Biomarkers of Cardiovascular Stress and Subclinical Atherosclerosis in the Community


BACKGROUND: Biomarkers of cardiovascular stress have been associated with incident cardiovascular outcomes. Their relations with measures of subclinical atherosclerosis, as assessed by carotid intima-media thickness, have not been well described.

METHODS: We measured plasma growth differentiation factor-15 (GDF-15), soluble ST2 (sST2), and high-sensitivity troponin I (hsTnI) in 3111 Framingham Offspring participants who also underwent carotid ultrasonography during the sixth examination (1995–1998, mean age 58 years, 54% women). Carotid measurements included maximal internal carotid artery (ICA) intima-media thickness (IMT), plaque presence (defined as ICA IMT >1.5 mm), and mean common carotid artery IMT. We carried out multivariable regressions for carotid measurements vs biomarkers using linear and logistic models; \( P < 0.0056 \) was deemed statistically significant.

RESULTS: Maximal ICA IMT was significantly associated with plasma GDF-15 \( [\beta\text{-estimate } 0.04 \text{ per } 1\text{-U increase in log(GDF-15)}, SE 0.01, P < 0.0001] \). Similarly, the odds of having carotid plaque increased 33% [odds ratio 1.33 per 1-U increase in log(GDF-15), 95% CI 1.20–1.48, \( P < 0.0001 \)]. In contrast, there was no significant association of maximal ICA IMT or plaque presence with sST2 or hsTnI, and none of the 3 biomarkers was significantly associated with mean CCA IMT. GDF-15 was a stronger predictor of maximal ICA thickness and plaque presence compared with BNP and CRP when these conventional biomarkers were tested together.

CONCLUSIONS: Increased GDF-15 concentrations are associated with subclinical atherosclerosis, including maximal ICA IMT and carotid plaque presence. Future studies investigating the role of GDF-15 for screening and management of patients with subclinical atherosclerosis are warranted.

Carotid ultrasonography, via carotid intima-media thickness (IMT) assessment, not only has been well established as a surrogate of generalized atherosclerosis \((1, 2)\) and linked with cardiovascular risk factors \((3, 4)\), but also has been shown to be a predictor for myocardial infarction, stroke, coronary heart disease, and combined cardiovascular outcomes \((5–7)\). In addition, carotid IMT has been shown to track subclinical atherosclerosis and help improve classification of cardiovascular risk in asymptomatic cohorts \((4, 8)\).

Recently, biomarkers of cardiovascular stress, including growth differentiation factor-15 (GDF-15), soluble ST2 (sST2), and high-sensitivity troponin I (hsTnI), have emerged as strong predictors of cardiovascular risk and outcomes in various community-based populations \((9–12)\). The exact mechanism by which these biomarkers are linked to cardiovascular disease, particularly in asymptomatic, population-based cohorts, are incompletely described to date.

Our group has previously demonstrated the longitudinal association of GDF-15, sST2, and hsTnI to incident cardiovascular outcomes in the community \((11)\). Given that all 3 biomarkers have been previously

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related to incident cardiovascular disease, we hypothesized that these biomarkers would be associated crosssectionally with measures of subclinical atherosclerosis, as assessed via carotid IMT of the common carotid artery and internal carotid artery. Further characterizing associations with subclinical cardiovascular disease measures may offer deeper insights into the role of these biomarkers in the development of atherosclerosis.

Materials and Methods

STUDY SAMPLE
The Framingham Offspring Study cohort, initiated in 1971 and comprising offspring (and their spouses) of the original Framingham cohort, underwent examinations every 4–8 years. The present investigation included participants who attended the sixth offspring examination (1995–1998) and underwent carotid ultrasonography. From 3380 participants, 37 were excluded for missing carotid IMT data, 21 for missing covariate data, 173 for prevalent cardiovascular disease, 4 for missing sST2 data, and 34 for missing hsTnI data, leaving 3111 participants for analysis. The Institutional Review Board at Boston Medical Center approved the study protocol, and all study participants provided written informed consent.

RISK FACTOR ASSESSMENT
Each examination included a comprehensive history and physical examination. Cardiovascular risk factors pertinent to our study included systolic blood pressure, diastolic blood pressure, antihypertensive drug treatment, diabetes (defined as fasting glucose ≥ 126 mg/dL (≥ 7 mmol/L) or the use of oral hypoglycemic medications or insulin), current smoking (defined as smoking at least 1 cigarette per day over the past year), total and HDL cholesterol concentrations (measured after an overnight fast), and body mass index.

