Utility of a Precision Medicine Test in Elderly Adults with Symptoms Suggestive of Coronary Artery Disease.
Utility of a Precision Medicine Test in Elderly Adults with Symptoms Suggestive of Coronary Artery Disease

Joseph A. Ladapo, MD, PhD,* Matthew J. Budoff, MD,† David Sharp, DO,‡ Jane Z. Kuo, MD, PhD,§ Lin Huang, PhD,‡ Bruce Maniet, DO,§ Lee Herman, MD, ** and Mark Monane, MD, MS§

BACKGROUND: Diagnosing obstructive coronary artery disease (CAD) is challenging in elderly adults, and current diagnostic approaches for CAD expose these individuals to risks from contrast dye and invasive procedures.

DESIGN: A Registry to Evaluate Patterns of Care Associated with the Use of Corus CAD in Real World Clinical Care Settings (PRESET; NCT01677156), pragmatic clinical trial.

SETTING: Community, 21 primary care practices.

PARTICIPANTS: Of 566 stable, nonacute outpatients presenting with symptoms suggestive of obstructive CAD, the 176 who were aged 65 and older (median age 70, 61% female) were the current study participants.

INTERVENTION: Blood-based precision medicine test, incorporating age, sex, and gene expression score (ASGES) to improve clinical decision-making and quality of care.

MEASUREMENTS: Information on demographic characteristics, clinical factors, ASGES results (range 1–40; low (≤15), high (>15)), referral patterns to cardiology and advanced cardiac testing, and major adverse cardiac events (MACEs) was collected in a subgroup analysis of elderly adults in the PRESET Registry. Follow-up was for 1 year after ASGES testing.

RESULTS: Median ASGES was 25, and 40 (23%) participants had a low score. Clinicians referred 12.5% of participants with a low ASGES and 49.3% with a high ASGES to cardiology or advanced cardiac testing (odds ratio for referral = 0.12, P < .001, adjusted for participants demographics and clinical covariates). Higher scores were associated with greater likelihood of posttest cardiac referral. At 1-year follow-up, the incidence of a MACE or revascularization was 10% (13/136) in the high ASGES group and 0% (0/40) in the low ASGES group (P = .04).

CONCLUSION: The ASGES test showed potential clinical utility in the evaluation of elderly outpatients with symptoms suggestive of obstructive CAD. Test use may reduce unnecessary referrals and the risk of procedure-related complications in individuals with low ASGES, who are unlikely to benefit from further testing, while also identifying individuals who may benefit from further cardiac evaluation and management. J Am Geriatr Soc 2017.

Key words: elderly; coronary artery disease; precision medicine; age, sex, gene expression score; clinical utility

The prevalence of obstructive coronary artery disease (CAD) increases with age, but diagnosis is challenging in elderly adults when they present with signs and symptoms suggestive of cardiac ischemia. Elderly adults are more likely to have atypical symptoms that complicate their evaluation, such as weakness, abdominal pain, shortness of breath, heartburn, nausea, and syncope. Because noninvasive testing for obstructive CAD frequently leads to invasive testing with cardiac catheterization, elderly adults also face risks from complications of invasive coronary angiography, such as bleeding, vascular complications, and kidney injury, all of which these individuals are more susceptible to than younger adults. Furthermore, the predictive value and diagnostic yield of current noninvasive and invasive testing are modest. Although stress testing has typically been reported to have sensitivity for obstructive CAD of 80% to 90%, its sensitivity has been found to be less than 50% in studies that adjusted for referral bias or attenuated this bias by referring all participants to coronary computed tomography angiography (CTA) when invasive coronary angiography was not performed. This finding suggests that a substantial proportion of individuals with obstructive disease may be missed. Finally, the examinations are costly for individuals and society, with several billions of dollars spent each year in insurance payments and out-of-pocket costs.
Advances in precision medicine may help augment current diagnostic tools and redefine the paradigm for evaluating CAD in elderly outpatients. Although most precision medicine efforts in the elderly population have focused on messaging and pharmacological approaches, diagnostic tests have received less attention.\(^\text{11-14}\) Recently, a quantitative test incorporating age, sex, and gene expression levels into an algorithmic score (ASGES) was developed to assess the current likelihood of obstructive CAD, defined as at least one atherosclerotic plaque causing 50% or more luminal diameter stenosis in a major coronary artery (≥1.5-mm lumen diameter).\(^\text{15-17}\) Three large prospective multicenter studies have independently validated the ASGES test, demonstrating that low scores are associated with lower probabilities of obstructive CAD and lower major adverse cardiac event (MACE) rates at follow-up.\(^\text{7,17-19}\) At a threshold of 15, the ASGES has 89% sensitivity and a 96% negative predictive value in symptomatic individuals without diabetes referred for myocardial perfusion imaging.\(^\text{7}\) Furthermore, in the more recent Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE trial) sponsored by the National Heart, Lung, and Blood Institute, the ASGES was validated in 2,380 individuals without diabetes presenting with symptoms suggestive of obstructive CAD. Across the ASGES range (1-40), higher scores were associated with greater current likelihood of obstructive CAD and of the composite endpoint of death, myocardial infarction (MI), unstable angina pectoris, and revascularization procedures at 2-year follow-up.\(^\text{18}\)

