Optimization of DOAC management services in a centralized anticoagulation clinic

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Abstract

Background: In 2017, the Brigham and Women’s Hospital Anticoagulation Management Service (BWH AMS) expanded services to patients on direct oral anticoagulants (DOACs). We have since updated our DOAC management plan and adjusted the workflow of our clinic.

Objectives: This report describes how our DOAC management has evolved and describes key interventions made. Additionally, we report on the results of a survey completed by referring physicians that assessed perspectives regarding centralized DOAC management by BWH AMS pharmacists.

Methods: An analysis was completed of all patients referred to the BWH AMS and the number of interventions completed and documented in our anticoagulation management software. A survey with eight questions was sent to 110 referring physicians (selected based on referring to the AMS within the past 1.5 years).

Results: Over 4 years, 1622 patients on DOACs were referred to the BWH AMS, amounting to 3154 DOAC encounters. A total of 212 interventions for medication procurement, 171 dose adjustment interventions, and 603 coordinated procedure plans were completed. Of the 32 physicians who responded to the survey, many believed that the quality and safety of anticoagulation therapy was improved with BWH AMS management. Despite provider satisfaction with pharmacist-led care in DOACs, physicians expressed concerns regarding the lack of provider awareness of the clinic and possible duplicative efforts.

Conclusion: We plan to evolve the DOAC clinic model to optimize its clinical and operational value and to improve our delivery of care using electronic tools to move toward a population management approach for DOAC management.

KEYWORDS
anticoagulant, burnout, clinical pharmacy services, direct-acting oral anticoagulant, quality improvement
1 | INTRODUCTION

Oral anticoagulants are among the 10 most common causes of adverse drug events resulting in emergency department visits among adults ≥65 years of age.\(^1\) Compared to vitamin K antagonists (eg, warfarin), direct oral anticoagulants (DOACs) are easier to manage due to their predictable pharmacokinetics, fixed-dose regimens, lack of routine monitoring requirements, and fewer dietary and drug interactions. Despite these advantages, DOACs remain high risk, requiring patient-specific dose adjustments and interventions to improve adherence, and necessitate advanced planning for procedures or interventions.\(^2\) In 2019, due to an increased number of adverse events related to DOACs, the Joint Commission revised its National Patient Safety Goal on anticoagulation, issuing a new sentinel event alert for managing the risks associated with DOACs. This alert provides guidance on the safe use and management of DOACs, indicating the importance of designing care systems to ensure the safety of patients on DOACs, which may require different strategies than those used to manage other anticoagulants, especially for urgent/emergent reversal of anticoagulation.\(^3,4\)

A prospective analysis of dabigatran and rivaroxaban in patients with nonvalvular atrial fibrillation found that 49% of patients had at least one criterion associated with inappropriate prescribing (ie, incorrect indication, choice of agent, dosage, or route of administration). Inappropriate prescribing was associated with an increased risk of thromboembolic and hemorrhagic events.\(^5\) Real-world data also demonstrate that poor adherence to DOACs results in decreased efficacy and increased risk of adverse events.\(^5,7\) These observations support the need for centralized management of patients on DOACs. An Anticoagulation Management Service (AMS) providing DOAC services can optimize anticoagulation therapy during transitions of care, where many opportunities for medication errors arise. Ineffective transitions of care can increase readmission rates, health care usage, adverse drug events, and patient dissatisfaction.\(^9,10\) In 2016, the Anticoagulation Forum published guidance on the management of the DOACs in venous thromboembolism (VTE) treatment, which included a strong recommendation for implementing specialized inpatient and outpatient DOAC anticoagulation services.\(^11\) Previous publications have also proposed models for outpatient DOAC management.\(^12-15\)

As AMS models expand to incorporate DOAC management, barriers remain. Lack of provider awareness for services provided by the clinic, budgetary challenges, and scope of care of anticoagulation staff pose potential barriers to optimizing the level and quality of care.\(^16,17\) Such barriers can lead to underuse of AMS services and duplicative and/or inconsistent efforts in DOAC management. In addition to the safety and quality added by centralized oversight and management of DOACs, centralized anticoagulation management by advanced practice providers (including pharmacists, nurse practitioners, and physician assistants) and registered nurses may also alleviate physician burnout by allowing each practitioner to practice at the top of their license.

