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ORIGINAL ARTICLE

Secondary thrombosis prevention practice patterns in pediatrics: Results of an international survey

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Abstract

Background: Pediatric venous thromboembolism (VTE) rates continue to increase. Although most children present with transient provoking factors, some have persistent prothrombotic risks beyond the initial treatment period warranting secondary anticoagulation. Current pediatric VTE guidelines provide limited recommendations in this regard.

Objectives: Our primary objective was to identify key influences on pediatric thrombosis physicians' decisions to initiate secondary anticoagulation.

Methods: We targeted pediatric hematologists/oncologists internationally using Duration of Therapy for Thrombosis in Children, Children's Hospital Acquired Thrombosis consortium, and Venous Thromboembolism Network US pediatric subgroup membership rosters, who self-identified as primary outpatient thrombosis providers. Of 124 total surveys distributed, 61 complete surveys were evaluable. We defined secondary anticoagulation as anticoagulant use beyond the initial treatment period, on a daily basis (extended) or limited to periods of superimposed clinical risk factors (episodic).

Results: Pediatric thrombosis physicians surveyed indicated that they prescribe secondary anticoagulation in <25% of children despite persistent risks. Among those who indicated use of secondary anticoagulation, the preferred modality was extended anticoagulation in children with a history of recurrent unprovoked VTE (98%), chronic central venous catheter (74%), and potent thrombophilia (73%). Episodic anticoagulation was preferred in children with a history of mild thrombophilia (54%). Respondents were more likely to prescribe secondary anticoagulation for adolescents as opposed to children <12 years old.

Conclusions: Among pediatric thrombosis physicians surveyed, they perceived the prevalence of persistent prothrombotic risks to be high in children who have completed a course of anticoagulation for provoked VTE; however, estimated use of

This work was carried out at the University of Alabama at Birmingham.

secondary anticoagulation was low. Studies involving real-world data are needed to further evaluate use of secondary anticoagulation in this setting.

KEYWORDS
anticoagulants, child, recurrence, thrombosis, venous thromboembolism

Essentials

- Pediatric thrombosis guidelines offer limited guidance for secondary thrombosis prevention.
- Some children have persistent prothrombotic risks requiring secondary anticoagulation.
- We found minimal prescription of secondary anticoagulation in young children.
- Further studies are needed to inform pediatric guidelines to aid physician decision making.

1 | INTRODUCTION

Venous thromboembolism (VTE) affects approximately 1 in 100 000 children, with an even higher incidence in hospitalized children.[1] Although VTE occurs less frequently in children as compared to adults, it can be associated with significant risk of long-term morbidity (ie, postthrombotic syndrome) and even mortality in cases of pulmonary embolism.[2] Most children present with transient provoking factors (ie, recent surgery, infection, temporary central venous catheter [CVC]) for an acute thrombotic event, which poses a low risk of VTE recurrence.[3] Previous reports estimate recurrence rates of 6% to 10% in these lower-risk children.[4] Unfortunately, a subset of children has persistent prothrombotic risks (examples in Table 1) beyond the initial treatment period and may warrant additional anticoagulation due to higher risk for recurrent VTE. The proportion of children with persistent prothrombotic risks is not well established.[5] Despite an increase in VTE among children and potential for an increased incidence in persistent prothrombotic risk factors, evidence-based standards are lacking to guide the ongoing management of this potentially fatal condition beyond the initial treatment period.[1]

The lack of systematic pediatric clinical trials limits the current pediatric VTE guidelines in providing recommendations for secondary anticoagulation.[6,7] The 2012 *CHEST* guidelines provide a strong recommendation for long-term anticoagulation in children who have suffered from recurrent idiopathic VTE.[7] However, such recommendations are lacking for the various other persistent prothrombotic risks. This limits pediatric thrombosis providers to rely on their anecdotal clinical experience and/or extrapolate from the adult literature to inform their treatment decisions. The recent DIVERSITY trial was the first to prospectively evaluate outcomes for secondary anticoagulation in children with persistent prothrombotic risks. It showed low rates of recurrent VTE and clinically relevant bleeding, suggesting the safety of such therapy. Nonetheless, it did not address which subgroups of children would potentially benefit most, with respect to risk of VTE recurrence.[5] The 2018 American Society of Hematology Pediatric VTE guidelines emphasize the need to determine the influence of various provoking factors on outcomes of VTE to optimize duration of therapy as an important priority for future research in the field of pediatric thrombosis.[6]

