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RESEARCH ARTICLE

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# Outpatient metformin use is associated with reduced severity of COVID-19 disease in adults with overweight or obesity

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## Abstract

Observational studies suggest outpatient metformin use is associated with reduced mortality from coronavirus disease-2019 (COVID-19). Metformin is known to decrease interleukin-6 and tumor-necrosis factor-α, which appear to contribute to morbidity in COVID-19. We sought to understand whether outpatient metformin use was associated with reduced odds of severe COVID-19 disease in a large US healthcare data set. Retrospective cohort analysis of electronic health record (EHR) data that was pooled across

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multiple EHR systems from 12 hospitals and 60 primary care clinics in the Midwest between March 4, 2020 and December 4, 2020. Inclusion criteria: data for body mass index (BMI) > 25 kg/m$^2$ and a positive SARS-CoV-2 polymerase chain reaction test; age ≥ 30 and ≤85 years. Exclusion criteria: patient opt-out of research. Metformin is the exposure of interest, and death, admission, and intensive care unit admission are the outcomes of interest. Metformin was associated with a decrease in mortality from COVID-19, OR 0.32 (0.15, 0.66; $p$ = .002), and in the propensity-matched cohorts, OR 0.38 (0.16, 0.91; $p$ = .030). Metformin was associated with a nonsignificant decrease in hospital admission for COVID-19 in the overall cohort, OR 0.78 (0.58–1.04, $p$ = .087). Among the subgroup with a hemoglobin HbA1c available ($n$ = 1193), the adjusted odds of hospitalization (including adjustment for HbA1c) for metformin users was OR 0.75 (0.53–1.06, $p$ = .105). Outpatient metformin use was associated with lower mortality and a trend towards decreased admission for COVID-19. Given metformin's low cost, established safety, and the mounting evidence of reduced severity of COVID-19 disease, metformin should be prospectively assessed for outpatient treatment of COVID-19.

## 1 | BACKGROUND

The novel severe acute respiratory syndrome virus-2 (SARS-CoV-2) continues to spread globally.[1] Although vaccine development is moving quickly, many obstacles will likely delay widespread vaccination.[2] There is also no proven early outpatient treatment or preventive therapy for COVID-19 that is inexpensive, widely available, and safe in most individuals. There are now several observational studies across three continents showing that outpatient metformin use, before having positive SARS-CoV-2 infection, is associated with reduced mortality and hospital admission from COVID-19.[3–7]

Before the COVID-19 pandemic, the anti-inflammatory and glucose-lowering mechanisms of metformin were a topic of debate. Metformin has been shown to decrease interleukin-6 (IL-6) and tumor-necrosis alpha (TNF-α),[8–11] and these cytokines may contribute to morbidity in COVID-19.[12–15] Possible evidence of this effect was seen in a retrospective study by Chen et al of 904 patients with COVID-19. They showed that metformin users had lower IL-6 levels compared to non-metformin users.[16] There are also data suggesting metformin has direct antiviral actions, including in-vitro activity against SARS-CoV-2.[17–19] Given these observational and mechanistic findings, metformin's excellent safety profile and low cost, metformin warrants further investigation for patients with COVID-19.[20,21]

We assessed whether outpatient metformin use is associated with improved outcomes in adults with positive SARS-CoV-2 polymerase chain reaction (PCR) in a large population of patients. We leveraged detailed electronic health record (EHR) data, including body mass index (BMI), demographic information, comorbidities, outpatient medications, and laboratory values. Our objective was to assess whether metformin was associated with reduced severity of COVID-19 disease, by assessing odds of hospital admission, intensive care unit (ICU) admission, and mortality from COVID-19.

## 2 | METHODS

### 2.1 | Design and setting

We performed a retrospective cohort analysis of EHR data that was pooled across multiple EHR systems from 12 hospitals and 60 primary care clinics in the Midwest area of the United States between March 4, 2020 and December 4, 2020. This COVID-19 datamart includes clinical and administrative data for individuals with a positive SARS-CoV-2 PCR test. Data were pooled across different EHRs to account for patient transfers and all encounters between systems for each patient, facilitated by generating a Master Patient Index serving as a unique patient identifier. In cases where a patient was seen in two different EHR systems, the most recent EHR comorbidity and outpatient medication records were used. All patients who opted out of research were excluded from the analysis. This study was approved by the University of Minnesota institutional review board (STUDY00001489), which provided a waiver of consent for this study.