BIOMARKER MEASUREMENTS
We obtained blood samples from study participants in the morning after an overnight fast. The citrated plasma samples were centrifuged immediately and stored at −80 °C until assayed. No freeze-thaw cycles were performed before the assays described below. Reference limits and assay characteristics have been described (11, 13, 14). In brief, we used a precommercial, automated electrochemiluminescent immunoassay utilizing a Cobas e 411 analyzer (Roche Diagnostics) at a core laboratory (K.C. Wollert) to measure plasma GDF-15 concentrations. The assay had an intraassay CV of 0.8% and interassay CV of 2.3% at low concentrations (1120 ng/L), and intra- and interassay CVs of 1.1 and 1.0% at high concentrations (9031 nL/L). We measured sST2 concentrations with a high-sensitivity sandwich immunoassay (Presage™ ST2, Critical Diagnostics) at Critical Diagnostics. This assay had an interassay CV of 7.5% at low (25.6 ng/mL) and 6.0% at high (70.9 ng/mL) sST2 concentrations. We used single-molecule counting technology (Erenna hsTnI, Singulex) for measurement of hsTnI at Singulex. The assay had an interassay CV of 10.0% at low (4.7 ng/L) and 7.7% at high (19.0 nL/L) hsTnI concentrations. B-type natriuretic peptide (BNP) and C-reactive protein (CRP) concentrations were measured as previously described (15). In brief, BNP was measured by use of a high-sensitivity immunoradiometric assay at Shionogi with mean interassay CV of 12.2%, and CRP was measured at the Framingham Heart Study core laboratory by use of a Dade Behring BN100 nephelometer with an mean interassay CV of 2.2%.

CAROTID ULTRASONOGRAPHY
A single sonographer, certified by the Registry of Diagnostic Medical Sonographers, performed all carotid ultrasonography. Ultrasound image acquisition was obtained at the end of the R wave of an electrocardiogram to capture end-diastole. By use of a standard 45° projection from vertical, we acquired data from images obtained at 3 levels: the common carotid artery (CCA), level of the carotid artery bulb, and proximal internal carotid artery (ICA). One additional image was taken of the carotid artery bulb and proximal ICA centered on the largest plaque. Intima-media thickness values were calculated from the intima-media interface lines drawn by a certified reader on each acquired image (4). Using a distance of approximately 0.5 cm below the carotid-artery bulb and measuring IMT over a 1-cm-long segment (deemed not to have any plaque presence), we determined the mean IMT of the CCA. The largest IMT in either the left or right ICA from 1 cm above the carotid sinus to the bulb determined the maximum ICA IMT. We also examined maximum ICA IMT as a dichotomous variable, defined as plaque presence if ICA IMT >1.5 mm. Replicate measurements in 37 participants was performed for assessment of reproducibility with Pearson correlation coefficients (between replicate measurements) for the mean CCA IMT and maximum ICA IMT, 0.94 and 0.76, respectively (4).

STATISTICAL ANALYSES
All biomarkers and 2 carotid IMT outcomes (maximum ICA IMT and mean CCA IMT) were natural-logarithmically transformed owing to their right-skewed distributions. In primary analyses, we used multivariable linear regression to examine the associations of maximum ICA IMT and mean CCA IMT with each biomarker (GDF-15, sST2, and hsTnI). β-Estimates were expressed as relative change in IMT per 1-SD change in log-transformed biomarker, and were back-transformed for
interpretation. For the carotid outcome of plaque presence, we applied multivariable logistic regression modeling, with reported odds ratios (ORs) per 1-SD change in log-transformed biomarker. Adjustment for age, sex, systolic blood pressure, hypertension treatment, total cholesterol, HDL cholesterol, diabetes, smoking, body mass index, and baseline estimated glomerular filtration rate was used in primary models. To account for testing of multiple biomarkers (n = 3) and carotid measures (n = 3), results for primary analyses were considered significant at a Bonferroni-corrected P-value threshold of 0.05/9 = 0.0056.

In secondary analyses, we tested effect modification by age and sex for associations of 3 biomarkers and carotid outcomes. In addition, we further adjusted multivariable models for CRP and BNP, which have previously been shown to be associated with carotid IMT measures (16, 17). A P-value threshold of 0.05 was deemed significant in secondary analyses. Analyses were conducted with SAS version 9.2.