A clinical trial that includes risk stratification of pediatric patients with provoked VTE and persistent prothrombotic risks needs to be performed. Until such a trial is undertaken, it is critical to understand expert consensus to help inform clinicians' decision making. Therefore, we conducted this international survey of pediatric thrombosis physicians to approximate the number of children with provoked VTE who have persistent prothrombotic risks following completion of initial anticoagulant therapy and to characterize the contemporary practice patterns for the use of secondary anticoagulation in such high-risk children. Our primary objective was to identify key factors that influence pediatric thrombosis providers' treatment decisions to initiate secondary anticoagulation. We also evaluated the impact of clinician experience, practice location/setting, and patient-specific factors on their decision making. We tested the hypothesis that older patient age and specific comorbidities conferring persistent prothrombotic risk are associated with higher frequencies of secondary anticoagulation use. Ultimately, by capturing the prevalence of prothrombotic risks following initial treatment and characterizing existing secondary anticoagulation practices, we hope to lay the groundwork for future randomized controlled trials aimed to establish standards for secondary anticoagulation use and ultimately reduce the incidence of VTE recurrence among children.

2 | METHODS

The University of Alabama at Birmingham (UAB) Institutional Review Board approved this study.

2.1 | Population

The targeted population for this survey was pediatric hematologists/oncologists who self-identified as primary outpatient thrombosis providers at their respective institutions. The objective of the survey was to assess the current practices and preferences for the

TABLE 1 Common persistent prothrombotic risks in pediatric VTE

Mild thrombophilia[a]
Potent thrombophilia[b]
Recurrent provoked VTE
Recurrent unprovoked VTE
Underlying inflammatory disorder[c]
Chronic CVC
Family history[d]
Chronic immobility

Abbreviations: CVC, central venous catheter; VTE, venous thromboembolism.

[a]Mild thrombophilia: heterozygous prothrombin or factor V Leiden mutations, protein C/S levels 20%-40%, antithrombin levels 30% to <65%.

[b]Potent thrombophilia e.g., homozygous prothrombin or factor V Leiden mutations, protein C/S levels <20%, antithrombin levels <30%.

[c]Presence of underlying inflammatory disorder: inflammatory bowel disease, systemic lupus erythematosus, sickle cell disease.

[d]Family history of young onset or unprovoked VTE.

use of secondary anticoagulation in children with provoked VTE who have persistent prothrombotic risks following a conventional course of anticoagulant treatment.

We identified potential participants using the membership registries of three of the primary pediatric thrombosis networks: Duration of Therapy for Thrombosis in Children Investigators, Children's Hospital Acquired Thrombosis Consortium and the Venous Thromboembolism Network US pediatric thrombosis subgroup. To prevent individual participants who were members of multiple organizations from completing multiple surveys, we excluded duplicate names and email addresses.

Surveys were distributed electronically via email to potential participants between December 2020 and January 2021. Reminder emails were sent on three occasions. No incentives were provided for completion of the survey. In the introductory email, participants were assured of the anonymous nature of the survey and were instructed to proceed only if they consented to participate voluntarily. The first survey question served as a screen to identify participants who self-identified as a primary outpatient pediatric thrombosis provider; no further questions were presented for respondents who did not self-identify as primary outpatient pediatric thrombosis providers.

2.2 | Survey design/characteristics

Two experts in pediatric thrombosis developed the survey using Qualtrics software (Provo, UT, USA). Subsequently, two hematologists at UAB and one expert in survey design tested the survey. Edits were made and the survey was retested until all five experts agreed on the final content and design. No formal validation of the survey was undertaken.

The survey consisted of three main sections: respondent characteristics, prescribing patterns for secondary anticoagulation, and clinical case vignettes (complete survey provided in Appendix S1). The survey used multiple-choice questions, with branch logic employed for specific follow-up questions. Participants could answer "other," but were then required to elaborate if their practice varied significantly from the answer choices given. Two independent reviewers reviewed these alternate responses, and once consensus was reached, the responses were grouped into main categories for data analysis.