### 2.2 | Population

The data set contained 17,396 persons with positive SARS-CoV-2 PCR who did not opt-out of research; and age at the time of the positive PCR test of 30 to 85 years, both inclusive. We excluded those with BMI < 25 kg/m$^2$.[22] After applying all inclusion and exclusion criteria, 9555 patients remained in the cohort. The specific inclusion and exclusion criteria were selected to reflect a population (1) at a higher risk of COVID-19-related complications (age > 30 years)[23] and (2) in whom metformin would have a greater metabolic benefit (BMI > 25 kg/m$^2$) with a proven safety profile (age < 85 years).

## 2.3 | Independent variable

Metformin use was determined as documented in the home medication list in the EHR within the 3 months before the positive SARS-CoV-2 PCR test. In addition to data documented directly in the primary health system EHRs, medication data from other health systems (beyond the 12 hospitals) using the same EHR software was also available using a functionality certified by the State of Minnesota as a Health Data Intermediary for Health Information Exchange.[24]

## 2.4 | Outcomes

The outcomes of interest were hospital admission for COVID-19; ICU admission for COVID-19, and mortality (in-hospital and before-hospital) from COVID-19 disease. Each outcome was assessed independently, not as a composite outcome.

## 2.5 | Covariates

Comorbidities were defined based on ICD codes; Table S1 contains a full list of the codes used to define each comorbidity. Chronic kidney disease (CKD) was dichotomized as no kidney disease, Stage 1, Stage 2, and Stage 3 CKD versus Stage 4 CKD, Stage 5 CKD, and end-stage renal disease. Demographic variables included age at the time of SARS-CoV-2 PCR, gender, race/ethnicity (White, Black, Asian, Latinx, or Other), and English-speaking versus Non-English speaking, all as defined in the EHR. Similar to metformin, other home medication covariates were defined as listed on the home medication list within 3 months before the positive SARS-CoV-2 PCR test.

## 2.6 | Analyses

Restricted cubic splines were used to model the continuous variable age. Univariate analyses compared covariates and outcomes between the Independent variable. For descriptive purposes, categorical variables were presented using count (%), continuous variables with a skewed distribution were presented as median and interquartile range (IQR), and variables with a normal distribution were presented as mean and standard deviation. $\chi^2$ test was used to compare categorical variables, Mann Whitney *U* was used for continuous with skewed distribution, the Student *t* test was used for continuous with a normal distribution.

Logistic regression was used to assess odds of mortality and of being hospitalized within 45 days between propensity-matched cohorts that were stratified by metformin use. The regression was adjusted for age, race/ethnicity, gender, English-speaking status, Type 2 diabetes (T2DM), BMI category, history of bariatric surgery,[4] nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH),[4] coronary artery disease, heart failure, CKD; hypertension, hyper- or hypo-coagulable state, interstitial lung disease, tobacco use; and home medications: steroids; insulin, glucagon-like-peptide-1 receptor agonists (GLP-1RA),[4] sulfonylureas, sodium-glucose transport protein 2 inhibitors (SGLT-2) inhibitors, dipeptidyl deptidase-4 (DPP4) inhibitors, statins, anti-dementia medications,[25] and angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs). To assess whether potential benefit from metformin was affected by disease severity of T2DM, a subgroup analysis was done with adjustment for hemoglobin A1C (HbA1c) in the subset of patients for whom it was available ($n = 1193$).

Outcomes were also assessed by logistic regression in propensity-matched cohorts, matched on the above covariates. Propensity scores were estimated with logistic regression and two evenly matched groups were formed with the common caliper set at 0.2 and a model with exact matching.[26,27] Even distribution of propensity scores was confirmed between matched groups ($n = 342$ each), with standardized differences less than 0.10 for all covariates (Figure S1).