Results
The study sample contained 3111 Framingham Offspring cohort participants with a mean age of 58 years, 54% of whom were female. Twenty-six percent were treated for hypertension, 15% were current smokers, and 9% had diabetes. Clinical, biomarker, and carotid measure observations are shown in Table 1.

 Associations of Carotid Measures with GDF-15, sST2, and hsTnI
In age- and sex-adjusted regression models, maximal ICA IMT was significantly associated with each biomarker. After multivariable adjustment (including age, sex, systolic blood pressure, hypertension treatment, total and HDL cholesterol, diabetes, smoking, body mass index) the association remained significant only for log(GDF-15) (β-estimate 0.04, SE 0.01, P < 0.0001) (Table 2). Specifically, maximal ICA IMT increased 4% per 1-SD increase in log(GDF-15). Neither sST2 nor hsTnI was associated with maximal ICA IMT after multivariable adjustment.

In age- and sex-adjusted models, plaque presence (defined as ICA IMT >1.5 mm) was significantly associated with each biomarker. After multivariable adjustment (including age, sex, systolic blood pressure, hypertension treatment, total and HDL cholesterol, diabetes, smoking, body mass index) the association remained significant only for log(GDF-15) (OR 1.33 per 1-SD increase in log(GDF-15), 95% CI 1.20–1.48, P < 0.0001) (Table 2). Neither sST2 nor hsTnI was associated with plaque presence after multivariable adjustment.

The risk of plaque presence across increasing quartiles of the 3 biomarkers, GDF-15, sST2, and hsTnI, are displayed in Fig. 1. Increasing quartiles of GDF-15 were associated with increasing risk of plaque in multivariable analyses (P for trend < 0.0001). Specifically, participants in the upper quartile of GDF-15 had a nearly 2-fold increased odds of carotid plaque compared with the lowest quartile (OR 1.95, 95% CI 1.44–2.64, P < 0.0001).

The associations of the biomarkers, GDF-15, sST2, and hsTnI, were evaluated with the outcome mean CCA IMT (Table 2). GDF-15, but not sST2 or hsTnI, was significantly associated with mean CCA IMT in age- and sex-adjusted models, and none of the 3 biomarkers was significantly associated after multivariable adjustment at the prespecified statistical threshold of P = 0.0056.

Comparison with Established Biomarkers
After further adjusting multivariable models for BNP and CRP, biomarkers that previously have been linked with carotid measures, GDF-15 remained a significant predictor of maximal ICA IMT, conferring a 1.04-fold increase in carotid ICA thickness per 1-SD increase of log(GDF-15) (P = 0.0002). In contrast, BNP was not associated with maximal ICA IMT in the multimarker model (P = 0.48), and CRP only nominally so (P = 0.04). Both GDF-15 and CRP were significant predictors of plaque presence in multivariable-adjusted models, and the association with GDF-15 appeared more significant [OR per

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of 3111 participants free of prevalent cardiovascular disease.a</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<td>----------------</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>Age, years</td>
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<tr>
<td>Female sex</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
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<tr>
<td>Treatment for high blood pressure</td>
</tr>
<tr>
<td>Diabetes</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Current smoker</td>
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<tr>
<td>Total cholesterol, mg/dL</td>
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<tr>
<td>HDL cholesterol, mg/dL</td>
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<tr>
<td><strong>Biomarker</strong></td>
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<tr>
<td>GDF-15, ng/L</td>
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<tr>
<td>sST2, ng/mL</td>
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<tr>
<td>hsTnI, ng/L</td>
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<tr>
<td><strong>IMT</strong></td>
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<tr>
<td>Maximum ICA IMT, mm</td>
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<tr>
<td>Plaque presence (ICA IMT &gt;1.5 mm)</td>
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<tr>
<td>Mean CCA IMT, mm</td>
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</tbody>
</table>

a Data are mean (SD), n (%), or median (25th, 75th percentile). To convert cholesterol in mg/dL to mmol/L, multiply by 0.02586.
1-SD unit increase in log(GDF-15) 1.32; 95% CI, 1.18–1.47; \( P < 0.0001 \); OR per 1-SD unit increase in log(CRP) 1.15; 95% CI, 1.04–1.27; \( P = 0.008 \) (Table 3).