In this study, we used the community-based Registry to Evaluate Patterns of Care Associated with the Use of Corus CAD in Real World Clinical Care Settings (PRESET Registry NCT01677156) to examine the clinical utility of the ASGES and its effects on medical decision-making, with an emphasis on referrals to cardiology or advanced cardiac testing.\(^\text{19}\) We focused on older adults (≥ 65) because of the unique cardiovascular risks and diagnostic challenges these individuals face.

**METHODS**

**Study Participants**

The PRESET Registry was a prospective, multicenter, observational study enrolling stable, symptomatic outpatients from 21 U.S. primary care practices from August 2012 to August 2014. Participants were individuals with nonacute chest pain and typical or atypical symptoms of obstructive CAD presented to their primary care clinicians for evaluation.

Study exclusion criteria included previous history of MI or a revascularization procedure, current diagnosis of diabetes mellitus or glycosylated hemoglobin greater than 6.5%, suspected acute MI, high-risk unstable angina pectoris, New York Heart Association Class III or IV heart failure symptoms, cardiomyopathy with ejection fraction of 35% or less, severe cardiac valvular diseases, current systemic infectious or inflammatory condition, or recent treatment with an immunosuppressive or chemotherapeutic agent. The study design, participant flow chart, and exclusion criteria have been described in detail (Figure S1).\(^\text{19}\)

Of 566 individuals in this PRESET Registry, 176 (31%) were aged 65 and older. The current study focused on subgroup analysis of this elderly population. Information was collected on participant demographic characteristics, medical history, vital signs, anthropometric measurements, referrals to cardiology or advanced testing, and MACEs. Clinicians classified the nature of the chest pain or other related symptoms and provided pre- and post-ASGES diagnoses and evaluation plan for each participant. All clinical assessments and treatment decisions were at the discretion of the clinician; neither the registry design nor protocol mandated them. The institutional review board of Quorum Review, Inc. (Seattle, WA), approved the study, and signed informed consent was obtained from each participant.

**Study Tool**

The age, sex, gene expression test (Corus CAD, CardioDx Inc., Redwood City, CA) is a quantitative in vitro blood test yielding an algorithmic score incorporating a gene expression profile of white cells from a peripheral blood sample and the participant’s age and sex. Venous blood was collected from study participants in blood ribonucleic acid (RNA) tubes (PAXgene tubes, PreAnalytiX, Valencia, CA) and shipped at 4°C. RNA was purified and analyzed for quantity and quality. The ASGES was determined using reverse transcriptase qualitative polymerase chain reaction following previously described protocols.\(^\text{7,16,17,19}\)

Samples were processed at a commercially available Clinical Laboratory Improvement Amendments–certified (05D1083624) and College of American Pathologists–accredited (8646908) laboratory (CardioDx, Inc., Redwood City, CA).