As a form of sensitivity analysis and assessment of residual confounding, we assessed the E-value using the method outlined by VanderWeele et al.,[28] including conversion of the OR to a RR for admission as the percent of persons who were admitted was >15% for both exposure groups.[28] The E-values indicate that an unmeasured confounder would need a RR magnitude of association with the treatment and outcome, above and beyond the measured confounders, that is greater than or equal to the E-value.[28] Statistical analyses were performed using Stata MP, version 16 (StataCorp). The University of MN IRB approved this study.

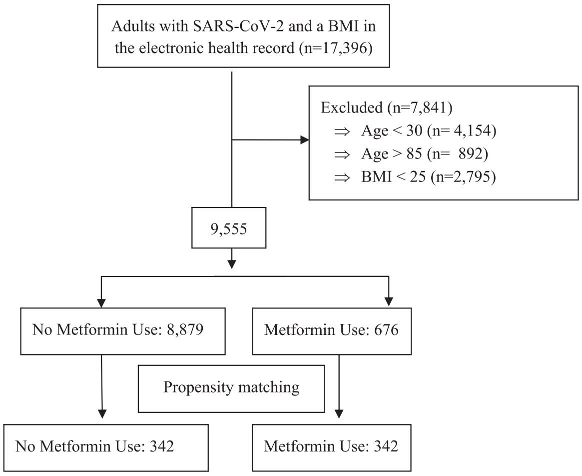


**FIGURE 1** This represents the number of patients included in the analysis. The logistic regression was done on the full cohort of 9555 patients after the exclusion criteria were applied. Propensity matching stratified by metformin use resulted in matched cohorts, 342 patients each

# 3 | RESULTS

## 3.1 | Characteristics of the cohort

After the inclusion and exclusion criteria were applied, 9555 individuals remained in the cohort (Figure 1). The cohort's median age

**TABLE 1** Demographic and clinical characteristics of persons with + SARS-CoV-2 PCR, comparing those with home metformin use to those without

| | | No metformin n = 8879 | Met-formin n = 676 | p value |
|---|---|---|---|---|
| Age, median (IQR), years | | 54.2 (42.4-65.3) | 60.4 (51.7-69.0) | <.001 |
| Age | 30 < 40 years | 1790 (20.2) | 39 (5.8) | <.001 |
| | 40 < 50 years | 2791 (31.4) | 191 (28.3) | |
| | 50 < 60 years | 2011 (22.6) | 204 (30.2) | |
| | 60 < 70 years | 1877 (21.2) | 224 (33.1) | |
| | ≥70 | 410 (4.6) | 18 (2.7) | |
| Female | | 4740 (53.4) | 296 (43.8) | <.001 |
| Race/ethnicity | White | 6109 (74.4) | 503 (78.1) | .002 |
| | Black | 859 (10.5) | 76 (11.8) | |
| | Asian | 689 (8.4) | 28 (4.3) | |
| | Hispanic/latinx | 52 (0.6) | 6 (0.9) | |
| | Declined | 296 (3.6) | 14 (2.2) | |
| | Other | 203 (2.5) | 17 (2.6) | |
| BMI, mean (SD), $kg/m^2$ | BMI, mean (SD), $kg/m^2$ | 32.9 (6.8) | 35.7 (7.7) | <.001 |
| | 25.0 $kg/m^2$ < 30.0 $kg/m^2$ | 3498 (39.4) | 151 (22.3) | <.001 |
| | 30.0 $kg/m^2$ < 35.0 $kg/m^2$ | 2703 (30.4) | 216 (32.0) | |
| | 35.0 $kg/m^2$ < 40.0 $kg/m^2$ | 1412 (15.9) | 145 (21.4) | |
| | ≥40.0 $kg/m^2$ | 1153 (13.0) | 161 (23.8) | |
| Comorbidities | | | | |
| Heart failure | | 547 (6.4) | 83 (12.3) | <.001 |
| Coronary artery disease | | 900 (10.6) | 151 (22.3) | <.001 |
| Hypo-coagulable state | | 612 (7.2) | 67 (9.9) | .010 |
| Hypercoagulable state | | 137 (1.6) | 14 (2.1) | .37 |
| Interstitial lung disease | | 106 (1.2) | 13 (1.9) | .14 |
| Tobacco use | | 552 (6.5) | 79 (11.7) | <.001 |
| Past bariatric surgery | | 211 (2.5) | 22 (3.3) | .22 |
| NAFLD/NASH | | 500 (5.6) | 81 (12.0) | <.001 |
| Hypertension | | 3890 (45.8) | 582 (86.1) | <.001 |
| Type 2 diabetes | | 1331 (15.7) | 632 (93.5) | <.001 |
| CKD stage 4, 5, ESRD | | 234 (2.6) | 10 (1.5) | .066 |
| Home medications | | | | |
| ACEi/ARBs | | 738 (8.3) | 301 (44.5) | <.001 |
| GLP-1 receptor agonist | | 120 (1.4) | 120 (17.8) | <.001 |
| Sulfonylureas | | 73 (0.8) | 185 (27.4) | |
| Insulin | | 302 (3.4) | 237 (35.1) | <.001 |
| Home oral steroid | | 604 (6.8) | 76 (11.2) | <.001 |
| Loop diuretics | | 492 (5.5) | 91 (13.5) | <.001 |
| Anti-dementia meds | | 30 (0.3) | 9 (1.3) | <.001 |