We evaluated intraindividual reliability of the survey by providing clinical case vignettes to assess provider preferences on the use of secondary anticoagulation. Case 1 was a 4-year-old child with total parenteral nutrition (TPN)-dependent short gut syndrome (chronic CVC) who had received treatment with therapeutic anticoagulation for 3 months for CVC-related deep vein thrombosis. Case 2 was a 5-year-old who had received a 3-month course of therapeutic anticoagulation for provoked VTE in which the provoking factor was transient, but the child was found to have a mild genetic thrombophilia trait (heterozygous factor V Leiden mutation) in the setting of a family history positive for early-onset VTE in a first-degree relative. Case 3 involved an 18-year-old with potent inherited thrombophilia (severe protein S deficiency).

2.3 | Definitions

We defined *secondary anticoagulation* as anticoagulant use beyond the initial treatment period, on a daily basis (extended) or limited to periods of superimposed clinical risk factors (episodic). *Persistent prothrombotic risks* were defined as any factors (chronic CVC, inherited thrombophilia, chronic immobility, etc) that persist following completion of a conventional course of anticoagulant treatment for VTE for which the risk for recurrence is deemed elevated. We categorized thrombophilia as mild or potent (Table 3) based on convention used in prior studies.[8–11]

2.4 | Statistical analysis

Survey responses were collected in Qualtrics and analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Data were summarized using counts and percentages. In testing our hypotheses, chi-squared tests (or Fisher's exact tests, as appropriate to the sample size for a given cell in the corresponding 2 × 2 contingency tables) were performed. Intraindividual reliability in reported use (main survey) versus applied (clinical case vignettes) treatment preferences was measured by the kappa statistic with Clopper-Pearson 95% confidence intervals (CIs). *P* values <0.05 were considered statistically significant.

3 | RESULTS

We received 80 responses (65%) of 124 primary outpatient thrombosis physicians surveyed (Figure 1). Six surveys were excluded as

"no" was selected for the initial screening question that limited respondents to primary outpatient thrombosis providers at each institution. After incomplete surveys were excluded, 61 surveys (49%) comprised the final analytic population.

3.1 | Respondent characteristics

Table 2 summarizes the clinical practice characteristics of the survey study population. The majority of respondents (87%) practice in the United States, and 52% had >10 years of experience in caring for pediatric thrombosis patients. Sixty-seven percent practiced at a freestanding children's hospital, and 82% were affiliated with an academic medical center. Sixty-four percent of respondents indicated that a formal pediatric thrombosis program existed at their institution, and nearly 50% reported an annual new case volume of ≥40 pediatric patients with provoked VTE.

3.2 | Respondent VTE management practice

We first assessed the initial anticoagulation management; 87% of respondents reported that they typically prescribe a 3-month course of anticoagulation for the treatment of provoked VTE. Forty-three percent of respondents estimated 10% to 30% of affected children at their institutions have persistent prothrombotic risks at the conclusion of a 3-month treatment course. These estimates did not differ appreciably by institutional annual volume of newly diagnosed pediatric provoked VTE. Forty-four percent of respondents reported use of secondary anticoagulation in <25% of pediatric patients with provoked VTE with persistent prothrombotic risks after completion of a conventional course of anticoagulation.

3.3 | Reported use of secondary anticoagulation

A higher proportion of pediatric thrombosis physicians prescribed secondary anticoagulation to adolescents (0.92; 95% CI, 0.82-0.97) as opposed to children <12 years old (0.48; 95% CI, 0.35-0.61).

Next, we analyzed physician preference for three common approaches to secondary anticoagulation (extended, episodic, and no secondary anticoagulation) by common risk factors. The use of secondary anticoagulation and management strategies by type of comorbidity constituting persistent prothrombotic risks are shown in Table 3. In most scenarios, the majority of pediatric thrombosis physicians indicated they would prescribe secondary anticoagulation (extended or episodic) to patients with persistent prothrombotic risk factors (Table 3). Extended anticoagulation was the preferred modality in patients with a history of recurrent unprovoked VTE (98%), in those with chronic CVC (74%), and those with potent thrombophilia (73%). Episodic anticoagulation was favored in children with a history of mild thrombophilia (54%). The numbers were nearly evenly split for use (extended and episodic) versus nonuse of secondary anticoagulation in cases of family history (51% vs 49%) and chronic immobility (46% vs 44%).