The ASGES test assesses the current likelihood of obstructive coronary artery disease, defined as at least one atherosclerotic plaque causing ≥50% luminal diameter stenosis in a major coronary artery, defined as ≥1.5 mm lumen diameter as measured by invasive quantitative coronary angiography (QCA) or ≥2.0 mm lumen diameter as measured by independent core-lab computed tomography angiography (CTA).\(^\text{7,17}\) The test measures gene selectively expressed in multiple types of circulating cells that play supporting roles in adaptive and innate immune responses in atherosclerosis, including neutrophils (such as CASP5 and S100A12), natural killer cells (SLAMF7 and KLRC4), and B- and T-lymphocytes.\(^\text{15}\) Two validated sex-specific algorithms with age and gene expression inputs are used to generate the ASGES.\(^\text{16}\) Approximately half of the ASGES is derived from the age and sex demographic components, and the gene expression component generates half, resulting in a composite score.\(^\text{17}\) With regards to the clinical validity of the ASGES over demographic information, results from the Cardiovascular OutcoMes for People Using Anticoagulation StrategieS (COMPASS) validity study showed an area under the curve (AUC; a measure of test accuracy) of 0.69 for the Diamond-Forrester classification (based on age and sex) and 0.79 for the ASGES (based on age, sex, and gene expression) \(P = .002\).\(^\text{7}\)

The ASGES ranges from 1 to 40 and is rounded to the nearest integer. There likelihood of obstructive disease and disease burden is greater with higher scores.\(^\text{7,17,18,20}\) The clinical laboratory reported the ASGES to primary care...
clinicians within a median of 3 days from the time of blood draw. Primary care clinicians and their staff at the PRESET Registry sites were educated and trained on the use and interpretation of the ASGES in a standardized inservicing program. No interventions or practice protocols were administered beyond this training. To accurately reflect real-world practice, these clinicians were solely responsible for determining whether participants met the ASGES intended use criteria and independently used their own discretion to incorporate the ASGES results into their clinical decision-making.

Main Outcome Measures

The primary outcome of this elderly cohort substudy was to evaluate the association of ASGES with clinical management, specifically cardiac referral, which was defined as referral to cardiology or advanced cardiac testing within 45 days of the ASGES testing. Advanced cardiac testing, including anatomical and functional evaluation, was defined as exercise tolerance testing, myocardial perfusion imaging, coronary CTA, exercise stress echocardiogram, or invasive coronary angiography. As a safety endpoint, participants were followed for 1 year to assess the incidence of MACE, defined as stroke, MI, cardiac-related hospitalization or death, or revascularization.

Additional exploratory endpoints included emergency department or outpatient visits, noncardiac referrals or evaluation, lifestyle changes, and medication use. A detailed description of the PRESET Registry is presented elsewhere.19

Statistical Analysis

Descriptive statistics were determined for continuous and categorical variables, for baseline characteristics. Continuous data were summarized as means or medians with standard deviations and categorical data as frequencies with percentages.

Association between cardiac referral with ASGES category as a binary variable (low (≤15), high (>15)) was determined using logistic regression with and without covariate adjustment, including for smoking, hypertension, dyslipidemia, race, and body mass index (BMI). Similarly, association between cardiac referral and advanced testing with ASGES as a continuous variable was determined using log-linear regression with and without covariate adjustment. As a secondary analysis, the association between ASGES and outcome events (MACE or revascularization) was determined at 1-year follow-up. We also compared referral patterns as a function of the ASGES to statistically significant on univariate analysis, with a referral rate of 12.5% (5/40) in those with low ASGES and 49.3% (67/136) in those with high ASGES (OR = 0.15, P < .001) (Table 2). This difference remained statistically significant

RESULTS

Participant Characteristics

There were 566 protocol-evaluable individuals in the PRESET study, of which 176 were aged 65 and older. This subgroup of older adults had a median age of 70 and was primarily female (61%) and Caucasian (92%). With regard to clinical characteristics, study participants had a median BMI of 27.5 kg/m²; 70% had a history of dyslipidemia (70%) and 61% of hypertension. Fifty-two percent of these participants presented with typical symptoms. The median ASGES was 25 (range 1–40), and 40 participants (23%) had low scores (Table 1).