In 2017, the Brigham and Women’s Hospital (BWH) AMS implemented a pilot program to expand services to include management of patients on DOACs.\(^18\) We have since updated our DOAC management plan and adjusted the workflow and operations of our clinic. This analysis aims to evaluate the progression of our DOAC management program, reflect upon the insights gained, and propose steps to further develop the model of DOAC management within an AMS.

2 | METHODS

The AMS at our institution is a pharmacist-run clinic managing patients on anticoagulation under a collaborative drug therapy management agreement, allowing pharmacists to write prescriptions for anticoagulants, associated reversal agents, and order-related labs. The clinic resources are funded by the hospital as a recognized best-practice service to improve care for patients who receive longitudinal care by providers credentialed at BWH. The clinic has two medical codirectors and pharmacy leadership, 9.6 full-time equivalent pharmacists, one program coordinator, and four pharmacy interns. All patients are managed remotely with telephonic visits, and orders for laboratory draws are sent to the patient’s preferred laboratory when needed. Before 2017, our clinic managed patients primarily on warfarin and infrequently low-molecular-weight heparin monotherapy. As the DOACs became more widely prescribed, and issues such as limited familiarity with their dosing (and dosing adjustments), difficulty with affordability and access, and the need for optimal transitions of care became more apparent, we recognized the need to expand the role of our current AMS providers to include management of DOACs. Before expanding to DOAC management, the clinic leadership evaluated and optimized current clinic operations to allow for the expansion without an increase in resource requirements.

Our expansion of services began with developing clinical guidelines and a pilot for outpatient longitudinal management by credentialed pharmacists.\(^18\) For patients referred to the AMS on DOACs, pharmacists select the most appropriate oral anticoagulant, assess the ongoing need for anticoagulation and the risk of bleeding and thrombosis, ensure laboratory follow-up, and complete medication
refills. The original DOAC management plan required pharmacist follow-up within the first week of treatment, at 3 months, and at 6 months, with an additional follow-up for patients prescribed a DOAC for VTE treatment requiring an induction phase. After the initial 6 months of follow-up, the frequency of subsequent follow-up visits is based on the risk for DOAC-associated adverse events. Patients are stratified into three groups: low-risk patients assessed yearly, moderate-risk patients every 6 months, and high-risk patients every 3 months.

BWH AMS manages patients on DOACs for a variety of indications such as atrial fibrillation, VTE, and coronary artery disease. Any patient who has longitudinal follow-up within our institution with either a primary care physician or cardiologist may be referred to our AMS for DOAC management services. In addition to the physician-initiated referrals, the AMS also reaches out proactively to referring physicians who have patients newly initiated on DOACs through our emergency department or during a BWH inpatient encounter. Through both of these processes it is estimated that BWH follows our emergency department or during a BWH inpatient encounter. Physicians who have patients newly initiated on DOACs through our electronic medical record (AMS) will initiate prior authorizations when necessary or evaluate the need for medication access barriers (eg, high copays, prior authorizations, or insurance formulary requirements); additionally, more contact with the patient early in management allows providers to establish relationships with the patients.20,21 After the first 6 months, patients are stratified into either active surveillance or maintenance phase of care depending on the likelihood of requiring a dose adjustment within the next 12 months based on the DOAC specific manufacturer recommendations (Table 2). Patients with a moderate or high risk of needing a dose adjustment are transitioned to active surveillance. A patient may be transitioned from maintenance to active management, which includes a minimum yearly follow-up.

Although there are relatively few indications for DOAC dose adjustments, the AMS makes an assessment during the initial telephone encounter and then on subsequent follow-up encounters to determine if a DOAC dose adjustment or change in therapy is needed due to comorbidities, a change in renal or liver function, weight, or dose deescalation in VTE after 6 months of treatment. For renal dose adjustments, a creatinine clearance (CrCl) is calculated using the Cockcroft-Gault equation using total body weight.19

After 3 years of managing patients anticoagulated with DOACs, we refined our DOAC management plan to create three management categories to optimize each patient contact and provide the most clinically relevant services (Figure 1). For the first 6 months, patients are enrolled in the AMS; they remain in active management and have follow-ups scheduled on the basis of our previous DOAC management plan. In the first few months after initiation of anticoagulation, patients are at the highest risk of adverse events and medication access barriers (eg, high copays, prior authorizations, or insurance formulary requirements); additionally, more contact with the patient early in management allows providers to establish relationships with the patients. After the first 6 months, patients are stratified into either active surveillance or maintenance phase of care depending on the likelihood of requiring a dose adjustment within the next 12 months based on the DOAC specific manufacturer recommendations (Table 2). Patients with a moderate or high risk of needing a dose adjustment are transitioned to active surveillance. A patient may be transitioned from maintenance to active management, which includes a minimum yearly follow-up.