3.4 | Applied preferences for secondary anticoagulation: Clinical case vignettes

As shown in Table 4, the case scenario of TPN dependence with a chronic CVC (clinical case vignette 1) in a 4-year-old elicited a majority (56%) of responses in favor of an extended anticoagulation approach upon completion of initial treatment. In contrast, the second case of a 5-year-old with a mild inherited thrombophilia (heterozygous factor V Leiden mutation) with a family history of early-onset VTE elicited a majority (54%) of responses favoring episodic anticoagulation. Finally, for the third scenario of an 18-year-old with potent inherited thrombophilia (severe protein S deficiency) responses were again in favor of extended anticoagulation (79%).

Kappa (k) values (and corresponding 95% CI) were calculated for use/nonuse (and modality) of secondary anticoagulation in the applied case scenarios relative to reported use in the main survey., as follows: chronic CVC with TPN dependence, k = 0.36 (95% CI, 0.17-0.54); mild inherited thrombophilia with a family history of early-onset provoked VTE, k = 0.23 (95% CI, 0.04-0.42); and potent inherited thrombophilia, k = 0.22 (95% CI, 0.28-0.41). Self-reported confidence in use/nonuse and modality of secondary anticoagulation in these case scenarios, using a 5-point Likert scale was generally in the mid-range. Specifically, in case vignettes 1 through 3, confidence score was between 2 and 4 on the scale of 5 in 84%, 71%, and 83% of respondents, respectively.

4 | DISCUSSION

This international survey of pediatric thrombosis physicians provides clinicians with expert opinion on decision-making approaches to secondary thrombosis prevention. Our key finding was that pediatric thrombosis physicians felt most comfortable prescribing secondary anticoagulation in children >12 years old than in younger children. Our findings likely reflect an increased comfort level of pediatric thrombosis physicians to extrapolate adult guidelines to adolescent patients in settings of perceived heightened VTE risk. While randomized clinical trials ensure high-quality evidence for secondary anticoagulation adult guidelines; adolescents and teenagers are underrepresented in these trials and may represent a unique population of interest.

Another important finding was that despite a general perception in the field of pediatric thrombosis that persistent prothrombotic risk factors increase the risk of recurrent VTE,[12,13] respondents reported low overall use of secondary anticoagulation with estimated use in <25% of high-risk children. Furthermore,

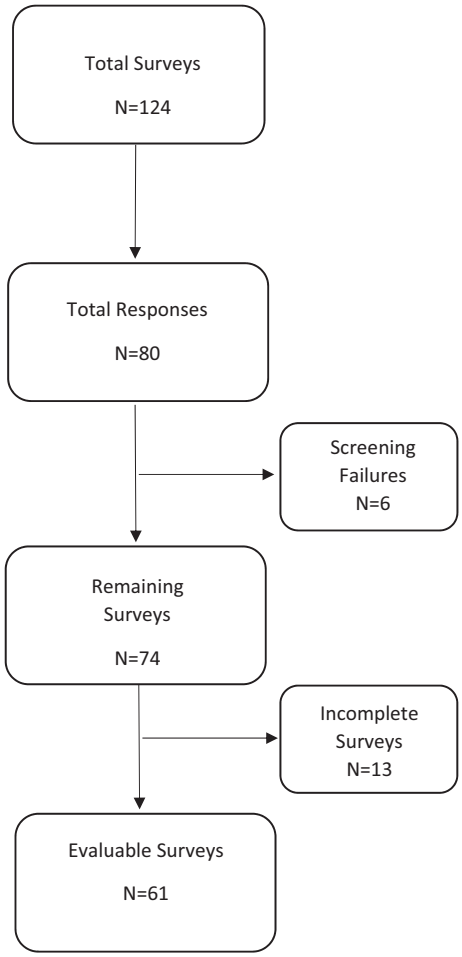

FIGURE 1 Diagram of Survey Responses and Exclusions

TABLE 2 Respondent characteristics

Variables	n (%)
Country of practice	
United States	53 (87)
Other[a]	8 (13)
Years in practice	
<5	12 (20)
5-10	17 (28)
>10	32 (52)
Hospital type	
Freestanding children's hospital	41 (67)
Combined adult and pediatric center	19 (31)
Other	1 (2)
Practice setting	
Academic medical center	50 (82)
Nonacademic/community-based hospital	6 (10)
Private practice	3 (5)
Other	2 (3)
Pediatric thrombosis program	
Yes	39 (64)
No	18 (30)
Not sure	4 (6)
Average annual volume of new pediatric cases of provoked VTE	
<20	6 (10)
20 to <40	21 (34)
40 to <60	14 (23)
≥60	14 (23)
Not sure	2 (3)