For a given CRP tertile, GDF-15 added further information with regard to plaque risk (Fig. 2). For example, when examining individuals in the highest tertile of CRP, those in the lowest tertile of GDF-15 had a 1.44-fold increased odds of plaque, compared with a 2.7-fold increased odds in the highest GDF-15 tertile (with those in the lowest tertile for both biomarkers serving as the reference group).

**Discussion**

GDF-15, sST2, and hsTnI have recently emerged as predictors of cardiovascular outcomes in patients with existing cardiovascular disease, as well as in the community-dwelling population. The present investigation extends these findings and supports the concept that GDF-15 is strongly associated with subclinical atherosclerosis as measured by carotid ultrasonography, even before clinical cardiovascular disease is recognized. Moreover, GDF-15 was associated with carotid plaque independent of established biomarkers of cardiovascular risk, CRP and BNP.

GDF-15 is a divergent member of the transforming growth factor \( \beta \) cytokine family (18) that is upregulated in response to stressors, including in macrophages exposed to oxidized LDL in atherosclerotic carotid arteries (19). It is expressed in several cell types, including macrophages, vascular smooth muscle cells, and endothelial cells in response to oxidative, inflammatory, or metabolic stressors (19–21).

Specific to atherosclerosis, GDF-15 has shown predictive abilities of coronary heart disease mortality and composite outcomes in stable and acute coronary syndromes in patients with prevalent cardiovascular risk factors (22–25). In community cohorts, GDF-15 has conferred prognostic abilities for composite car-

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**Table 2. Association of carotid measures with GDF-15, sST2, and hsTnI.**

<table>
<thead>
<tr>
<th>Outcome and biomarker</th>
<th>Age- and sex-adjusted model</th>
<th>( P^c )</th>
<th>Multivariable-adjusted model</th>
<th>( P^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum ICA IMT (log-transformed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDF-15</td>
<td>0.070 (0.009)</td>
<td>&lt;0.0001</td>
<td>0.04 (0.010)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>sST2</td>
<td>0.025 (0.008)</td>
<td>0.003</td>
<td>0.013 (0.008)</td>
<td>0.10</td>
</tr>
<tr>
<td>hsTnI</td>
<td>0.024 (0.008)</td>
<td>0.004</td>
<td>0.02 (0.008)</td>
<td>0.01</td>
</tr>
<tr>
<td>Plaque presence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDF-15</td>
<td>1.48 (1.34–1.63)</td>
<td>&lt;0.0001</td>
<td>1.33 (1.20–1.48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>sST2</td>
<td>1.15 (1.05–1.25)</td>
<td>0.002</td>
<td>1.10 (1.00–1.20)</td>
<td>0.05</td>
</tr>
<tr>
<td>hsTnI</td>
<td>1.11 (1.02–1.21)</td>
<td>0.02</td>
<td>1.09 (1.00–1.19)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean CCA IMT (log-transformed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDF-15</td>
<td>0.014 (0.004)</td>
<td>0.0003</td>
<td>0.004 (0.004)</td>
<td>0.30</td>
</tr>
<tr>
<td>sST2</td>
<td>0.009 (0.003)</td>
<td>0.01</td>
<td>0.003 (0.003)</td>
<td>0.31</td>
</tr>
<tr>
<td>hsTnI</td>
<td>0.009 (0.003)</td>
<td>0.007</td>
<td>0.007 (0.003)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Data are \( \beta \)-estimate (SE) or OR (95% CI). \( \beta \)-estimate and OR reflect per 1-SD increase in log-transformed biomarker.
* Adjusted for age, sex, systolic blood pressure, hypertension treatment, total cholesterol, HDL cholesterol, diabetes, smoking, body mass index, and estimated glomerular filtration rate.
* Corrected \( P \)-value threshold 0.0056.
diovascular outcomes as well as hard mortality outcomes (9–11, 26). Our findings support the concept that GDF-15 is in fact associated with subclinical atherosclerosis as assessed by maximal ICA IMT as well as the presence of carotid plaque.

In contrast to the strong association of GDF-15 with maximal ICA IMT, we found no such association with mean CCA IMT. Previous studies suggest that maximum ICA IMT and mean CCA IMT may reflect different underlying processes, the former related to localized atherosclerotic plaque (27) and the latter representing diffuse arterial wall hypertrophy (28). Interestingly, maximal ICA and plaque presence, but not mean CCA IMT, improved risk classification for incident cardiovascular disease in a previous study (29). Our findings suggest that GDF-15 is associated with focal atherosclerosis, rather than diffuse inflammatory processes and arterial thickening. Similar results were found in an older community-based cohort, in which GDF-15 was associated with carotid plaque but not IMT (10). Our results extend these findings to a population more than a decade younger than the previous study, without known prevalent cardiovascular disease, and directly compare GDF-15 to other emerging and established biomarkers.