A patient review occurs annually for all patients. The referring physician must cosign a renewal of the referral. DOAC management with AMS includes perioperative management plans, ongoing education, 24/7 on-call support for anticoagulation-related emergencies—provided by the same group of AMS pharmacists, and access to the pharmacist for any other medication-related questions regarding anticoagulation. A patient may be transitioned from maintenance back to active management if there is a relevant change in a patient’s clinical status requiring closer follow-up. This transition would be identified if AMS was notified by the provider, if the patient reaches out to the AMS clinician, or if a change in clinical status is identified during a scheduled encounter.

To evaluate the impact of AMS management of DOAC patients on provider workflow and satisfaction, we sent an informal eight-question survey to 110 attending physicians across the institution in May 2021 to assess the perceived value, quality, and safety of centralized DOAC management by BWH AMS pharmacists (see Appendix S1 for survey questions). Physicians were selected to receive this survey if they referred a patient to the AMS within the past 1.5 years. Physicians were sent an email with a link to a RedCap secure survey and given 2.5 weeks to complete the survey. One reminder email was sent to the recipients 3 days before the survey period ended.
RESULTS

Over 4 years, from June 1, 2017, to May 31, 2021, a total of 1622 patients on DOACs were referred to the BWH AMS for management. Of the 1622 patients, 1198 (73.9%) patients were being managed on apixaban, 394 (24.3%) patients on rivaroxaban, 22 (1.4%) patients on dabigatran, and 8 (0.5%) patients on edoxaban. The median age of patients on DOACs was 72 years (interquartile range [IQR], 62-79), median body weight was 82 kg (IQR, 70-98), and median CrCl was 75 mL/min (IQR, 55.3-102) (Table 3).

For each DOAC patient referred to AMS, an introduction to the service and education was provided. For those needing an induction phase, the pharmacist counseled the patient to ensure transition from the induction to maintenance dose at the appropriate time interval. For most patients (n = 730), the time spent per patient on new patient education and introduction to the service was between 15 and 30 minutes. There were 663 patients (40.9%) who took <15 minutes and 229 patients (14.1%) who required >30 minutes. Additionally, of the 1622 patients on DOACs, 149 (9.2%) patients required assistance with initial medication procurement (eg, prior authorization required, medication switch required).

Since initiation with the service, BWH AMS has completed 3154 DOAC follow-up encounters. At the follow-up, 127 patients (4.0%) were identified as not taking their DOACs as prescribed. An

TABLE 1 Encounter checklist for follow-up visits

| Objective                          | Interval        | Description                                                                 |
|------------------------------------|-----------------|-----------------------------------------------------------------------------|
| Assess adherence                   | Each visit      | • Assess adherence by asking patients questions relating to how they take their medication.  
                                 |                  | • Reinforce education regarding the importance of strict adherence to medication regimen.  
                                 |                  | • Inform patient about adherence tools such as medication boxes, phone services, and smartphone applications (reminder dabigatran must remain in original packaging).  
                                 |                  | • Assist with medication procurement if needed.  
                                 |                  | • Provide patient with refill of DOAC prescription if needed. |
| Assess for thromboembolism         | Each visit      | • Arterial (transient ischemic attack, stroke, peripheral)  
                                 |                  | • Pulmonary  
                                 |                  | • Deep vein thrombosis |
| Assess for bleeding                | Each visit      | • If minor (nuisance) bleeding, are preventable measures possible (eg, proton pump inhibitor, saline nose spray, etc)? Motivate patient to continue anticoagulation diligently.  
                                 |                  | • If bleeding impacts quality of life, assess the need for ongoing anticoagulation and consider changing anticoagulant. |
| Assess for other side effects      | Each visit      | • Assess for link to DOAC and decide whether to continue, temporarily stop, or change to different anticoagulant. |
| Assess for new medications         | Each visit      | • Assess for P-gp inhibitors/inducers (if on dabigatran or edoxaban) or dual P-gp/CYP3A4 inhibitors (if on rivaroxaban or apixaban).  
                                 |                  | • Assess for other medications that may increase risk of bleeding, such as antiplatelets.  
                                 |                  | • DOAC dose adjustments or a change in therapy may be required if patient initiates medication/supplement that interacts with DOAC. |
| Assess for upcoming procedures     | Each visit      | • Assess need to interrupt DOAC therapy.  
                                 |                  | • DOAC periprocedural plans may need to be developed. |
| Assess labs                         | Yearly          | • Liver function, CBC, creatinine  
                                 |                  | a. For patients in active surveillance—may require renal function as often as every 3 months.  
                                 |                  | b. DOAC dose adjustments or a change in therapy may be required in some situations for changing renal or liver function. |