Abbreviation: VTE, venous thromboembolism.

[a]Canada (n = 4), Australia (n = 1), Austria (n = 1), Germany (n = 1), and the Netherlands (n = 1).

there was low concordance between reported use of secondary anticoagulation (main survey) and applied use as elicited through case vignettes. This is likely a direct reflection of the lack of high-quality evidence to support the efficacy and/or safety of primary or secondary thromboprophylaxis in children. Additional barriers may include the limitations of the lack of pediatric formulations of anticoagulant medicine and barriers associated with daily medication use in children. The most common approach to secondary anticoagulation in children remains either low-dose daily warfarin (target international normalized ratio <2), low-molecular-weight heparin (LMWH) once daily at therapeutic dose (targeting an anti-Xa range of 0.5-1.0 IU/mL 4 hours after dosing) or twice daily at low dose. LMWH requires daily subcutaneous injections, while warfarin requires frequent blood draws for monitoring, both of which present barriers to patient acceptance of and subsequent adherence to secondary anticoagulation. In contrast, some adolescents are being treated with direct oral anticoagulants (DOACs).[14] The Apixaban Compared to Standard of Care for Prevention of Venous Thrombosis in Paediatric Acute Lymphoblastic Leukaemia (PREVAPIX-ALL) trial recently completed recruitment, investigating the safety and efficacy of prophylactic/low-dose daily use of the DOAC apixaban for VTE prevention in children and adolescents with acute leukemia with a CVC undergoing induction chemotherapy.[15] As pediatric DOAC formulations represent a potentially more acceptable approach for secondary anticoagulation in pediatric patients, it will be important to reassess pediatric thrombosis physician comfort with use of secondary anticoagulation in children with persistent prothrombotic risks after completion of pertinent clinical trials.

Another limitation in the field and literature in pediatric VTE is the lack of standardized definitions for persistent prothrombotic risks. Our survey identified that pediatric thrombosis physicians can recognize risk factors that influence their decision making regarding use of secondary anticoagulation, including the degree to which index VTE was provoked, the presence and nature of underlying thrombophilia, patient age, and family preferences. While prior literature[16] provides the basis for incorporation of thrombophilia status (eg, presence/absence of protein C/S, or antithrombin deficiency) into the assessment of persistent prothrombotic risks, this is challenged by the fact that cost effectiveness of such testing in

TABLE 3 Management strategy by prothrombotic risk factor

Risk factor[a]	Management strategy, N (%)		
	Extended secondary anticoagulation	Episodic secondary anticoagulation	No secondary anticoagulation
Mild thrombophilia[b]	7 (11)	33(54)	21 (34)
Potent thrombophilia[c]	45 (73)	14 (23)	2 (3)
Recurrent provoked VTE	33 (54)	26 (42)	2 (3)
Recurrent unprovoked VTE	60 (98)	1 (2)	0 (0)
Underlying inflammatory disorder[d]	33 (54)	18 (30)	10 (16)
Chronic CVC	45 (74)	5 (8)	11 (18)
Family history[e]	12 (20)	18 (29)	31 (51)
Chronic immobility	18 (29)	15 (25)	28 (46)

Abbreviation: VTE, venous thromboembolism.

[a]Total N for each row = 61, which was used to compute the percentages for each row.

[b]Mild thrombophilia: heterozygous prothrombin or factor V Leiden mutations, protein C/S levels 20%-40%, antithrombin levels 30% to <65%.

[c]Potent thrombophilia, eg, homozygous prothrombin or factor V Leiden mutations, protein C/S levels <20%, antithrombin levels <30%.