We found that the association of GDF-15 and carotid plaque is independent of CRP, a marker of inflammation. Notably, in multimarker models with CRP and BNP, the association of GDF-15 with maximum ICA IMT and carotid plaque was more robust than that of either BNP or CRP. This suggests that GDF-15 may reflect an orthogonal pathway associated with cardiovascular disease, the mechanism of which remains unclear. Experimental studies suggest antithrombotic and antiplatelet effects (30). However, in vascular tissue studies, there is growing evidence that GDF-15 may promote increased inflammation and atherosclerosis progression, a process that may involve p53 pathway activation (31, 32). Whether GDF-15 is a mediator of cardiovascular disease or upregulated in response to cardiovascular injury remains unclear.

In comparison to GDF-15, sST2 and hsTnI exhibited no significant associations with carotid measures in our study. Soluble ST2, a member of the interleukin-1 cytokine family, has been shown to serve as a decoy receptor, binding IL-33, a cytokine shown to have protective effects in the cardiovascular system (33, 34). In atherosclerosis, IL-33 administration in murine models of atherosclerosis led to significantly smaller atherosclerotic plaques, whereas sST2 administration led to larger aortic sinus atherosclerotic plaques (35). Although sST2 has shown associations

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**Table 3. Association of GDF-15 and established biomarkers with carotid measures.**

<table>
<thead>
<tr>
<th>Model</th>
<th>Maximum ICA IMT</th>
<th>Plaque presence</th>
<th>Mean CCA IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-estimate (SE)</td>
<td>OR (95% CI)</td>
<td>β-estimate (SE)</td>
</tr>
<tr>
<td>Individual biomarker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDF-15</td>
<td>0.040 (0.01)</td>
<td>1.33 (1.20–1.48)</td>
<td>0.004 (0.004)</td>
</tr>
<tr>
<td>Biomarker combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDF-15</td>
<td>0.037 (0.01)</td>
<td>1.32 (1.18–1.47)</td>
<td>0.004 (0.004)</td>
</tr>
<tr>
<td>BNP</td>
<td>0.006 (0.009)</td>
<td>0.98 (0.89–1.08)</td>
<td>0.003 (0.004)</td>
</tr>
<tr>
<td>CRP</td>
<td>0.019 (0.009)</td>
<td>1.15 (1.04–1.27)</td>
<td>0.002 (0.004)</td>
</tr>
</tbody>
</table>

*a* All models adjusted for age, sex, systolic blood pressure, hypertension treatment, total cholesterol, high-density cholesterol, diabetes, smoking, body mass index, and estimated glomerular filtration rate. β-estimate and OR reflect per 1-SD increase in log-transformed biomarker.

*b* Corrected P-value threshold 0.0056.

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**Fig. 2.** Multivariable-adjusted ORs for carotid plaque presence across increasing tertiles of GDF and CRP. Reference groups for OR were GDF-15 tertile 1 and CRP tertile 1.
with cardiovascular outcomes in acute coronary syndrome (36, 37), more recent studies have not shown sST2 to be predictive of atherosclerotic plaque in patients with carotid atherosclerotic disease (38) or patients free of vascular disease (39).

There are several limitations to the present study that merit discussion. Ours is an observational cross-sectional study, and causal inferences cannot be drawn. It is also important to note that carotid IMT may incompletely capture the complex process of atherosclerosis in multiple vascular beds (40), and interval carotid IMT measurements may confer more specificity in this process and relation with atherosclerotic outcomes. The use of our Bonferroni-corrected P-value threshold may have been too conservative, given that 2 of the carotid measures (ICA IMT and plaque presence) are not independent of one another. However, even when using a less conservative P-value threshold, the main results did not differ materially. Last, our population was predominantly white, limiting generalizability to other ethnic groups.

In summary, we found that GDF-15 was associated with subclinical atherosclerosis, including higher maximum ICA IMT and the presence of carotid plaque in an ostensibly healthy community-based population without prevalent cardiovascular disease. This association was independent of other established biomarkers, including CRP and BNP. Future studies are warranted to elucidate the potential use of GDF-15 for screening and management of patients with subclinical atherosclerosis.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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