Abbreviations: CBC, complete blood count; CYP, cytochrome P450; DOAC, direct oral anticoagulant; P-gp, P-glycoprotein.
additional 63 patients required assistance with medication procurement at the time of follow-up encounter. Pharmacists documented 171 DOAC dose adjustments and coordinated 603 periprocedural plans. Times spent per DOAC patient follow-up were categorized as <15 minutes (n = 1989, 63.1%), 15 to 30 minutes (n = 989; 31.4%), and >30 minutes (n = 177; 5.6%).

Of the 110 physicians who received the survey, 32 (29.1%) responded. The majority of physicians (n = 28; 87.5%) found value in BWH AMS management of patients on DOACs and agree or strongly agree that BWH AMS management of patients on DOACs improves the quality (n = 28; 90.3%) and safety (n = 29; 93.5%) of anticoagulation management. Of the 31 respondents, 24 (77.4%) reported that they were likely to refer their patients on DOACS to the BWH AMS to initiate or manage anticoagulation-related care. Of the services provided by BWH for DOAC management, physicians found transitions to or from warfarin and periprocedural management the most helpful. Additionally, physicians reported that essential benefits to having DOAC patients managed the BWH AMS included the availability of pharmacists as a resource and a decrease in their daily workload.

When asked about their reservations to the DOAC clinic, 5 (15.6%) physicians felt that the work required to submit a referral
was a barrier, and 4 (12.5%) physicians did not recognize the value of the services provided. Physicians were also asked to note any suggestions or additional comments. A recurring comment was that providers were not fully aware of the scope of services offered by BWH AMS for patients on DOACs and that reeducation of providers on this service may be helpful.

TABLE 2 Patient stratification after 6 months of BWH AMS active management

| DOAC     | Indication                      | Required active surveillance                                                                 | Reason for active surveillance                                                                 |
|----------|---------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Apixaban | Nonvalvular atrial fibrillation | On apixaban 5 mg twice daily and has least 1 of the following characteristics:               | Assess for meeting second criterion and needing a dose adjustment to apixaban 2.5 mg twice daily.|
|          | VTE                              | N/A; no dose adjustments required                                                            | N/A                                                                                              |
|          | Extended duration VTE            | N/A; no dose adjustments required                                                            | N/A                                                                                              |
| Rivaroxaban | Nonvalvular atrial  | On rivaroxaban 20 mg once daily and CrCl ≤60 mL/min or fluctuating                          | Assess for drop in CrCl to ≤50 mL/min requiring dose adjustment to rivaroxaban 15 mg once daily.|
|          | VTE                              | N/A; no dose adjustments required                                                            | N/A                                                                                              |
|          | Extended duration VTE            | N/A; no dose adjustments required                                                            | N/A                                                                                              |
| Edoxaban | Nonvalvular atrial fibrillation  | On edoxaban 60 mg and CrCl ≤60 mL/min or fluctuating                                          | Assess for drop in CrCl ≤50 mL/min requiring dose adjustment to edoxaban 30 mg once daily.       |
|          | VTE                              | N/A; no dose adjustments required                                                            | N/A                                                                                              |
|          | CAD/PAD                          | N/A; no dose adjustments required                                                            | N/A                                                                                              |
| Dabigatran | Nonvalvular atrial fibrillation | On dabigatran 150 mg twice daily and CrCl ≤40 mL/min                                        | Assess for drop in CrCl ≤30 mL/min requiring dose adjustment to dabigatran 75 mg twice daily.     |
|          | VTE                              | On dabigatran 150 mg twice daily and CrCl ≤60 mL/min with concomitant use of a P-gp inhibitor (dronedarone/ketoconazole) | Assess for drop in CrCl ≤50 mL/min requiring dose adjustment to dabigatran 75 mg twice daily.     |
|          | Extended duration VTE            | Same as above for treatment of VTE                                                           | Same as above for treatment of VTE                                                               |