*Note*: Data are *n* (%) unless otherwise noted.

Abbreviations: BMI, body mass index. ICU, intensive care unit; IQR, inter-quartile range; PCR, polymerase chain reaction; SARS-Cov-2, novel severe acute respiratory syndrome virus-2; *SD*, standard deviation.

was 55.0 (IQR, 42.9–65.6), 53% female, and 676 (7.1%) had outpatient metformin use in the previous 3 months, 69% identified as white (Table 1). Patients in the metformin group were more likely to have T2DM and hypertension, and more likely to use insulin, GLP-1 receptor agonists, sulfonylurea, or oral steroids (Table 1).

#### 3.1.1 | Admission

Overall 17% of the cohort were admitted to the hospital, (16.8% of the non-metformin and 19.5% of the metformin group). Metformin use was associated with a nonsignificant decrease in hospital admission for COVID-19 in the overall cohort, OR 0.78 (0.58, 1.04; $p = .087$). Among the subgroup with a hemoglobin HbA1c available ($n = 1193$), the adjusted odds of hospitalization (including adjustment for HbA1c) for metformin users was OR 0.75 (0.53, 1.06; $p = .105$) (Figure 2).

#### 3.1.2 | ICU admission

Overall 6.9% of the cohort were admitted to the ICU (6.9% of the non-metformin group and 6.5% of the metformin group). There was a nonsignificant reduction in ICU admission in the overall cohort, OR 0.68 (0.45, 1.02; $p = .060$), and a nonsignificant increase in risk of ICU admission in the propensity-matched cohorts, OR 1.09 (0.62, 1.91; $p = .77$).

#### 3.1.3 | Mortality

Overall 2.3% of the cohort died (2.3% in the non-metformin group and 1.5% in the metformin group). Metformin use was associated with a significant decrease in mortality from COVID-19 disease in the overall cohort, OR 0.32 (0.15, 0.66; $p = .002$), and in the propensity-matched cohorts, OR 0.38 (0.16, 0.91; $p = .030$).