Cardiac Referral Patterns

Of the 176 study participants, 72 (41%) had a cardiac referral, defined as referral to cardiology or advanced cardiac testing in the 45-day period after testing. For the primary outcome, the difference in cardiac referral rates between participants with low and high ASGES was statistically significant on univariate analysis, with a referral rate of 12.5% (5/40) in those with low ASGES and 49.3% (67/136) in those with high ASGES (OR = 0.15, P < .001) (Table 2).

<table>
<thead>
<tr>
<th>Characteristic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range) 70 (65–96)</td>
</tr>
<tr>
<td>Female, n (%) 108 (61)</td>
</tr>
<tr>
<td>Race, n (%)</td>
</tr>
<tr>
<td>White 162 (92)</td>
</tr>
<tr>
<td>Black 9 (5)</td>
</tr>
<tr>
<td>Asian 2 (1)</td>
</tr>
<tr>
<td>Other 3 (2)</td>
</tr>
<tr>
<td>Body mass index, kg/m², median (range) 27.5 (15.3–67.2)</td>
</tr>
<tr>
<td>Blood pressure, mmHg, mean ± standard deviation</td>
</tr>
<tr>
<td>Systolic 133.2 ± 17.5</td>
</tr>
<tr>
<td>Diastolic 73.5 ± 10.7</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
</tr>
<tr>
<td>Current 21 (12)</td>
</tr>
<tr>
<td>Former 47 (27)</td>
</tr>
<tr>
<td>Never 108 (61)</td>
</tr>
<tr>
<td>Cardiac symptoms, n (%)</td>
</tr>
<tr>
<td>Typical 92 (52)</td>
</tr>
<tr>
<td>Atypical 84 (48)</td>
</tr>
<tr>
<td>New York Heart Association class, n (%) (n = 105)</td>
</tr>
<tr>
<td>I 71 (68)</td>
</tr>
<tr>
<td>II 34 (32)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
</tr>
<tr>
<td>Hypertension 107 (61)</td>
</tr>
<tr>
<td>Dyslipidemia 123 (70)</td>
</tr>
<tr>
<td>ASGES, median, mean 25, 24</td>
</tr>
<tr>
<td>ASGES, n (%)</td>
</tr>
<tr>
<td>≤15 (low) 40 (23)</td>
</tr>
<tr>
<td>&gt;15 (high) 130 (77)</td>
</tr>
</tbody>
</table>

ASGES = age, sex, gene expression score.
in multivariate analysis adjusting for participant demographic characteristics and clinical covariates (OR = 0.12, \( P < .001 \)) (Table 2).

Analysis of the ASGES as a continuous variable showed that the rate of cardiac referral increased proportionally with the score. The referral pattern for patients in the PRESET Registry parallels the current likelihood of obstructive CAD as determined in the COMPASS study: the higher the ASGES, the higher the referral rate, and the higher the likelihood of obstructive CAD (\( P < .001 \)) (Figure 1).\(^7\) Furthermore, for every 5-point increase in ASGES, the unadjusted odds of referral were 1.40 times higher in the univariate model (\( P < .001 \)). In further analyses, we found referral rates of 12.5% (5/40) in participants with low ASGES (1–15), 43.3% (29/67) in those with intermediate ASGES (16–27), and 55.1% (38/69) in those with high ASGES (28–40) (\( P < .001 \)).

**MACE or Revascularization**

At 1-year follow-up, there was a higher incidence of MACE or revascularization in the high ASGES group, predominantly associated with ASGES of 28 to 40. Thirteen of 136 (10%) participants with high ASGES had a major cardiac event or revascularization (3 strokes or transient ischemic attacks, 3 myocardial infarctions, 3 deaths, 4 revascularizations) and 0 of 40 with low ASGES (\( P = .04 \)) (Figure 2).