Abbreviations: BWH AMS, Brigham and Women’s Hospital Anticoagulation Management Service; CAD, coronary artery disease; Cr, creatinine; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; N/A, not applicable; NVAF, nonvalvular atrial fibrillation; PAD, peripheral artery disease; VTE, venous thromboembolism.

**DISCUSSION**

During the 4 years that our AMS has been managing anticoagulation for patients on DOACs, 1622 patients have been referred, resulting in 212 interventions for initial or ongoing medication procurement (including medication access and affordability), 171
dose-adjustment interventions, and 603 procedure plans coordinated. Additionally, all patients received initial and continuing education and assessment for adherence, and access to our pharmacist 24/7 on-call emergency paging service. To expand this service to the greatest number of patients, we improved our management plan to ensure the pharmacists’ time is being used to optimize clinical benefit. We adjusted our risk stratification classification to focus on requiring a dose adjustment rather than the risk of bleeding/thrombotic events, since a pharmacist intervention is likely to be most valuable for patients requiring a dose adjustment. Making a timely dose adjustment may have a greater impact on long-term bleeding and thrombotic risk.

The value of centralized management of DOACs continues to be recognized across the country, with more anticoagulation clinics being restructured to accommodate DOAC management and optimize patient care. A single-center, retrospective observational study comparing pharmacist-led DOAC services with usual physician care found an increase in appropriate dosing of DOACs at baseline and follow-up and increased patient adherence. Pharmacists in the DOAC service can provide baseline patient education about the importance of medication adherence, recommend changes to DOAC therapy, and provide additional assistance with medication access and affordability, similar to what has been done in our DOAC ambulatory clinic. Various models for centralized DOAC management have been reported, ranging from the traditional anticoagulation clinic models where patients are seen in clinic or through telephone encounters on a regular interval of 3 to 6 months to a population health model that leverages technology to identify patients who require intervention.

Our management plan is more of a hybrid approach that provides a more traditional model for the first 6 months and then stratifies patients on the basis of the potential need for a dose adjustment to determine the subsequent follow-up intervals. All patients remain in active in our clinic so that we can provide education, on-call support, oversight of procedure plans, yearly assessment of bleeding and clotting risk, refilling prescriptions, completing necessary prior authorizations, and ordering labs as needed. This model allows us to manage patients in a way that maximizes the clinical benefit of our services while reducing the number of resources required. Different models of centralized DOAC management have not been compared directly, and the optimal model may be influenced by the resources and technology available, the patient population, and the goals of the stakeholders.

Centralized management of DOACs also allows providers to feel confident transitioning patients from warfarin to DOACs, which are now considered the standard of care for many indications. Providers, especially primary care providers, manage more patients with chronic conditions than ever before, and burnout has received more focus. Excessive workloads, long working hours, and documentation requirements contribute to physicians’ rising prevalence of burnout. In a meta-analysis of 47 studies including 42,473 physicians, burnout was associated with a significant increase in patient safety incidents, poorer quality of care due to low professionalism, and reduced patient satisfaction.

Targeting physician burnout requires a multifaceted approach, with physician-directed interventions that equip physicians with stress reduction and cognitive-behavioral techniques and systematic changes that restructure the delivery of care. To this end, we believe that incorporating DOACs into the traditional AMS care model is one example of maximizing care provided by advanced practice providers to allow for a team-based care model by ultimately moderating physician workload and improving the quality and efficiency of patient care.