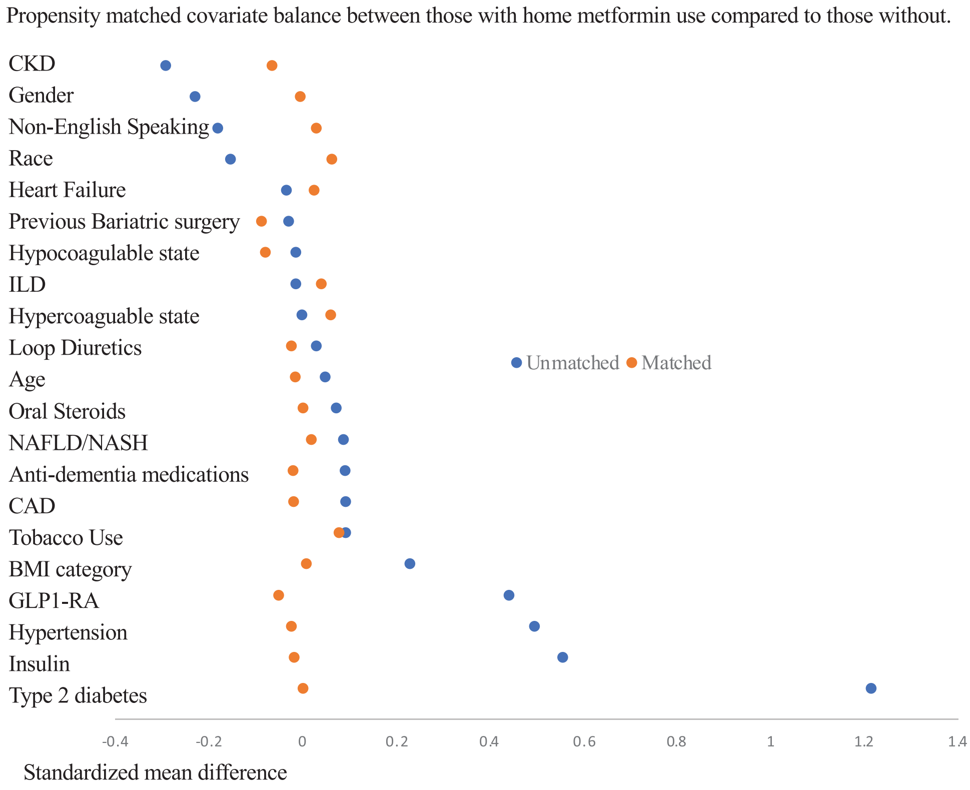


**FIGURE 2** This figure represents the odds ratios and associated confidence intervals, *p* values, and LROC (area under the curve) for the outcomes of mortality, hospital admission, or intensive care unit (ICU) admission. The top four lines represent analyses by logistic regression; the bottom three represent logistic regression in propensity-matched cohorts. Analyses were adjusted for age, race/ethnicity, gender, English-speaking status, Type 2 diabetes (T2DM), body mass index (BMI) category, history of bariatric surgery,[4] nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH),[4] coronary artery disease, heart failure, CKD; hypertension, hyper- or hypo-coagulable state, interstitial lung disease, tobacco use; and home medications: steroids; insulin, glucagon-like-peptie-1 receptor agonists (GLP-1RA),[4] sulfonylureas, sodium-glucose transport protein 2 inhibitors (SGLT-2) inhibitors, dipeptidyl deptidase-4 (DPP4) inhibitors, statins, anti-dementia medications,[25] and angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs)

## 4 | DISCUSSION

We evaluated the odds of severe outcomes from COVID-19 in those with outpatient metformin use at the time of infection compared to those who did not use metformin using data from a large comprehensive US healthcare database. We found an association between outpatient metformin use and decreased odds of mortality, and nonsignificant associations with hospital admission and ICU admission. Our findings are consistent with previous observational studies.[3–7] If these findings are replicated in a prospective study, the implications could be significant given metformin's well-established safety profile, low cost, and worldwide availability.

Metformin has a known history of beneficial immune-modulatory effects, pre-COVID-19, including IL-6 and TNF-α, neutrophil extracellular traps,[8,29–35] and improved T cell immunity.[36,37] Outpatient metformin has been associated with lower IL-6 in persons with COVID-19.[16] These anti-inflammatory effects of metformin may explain its association with reduced severity of COVID-19.

Other possible ways in which metformin could improve outcomes in COVID-19 beyond glucose control and immune modulation could potentially include antiviral actions. Metformin reduced viral replication of Zika in vitro, another RNA virus, but was not prospectively assessed against Zika.[18,19] In COVID-19, inhibition of the mammalian target of rapamycin (mTOR),[38] may be important for reducing viral lifecycle through the Orf9c and Nsp7 proteins.[17] Metformin has been shown to inhibit mTOR,[39] including inhibition of HCV-infected cells and suppressed HCV replication via mTOR.[40,41] In a study of 200 patients with H3N2 influenza, metformin was associated with reduced incidence of influenza (5% vs. 24%, $p < .001$).[42] As observational studies are not conclusive, retrospective trials should assess metformin for early outpatient treatment and prevention of SARS-CoV-2 infection, and assess possible anti-viral and anti-inflammatory affects in the setting of SARS-CoV-2 infection.

