit = mean + ($z_{1-\alpha} \times$ SE). α is defined as 0.05 and $z_{1-\alpha}$ is 1.96. The SE for the ROC was calculated using the method presented by DeLong et al.[18] Sensitivity and specificity were calculated using the Clopper-Pearson formula.[19]

The test significance level (p-value) was calculated using AUC = 0.5 as the null hypothesis:

$$p = 1 - \frac{1}{2}\mathrm{ERFC}\left\{-\frac{\mathrm{AUC} - 0.5}{\sqrt{2}\mathrm{SE}}\right\}$$

ERFC is the complementary error function and SE is the standard error.

We performed an analysis of the non-noxious events in which the threshold of 25 was crossed and of the noxious events in which the NOL value was less than 25 to estimate the false positive and false negative rates. At least 30 noxious stimuli and 30 non-noxious stimuli were needed to achieve the target sensitivity and specificity of 0.75 for the lower CI, based on MedCalc software (version 19.8, MedCalc Software Ltd., Ostend, Belgium). Since the actual numbers of events exceeded 30 by a factor of 3–16 our analysis was well powered.

Data were processed using MATLAB version R2018a (The MathWorks Inc.) and analyzed using MedCalc Statistical Software.

3 | RESULTS

A total of 522 eligible patients from 8 studies were considered and 447 were included in our analysis (Table 1). A total of 1271 events were collected from the NOL monitors. A total of 595 events were excluded because CISA scores were between 2.5 and 4.9, making it unclear whether stimuli should be considered noxious or non-noxious. We therefore analyzed 676 events: 315 noxious events and 361 non-noxious events (Table 2).

TABLE 4 Sensitivity and specificity of the NOL index across the groups.

Subgroup	N (data points)	NOL cutoff point	AUC	Specificity	Sensitivity	Accuracy
Female	451	25	0.96 (0.92–0.98) $p < .0001$	0.90 (0.88–0.92)	0.92 (0.88–0.95)	0.91
Male	225	25	0.96 (0.92–0.98) $p < .0001$	0.93 (0.87–0.97)	0.90 (0.83–0.96)	0.92
Age < 65	470	25	0.96 (0.94–0.98) $p < .0001$	0.90 (0.85–0.93)	0.92 (0.86–0.94)	0.91
Age > 65	206	24	0.96 (0.93–0.99) $p < .0001$	0.94 (0.87–0.97)	0.93 (0.86–0.97)	0.93
Normal, BMI 18–25 kg/m^2	255	25	0.96 (0.93–0.98) $p < .0001$	0.90 (0.85–0.95)	0.93 (0.87–0.97)	0.91
Overweight, BMI 25–30 kg/m^2	242	24	0.95 (0.92–0.98) $p < .0001$	0.89 (0.83–0.94)	0.89 (0.83–0.95)	0.89
Obese, BMI > 30 kg/m^2	179	25	0.98 (0.94–0.99) $p < .0001$	0.96 (0.89–0.99)	0.92 (0.85–0.97)	0.94
Desflurane	137	25	0.95 (0.90–0.98) $p < .0001$	0.91 (0.82–0.96)	0.89 (0.78–0.95)	0.90
Sevoflurane	342	25	0.96 (0.93–0.98) $p < .0001$	0.89 (0.84–0.93)	0.95 (0.90–0.98)	0.92
Propofol	186	24	0.98 (0.95–0.99) $p < .0001$	0.96 (0.89–0.99)	0.90 (0.82–0.95)	0.92
ASA physical status I	156	25	0.97 (0.92–0.99) $p < .0001$	0.85 (0.76–0.92)	0.92 (0.83–0.97)	0.88
ASA physical status II	412	25	0.96 (0.93–0.98) $p < .0001$	0.92 (0.88–0.96)	0.92 (0.87–0.96)	0.92
ASA physical status III	99	25	0.97 (0.91–0.99) $p < .0001$	0.94 (0.83–0.99)	0.90 (0.79–0.97)	0.92
Remifentanil	265	24	0.97 (0.95–0.99) $p < .0001$	0.92 (0.87–0.96)	0.92 (0.85–0.96)	0.92
Fentanyl	389	25	0.96 (0.94–0.98) $p < .0001$	0.90 (0.85–0.94)	0.92 (0.88–0.96)	0.91

There were distinct differences in the NOL response to noxious and non-noxious stimuli. The average NOL in response to 315 noxious stimuli was 47 ± 15 (95% CI = 45–49). The average NOL in response to 361 non-noxious stimuli was 10 ± 12 (95% CI = 9–11). Thus, NOL values during non-noxious stimuli were largely below 25, whereas noxious stimuli provoked NOL values exceeded 25 (Figure 1).