In a survey to referring physicians to assess their view of the impact of our centralized DOAC management, the majority responded that they found the clinic valuable in improving both the quality and safety of patient anticoagulation care. Pharmacist involvement in DOAC management is especially valued during transitions of care (eg, periprocedural management, transitions to or from warfarin). The major barriers included not recognizing the value in the AMS for DOAC management and the work required to submit a referral. Referrals are submitted in our electronic medical

| TABLE 3 BWH DOAC Clinic Workload and Interventions |
|-----------------------------------------------|----------|
| **Metric**                                    | **Result**|
| Patient referrals                             | 1622     |
| DOAC (n, %)                                   |          |
| Apixaban                                      | 1198 (73.9) |
| Rivaroxaban                                   | 394 (24.3)  |
| Edoxaban                                      | 8 (0.5)    |
| Dabigatran                                    | 22 (1.4)   |
| Patients requiring medication procurement assistance upon referral (n, %) | 149 (9.2) |
| Follow-up visits                              | 3154     |
| Patients identified as not taking DOAC as prescribed upon follow-up (n, %) | 127 (4.0) |
| Patients requiring medication procurement assistance upon follow-up (n, %) | 63 (1.9)  |
| Patients requiring DOAC dose adjustment (n, %) | 171 (5.4) |
| Patients requiring procedural management plans (n, %) | 603 (19.1) |

Abbreviations: BWH, Brigham and Women’s Hospital; DOAC, direct oral anticoagulant.
record (EPIC) and are entered similarly to new prescriptions but are not linked to the ordering of a DOAC. In the future, we may be able to create decision support to link the referral to the prescription to reduce this barrier. The free-text responses indicate a lack of provider awareness regarding the services provided by the clinic, which may lead to duplicative efforts in DOAC care and decreased use of the service. Suggestions to overcome this barrier include having decision support in the electronic health record to alert physicians of the service when ordering DOACs and establishing an E-consult service.

As we continue to learn from our experiences and those of the larger anticoagulation provider community, we look to continually improve our model to balance the right amount of management for each patient. This analysis was limited to the data available in our anticoagulation management tracking software. We currently do not have detailed information on the reasons for dose adjustment, time needed to complete a prior authorization, the number of prior authorizations approved and denied, or the number of patients transitioned between each of the management statuses (i.e., active management vs maintenance). The survey conducted of our referring physicians also represents a small portion of our larger referring provider pool and is reflective of a single point in time.

5 | CONCLUSION

As the use of DOACs increases worldwide, the need for centralized management of all oral anticoagulants is becoming essential. Anticoagulation management involves many transition periods, putting patients at higher risk of bleeding and thrombotic events. These scenarios can be managed through coordinated efforts of the anticoagulation management service. After 4 years of managing DOACs at our clinic, we have improved patient safety and provider satisfaction. Our principal strategies are to provide patient education, triage medication procedure issues, address dose adjustments, and coordinate anticoagulation periprocedural plans. Our goal for the future is to leverage electronic tools to move toward a population management structure for DOAC management.

RELATIONSHIP DISCLOSURE

KWS has received faculty honoraria and travel expenses from Portola Pharmaceuticals, Inc and has received a National Institutes of Health Grant for Funded Research paid to the institution, which is unrelated to this article. JF has received consulting fees from Vifor Pharmaceuticals, Inc. SZG has received grants/contracts from Bayer, Boston Scientific BTG EKOS, NHLBI, BMS, Janssen, and Pfizer as well as has received payment or honoraria from Lankenau Grand Rounds Medicine, The Brigham Board Review in Critical Care “Virtual Studio/Distance Learning,” Latin American Anticoagulation Series Conference, Mount Sinai Grand Rounds, Westchester Medical Center Grand Rounds, Bakken Symposium—University of Minnesota, New York Cardiovascular Symposium, Jeresaty Symposium—Trinity Health of New England, SBACV Symposium—Brazil Society of Angiology and Vascular Medicine, and consulting fees from Agile, Pfizer, and Bayer. JMC has received grants/contracts from CSL Behring (research support to institution), consulting fees from Abbott, Alnylam, Portola Pharmaceuticals, Anthos, Bristol-Myers Squibb, Payment/Honoraria from Sanofi, and has participated on a DSMB/Advisory Board for Abbott, Bristol-Myers Squibb, Anthos and Takeda. AL and AC have no conflicts of interest to report.

AUTHOR CONTRIBUTIONS

KWS, AL, AC, JF, SZG and JMC all contributed to writing, critically editing, revising, and reviewing the manuscript.

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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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