**DISCUSSION**

In this prospective registry of elderly adults presenting with stable symptoms suggestive of obstructive CAD, we found evidence that the ASGES was associated with clinical decision-making. Participants with low scores with low likelihood of obstructive CAD were referred for further evaluation at low rates, with higher rates of referral to cardiology and advanced cardiovascular tests for elderly adults with higher scores. We also found that the incidence of MACE or revascularization was higher at 1-year follow-up in elderly adults with high than with low ASGES. Although the absence of a control group limits our ability to compare results with usual care, the difference in health outcomes between individuals with high and low ASGES suggests that the score may discriminate between symptomatic elderly adults with

---

**Table 2. Univariate and Multivariate Analysis of Referral to Cardiology or Advanced Cardiac Testing**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate: low ASGES (≤15)</td>
<td>0.15 (0.04–0.41) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low ASGES (≤15)</td>
<td>0.12 (0.04–0.31) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.23 (0.44–3.43) .69</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.92 (0.45–1.91) .83</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.51 (0.24–1.06) .07</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0.39 (0.11–1.31) .13</td>
<td></td>
</tr>
<tr>
<td>Body mass index ≥30 kg/m²</td>
<td>1.29 (0.63–2.67) .49</td>
<td></td>
</tr>
</tbody>
</table>

Advanced cardiac testing: exercise tolerance testing, echocardiogram, myocardial perfusion imaging, coronary computed tomographic angiography, invasive coronary angiography.

ASGES = age, sex, gene expression score.

---

**Figure 1.** As the age, sex, gene expression score (ASGES; in sets of 5 units) increases, there is an increase in referral rates to cardiology and advanced cardiac testing (dark line) and an increase in the likelihood of obstructive coronary artery disease (light line). For every 5-point increase in ASGES, the unadjusted odds of referral were 1.40 times higher in the univariate model (\( P < .001 \)).
different likelihoods of experiencing adverse cardiovascular events.

Improving the accuracy and efficiency of the diagnostic process for individuals suspected of having obstructive CAD is of particular importance in elderly adults. This study specifically informs how clinicians may incorporate the ASGES into the management of older adults, who are often underrepresented in clinical trials and other types of comparative effectiveness research.21,22 For example, the 2013 American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease Risk Algorithm is only formally approved to be used in individuals up to the age of 75, despite the fact that individuals exceeding this threshold in age experience higher rates of adverse cardiovascular events.23 Elderly adults evaluated for CAD have a higher pretest probability of CAD but are also at higher risk of experiencing procedure-related complications during their evaluation.3,4 This heightened risk suggests that older adults may have the most to gain from timely and accurate determination of their current likelihood of obstructive CAD. The ASGES may be an alternative to conventional cardiac stress testing, which has typically been reported to have a sensitivity of 80% to 90%5 but has been found to be less than 50% in studies adjusted for referral bias.6–9

There may be other considerations for older adults evaluated according to the ASGES instead of conventional diagnostic technologies. For example, exertional capacity is a predictor of cardiovascular health, but some older adults may be unable to reach an ideal workload during an exercise stress test because of physical impairments unrelated to their risk of cardiac disease. In addition, the short time required to determine the ASGES—which can be done during an office visit without the need for referral to a stress testing laboratory—may be an advantage over usual care strategies. Overall, the ASGES is an innovation in diagnostic technology for obstructive CAD that appears to be similarly effective in older and younger adults. In prior work, we also showed that the test is cost-effective, although these analyses did not specifically focus on older adults.24

The findings in this article are from a subgroup analysis of the community-based PRESET Registry study. A wide variety of healthcare agencies have encouraged such subgroup analyses in elderly adults. Healthy People 2020 (HP2020) defines specific targets for older adults nationwide.25 The U.S. Centers for Disease Control and Prevention State of Aging report26 focuses on specific problem areas for intervention and cites the HP2020 goals. With respect to drug treatment effects, the recent Systolic Blood Pressure Intervention Trial, which studied hypertension management and cardiovascular outcomes, focused on a subgroup analysis of older adults and found beneficial effects similar to those seen in the general population.27 Lastly, there is a question as to the role of precision medicine in elderly adults given that the inherent variability in physical and cognitive function in older adults may limit the effectiveness of precision medicine initiatives.14