The low-cost of metformin, and need for monitoring labs after starting metformin only every 12 months, means that metformin could be realistically and safely distributed large scale to individuals with low access to healthcare.[43] A recent Cochrane review of prospective and observational studies showing no increased risk of lactic acidosis from outpatient metformin use.[21] Metformin was not continued during hospital admission in our sample, and we would not recommend that metformin be continued in the hospital, or started at the time of hospital admission for COVID-19. The observational data of outpatient metformin use improving outcomes in COVID-19 are all from metformin use before diagnosis, suggesting that the benefit is early on in the disease course.

This study has several limitations. Home metformin use may indicate a level of access to and engagement in healthcare that would also be protective against poor outcomes from COVID-19 disease. Our propensity matching did not result in perfect balance, but the imbalance was such that the metformin group has slightly more comorbidities. Ascertainment bias may be present as hospitalizations outside of the 12 hospitals covered by these EHR systems were not captured in this database. As this analysis was restricted to patients who had a measured height and weight in these EHR systems, it suggests that both exposure groups were established patients within the hospital systems, and would theoretically have the same likelihood of being hospitalized within these hospital systems. Thus, there is reason to believe ascertainment bias may be evenly distributed between both groups. Findings related to ICU admission differed between the propensity-matched cohort and overall cohort, and this may be due to the reduced number in the propensity-matched cohorts, or hospitals' definitions of ICU. Observational studies are subject to residual unmeasured confounders, such as confounding by indication. We attempted to address this by controlling for comorbidities that are relevant to both T2DM and COVID-19, and to adjust for HbA1c levels. Although we limited the window of time in which metformin was used to 3 months before SARS-CoV-2, we have no information on compliance with taking the metformin that was prescribed.

## 5 | CONCLUSIONS

In this large comprehensive population of persons with a positive SARS-CoV-2 PCR result, persons with outpatient metformin use had nonsignificantly lower odds of hospitalization and significantly lower odds of mortality from COVID-19 disease. Our data add to the growing observational evidence suggesting reduced severity of COVID-19 disease in persons with metformin use. Given the biologic plausibility of benefit, metformin should be prospectively assessed for prevention and early outpatient treatment of SARS-CoV-2.[3–7]

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### CONFLICT OF INTERESTS

Dr. Tignanelli is PI on randomized trials for COVID-19, but not related to metformin. Dr. Bramante holds an IND for a prospective trial for metformin for outpatient treatment and prevention of COVID-19 and is PI for an outpatient COVID-19 treatment trial with metformin. Dr. Buse has support from an SBIR awarded to NovaTarg (R44DK096803).

### AUTHOR CONTRIBUTIONS

Dr. Tignanelli is the guarantor with responsibility for the work as a whole given his full access to the data. Carolyn T. Bramante contributed to study design, interpretation, and writing. John Buse contributed to study design, interpretation, and writing. Ana Palacio contributed to study design, interpretation, and critical review. Leonardo Tamaritz contributed to study design and critical review. Ken Cohen contributed to study design and critical review. David Liebovitz contributed to study design, interpretation, and writing. Nia Mitchell contributed to interpretation and writing. Jacinda Nicklas contributed to interpretation and writing. Ildiko Lingvay contributed to study design, interpretation, and critical review. Jeanne M. Clark contributed to design and critical review. Louis J. Aronne contributed to critical review. Erik Anderson contributed to writing. Michael Usher contributed to design and analysis. Ryan Demmer contributed to design, analysis, and critical review. Genevieve B. Melton contributed to design and analysis and writing. Nicholas Ingraham contributed to analysis and writing. Christopher J. Tignanelli contributed to study design, analysis, interpretation, and critical review.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from Dr. Tignanelli. The data are not publicly available due to privacy restrictions.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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