[d]Presence of underlying inflammatory disorder: inflammatory bowel disease, systemic lupus erythematosus, sickle cell disease.

[e]Family history of young onset or unprovoked VTE.

TABLE 4 Secondary anticoagulation preferences: clinical case vignettes

Management strategies	Case 1[a] n (%)	Case 2[b] n (%)	Case 3[c] n (%)
Extended secondary anticoagulation	34 (56)	1 (2)	48 (79)
Episodic secondary anticoagulation	16 (26)	33 (54)	10 (16)
No secondary anticoagulation	9 (15)	25 (41)	2 (3)
Total	59 (97)	59 (97)	60 (98)

[a]Case 1: 4-year-old; total parenteral nutrition dependence with a chronic central venous catheter.

[b]Case 2: 5-year-old; heterozygous factor V Leiden mutation with positive family history.

[c]Case 3: 18-year-old; severe protein S deficiency.

unselected cases of pediatric VTE has not been demonstrated.[17] Future studies must assess cost analysis of integrating thrombophilia screening into VTE risk assessment.

We identified a strong consensus among respondents for the use of secondary anticoagulation in pediatric VTE in cases with a history of recurrent unprovoked VTE (100%) and in those with chronic indwelling CVC (82%) upon completion of therapeutic anticoagulation (Table 3). This reflects acceptance of the recommendations from current pediatric VTE guidelines.[6,7] Importantly for future clinical trial design, we identified equipoise among experts in several areas, namely, as it relates to use versus nonuse of secondary anticoagulation and the modalities thereof in the scenarios of persistent prothrombotic risks, including recurrent provoked VTE, underlying inflammatory conditions, chronic immobility, and potent thrombophilia states (eg, homozygous factor V Leiden or factor II G20210A variants; moderate/severe anticoagulant protein deficiencies). These findings clearly define a clinical need to conduct a pediatric secondary anticoagulation study.

4.1 | Limitations

Several limitations of this study are noteworthy. As with any survey study evaluating experience, there is a potential for recall bias—in this case, patient case volumes, proportions, and management practices. In addition, because the respondents were predominantly from the United States, caution should be exercised when attempting to generalize our findings to everyday practice on a truly "worldwide" scale. Future research employing real-world data must assure representation from health care organizations on an international level. Similarly, 82% of respondents practice at academic medical centers, and may therefore not reflect the full spectrum of practice locations. However, recent research suggests that in at least some countries (like the United States), the vast majority of pediatric VTE cases are managed at academic medical centers, and therefore it is unlikely that this potential limitation has a significant impact on the present findings.

Finally, our study may be limited by the fact that responses to hypothetical scenarios do not necessarily reflect actual practice. Our findings on reported practice experience and preferences must be interpreted with caution, given that we found a weak concordance in intraindividual response between reported use and

applied use as indicated in corresponding clinical case vignettes. This highlights the fact that without sufficient evidence to support or guide clinical decision making, practice is often both variable (among individuals) and inconsistent (for a given individual). Therefore, cooperative multicenter prospective observational studies in this low-incidence but high-risk population are needed to accurately define the use of and approach to secondary anticoagulation, as well as estimates of VTE and bleeding outcomes in cases of pediatric provoked VTE with persistent prothrombotic risks.

Notwithstanding these limitations, the findings of our survey highlight critical opportunities for improvement in and standardization of the care of children affected by VTE. Reported management strategies were most consistent in the areas specifically addressed by current pediatric VTE guidelines. These findings suggest that we desperately need development of guidelines surrounding the use of secondary anticoagulation to guide physician's treatment decisions, in turn streamlining practice patterns. Future research should further investigate and expand upon these findings via a multicenter retrospective analysis of real-world data with ultimate goal of designing and conducting interventional trials that assess the safety and efficacy of secondary anticoagulation in children with provoked VTE and persistent prothrombotic risks following completion of a therapeutic course of anticoagulation.

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AUTHOR CONTRIBUTIONS

HPW developed this research concept and design, drafted the initial manuscript, and performed critical revisions. RC and IA participated in data analysis and manuscript revisions. JL participated in data interpretation and revision of intellectual content of the manuscript. NAG participated in research concept and design along with data interpretation, writing, and revision of intellectual content of the manuscript. All authors approved the final manuscript version submitted for publication.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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