Nociception level values were similar across various populations, with no clinically meaningful or statistically significant differences across age, BMI, ASA physical status, analgesia, or anesthetic group for either noxious or non-noxious stimuli (Table 3). The area under the curve across the populations exceeded 0.9 in all groups, thus easily meeting our predefined target criteria of 0.75 (Table 4).

Only 5% of non-noxious stimuli provoked a NOL value more than 25, and 94% of these events lasted less than 1 min long which would not generally be considered a clinically meaningful event. The remaining false positive events represented just 0.3% of the events included in our analysis. For noxious events, the false negative rate (NOL <25 in the presence of a noxious stimulus) was under 8%.

4 | DISCUSSION

Previous studies have shown that NOL reliably distinguishes non-nociceptive and nociceptive events.[7,10,20,21] Sensitivity and specificity are both high with a cutoff of 25 which is what we used in this analysis.[22] Our summary results from eight prospective studies are consistent, showing that NOL was nearly always <25 without noxious stimulation or when stimulation was blunted by opioids. In contrast, NOL nearly always exceeded 25 shortly after noxious stimuli.

Specifically, NOL responded to more than 300 noxious stimuli with an average NOL score of 47 ± 15, well above the manufacturer's threshold of 25 for identifying noxious versus non-noxious stimuli. Only about 8% of noxious stimulation events failed to provoke NOL scores exceeding 25. NOL also responded to 5% of non-noxious stimuli with NOL scores above 25, but nearly all such events lasted less than a minute and therefore would not normally initiate clinical responses. Only 0.3% of false positive responses to non-noxious stimuli exceeding 60 seconds and might thus provoke inappropriate opioid administration. During surgery, clinicians should always employ clinical judgment, taking into account transient effects that may influence the NOL index.

Too often, devices and drugs are validated on narrow populations that are selected to respond optimally and be at low risk for complications. But once devices and drugs are cleared, they are usually used broadly in populations that may not be appropriate. Our analysis was in response to a frequent question by anesthesia providers about the generalizability of NOL nociception assessments. Overall, NOL achieved adequate sensitivity across all sub-groups and reliably responded to noxious stimuli across all pre-specified subgroups: under 65 versus above 65 years of age, intraoperative opioids management using remifentanil versus fentanyl, desflurane versus sevoflurane versus propofol for anesthesia maintenance, patient's physical status 1 versus 2 versus3, normal versus overweight versus obese (BMI), and female versus male. Our results thus indicate that NOL provides accurate estimates of nociception over a broad range of patients and anesthetic conditions. The threshold of 25 thus appears generalizable, which was not previously established.

A limitation of our analysis is that we were restricted to eight NOL studies where Medasense had access to data. For various reasons, we were unable to obtain necessary raw data from three other studies, but those studies represented only 12% of available data. Furthermore, 75 patients from the eight included studies were excluded from analysis because of poor data quality. Nonetheless, our analysis is based on nearly 450 patients and presumably reasonably characterizes noncardiac adult surgical patients. NOL performed well over the range of characteristics and anesthetic approaches we evaluated, but of course there are many other factors that we did not specifically evaluate.

Another possible limitation of this study may be related to inaccurate annotations that remained after data review. The data review process included both manual and automated data checks, and we are therefore confident, that the probability is low. Variability among anesthesia providers and study protocols may further add another source of bias. By nature, surgical stimuli varied in duration and intensity, and responses to nociceptive stimuli in NOL guided patients may have varied.

In summary, we evaluated NOL over six patient demographic and anesthetic approaches and found that nociception was assessed comparably well across all tested groups. NOL thus appears to provide accurate estimates of nociception over a broad range of patients and anesthetic conditions.

AUTHOR CONTRIBUTIONS

KR, MM, OMR and DS conceived and designed the project. OMR made all statistical analysis. KR, AD, YG, PR and BF have been the PI's of the trials included in this analysis. KR wrote the first draft of the manuscript and submitted the manuscript for publication. All authors contributed to development of the protocol and critically reviewed the manuscript prior to submission. All authors approved the final draft of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Dr. Daniel I. Sessler is a consultant for Medasense and a shareholder. Omer Miller Rotem is a Medasense employee.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

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

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