Our study has several limitations. The PRESET Registry did not include a control group, so it is challenging to definitively determine better patterns or outcomes of care with ASGES-directed management than with usual care. To address this major limitation, we performed logistic regression analysis with adjustments for confounders to examine the independent association between ASGES and cardiac referral, yet these models may not have accounted for all clinically significant confounders. Because this study did not include a control group, we could not determine whether a high ASGES score increased subsequent testing, revascularization procedures, and clinical encounters (such as hospitalizations for unstable angina in the setting of clinical uncertainty) that may not have improved health outcomes. This phenomenon is sometimes referred to as a testing cascade. Another limitation is that we did not collect detailed information about individual or physician preferences. Although we know that higher ASGES scores were associated with greater likelihood of cardiac referral, we were unable to characterize physicians’ reasons for referring patients to subsequent testing and procedures, or explain the variation in this decision-making. Nevertheless, variation in referral rates after initial diagnostic testing for obstructive CAD is common; test results and

Figure 2. At 1-year follow-up, the high score group had a higher incidence of major adverse cardiac events (MACEs) and revascularizations than the low score group ($P = .04)$.
sociodemographic factors may be influential in these decisions.\textsuperscript{3,10} In addition, although we specifically focused on elderly adults and enrolled from a geographically diverse population, it is possible that the distribution of clinical characteristics and risk factors in this study cohort differs from the distribution of these characteristics in the general population of elderly adults with suspected obstructive CAD. These differences would be relevant to the extent that they influence clinical decision-making. Lastly, our results cannot be generalized to individuals for whom the ASGES has not been validated, such as individuals with diabetes.

The referral rates from Investigation of a Molecular Personalized Coronary Gene Expression Test on Primary Care Practice Pattern (IMPACT-PCP) and Investigation of a Novel Gene Expression Test for Diagnosis of Obstructive Coronary Artery Disease (REGISTRY 1), two other clinical utility studies of ASGES, were higher than those we report in this elderly subgroup of PRESET. We are uncertain of the reasons for these differences, but it may be because physicians in this PRESET Registry were more diverse, practicing in 21 U.S. primary care practices, and less experienced using the ASGES than physicians in the IMPACT-PCP or REGISTRY-1 studies.\textsuperscript{28,29} For these same reasons, it is possible that the results in this PRESET subgroup are more generalizable.

In summary, the ASGES test showed clinical utility in the evaluation of elderly outpatients with symptoms suggestive of obstructive CAD. Test use may reduce unnecessary referrals and the risk of procedure-related complications in this subgroup are more generalizable. However, it is possible that the results in this PRESET subgroup are more generalizable.

ACKNOWLEDGMENTS

The authors would like to acknowledge Michael Zapien, Linda Ross, study participants and families, research coordinators, and investigators of the PRESET study.


Financial Disclosure: This work was funded by CardioDx, Inc.

Clinical Trial Registration: NCT01677156, https://clinicaltrials.gov/ct2/show/NCT01677156

Conflict of Interest: Joseph A. Ladapo, MD, PhD and Lee Herman, MD have received honoraria, consulting fees, and research support from CardioDx, Inc.. Matthew Budoff, MD, David Sharp, DO, and Bruce Maniet, DO, have received research support from CardioDx, Inc. Jane Z. Kuo, MD, PhD, Lin Huang, PhD, and Mark Monane, MD are current employees of CardioDx.

Author Contributions: All authors had substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; contributed to drafting the article or revising it critically for important intellectual content; and gave final approval of the version to be published. The study authors include the lead research physicians (Joseph A. Ladapo and Matthew Budoff), three primary care providers who enrolled the most participants in the study, and supporting clinical research team at CardioDx. All analyses, including the definition of the composite and secondary endpoints, were prespecified as part of a statistical analysis plan that was finalized before analyses were performed.

Sponsor’s Role: Funding sources and disclosures for the authors have been included in the manuscript. The sponsor was not involved in subject recruitment or data collection. The decision to order the blood-based precision medicine test as well as the interpretation of the test results were at the physician’s own discretion without sponsor involvement.

REFERENCES


SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study design and participant flow chart for the PRESET study are described.

Please note: Wiley-Blackwell is not responsible for the content, accuracy, errors, or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.