

Our experience with disease comorbidity analysis shows that time-ordered disease comorbidity relationships offer important insights on patient outcomes. Furthermore, these progression studies often reveal the association between seemingly unrelated diagnoses and the major diagnoses highlighted by indices such as the Elixhauser comorbidity index. Using this approach, our research group built temporal comorbidity trajectories to examine disease associations in an entire population.³ When applied to the single diagnosis of sepsis, this approach gave important information on outcome, even when the details of the sepsis hospitalization were not available.⁴

In addition, machine learning techniques can help create dynamic comorbidity indices that evolve with changes in patient outcomes. A neural network approach combined high-frequency clinical data from intensive care unit hospitalizations with 20-year disease comorbidity trajectories to predict outcome in individual patients in the intensive care unit.⁵ In this case, especially for sepsis, the analysis of comorbidities was a far better predictor of outcome than previously used methods and the addition of acute physiology measures added to the predictive value.

We do not know the effect such a disease comorbidity analysis could have on the results of the study by Dr Seymour and colleagues.¹ We suggest that understanding the phenotype of critically ill patients should include a more thorough accounting of the medical history than can be obtained through commonly used comorbidity indices in addition to high-frequency clinical measures and laboratory analyses.

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In Reply We agree with Dr Moser and colleagues that heterogeneity in sepsis is an important area of study. Many of the differences in patients with sepsis are clinically apparent, and yet

unsupervised methods may identify emerging patterns or phenotypes not otherwise discernible at the bedside.

We also agree that “unsupervised” methods were not wholly unsupervised in our study because we relied on the inherent choices of clinicians to order examinations or laboratory tests or obtain measurements found in the electronic health record.¹ Broadly speaking, these data do not capture the theoretical universe of randomly observable data in a patient with sepsis. It may even be that pertinent tests or data that offer a full permutation of this universe are not yet developed. For now, our models could run only on the observable data.

We also agree that it is a scientific priority to identify phenotypes with strong links to the underlying pathophysiological mechanism. Further study is warranted to link clinical sepsis phenotypes, not just to measurable biomarkers but to the biology that might explain why one phenotype differs from another. Such steps will move forward novel therapies that are better predictive of treatment response.

Drs Moseley and Brunak comment that medical history and comorbidities, and perhaps their underappreciated dynamic trajectory before sepsis, could contribute to phenotypes. We agree that many additional data domains could refine clustering or partitioning models in patients with sepsis. Because this was an “opening volley” using clinical data in the electronic health record, we made a design choice to include variables immediately available at presentation in the emergency department. These steps led to a more constrained view of chronic illness. Future embedding of comorbidity analysis across electronic health records, both inpatient and outpatient, may facilitate their clinical use in point-of-care phenotyping.

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Notice of Retraction. Aboumatar et al.
Effect of a Program Combining Transitional Care and Long-term Self-management Support on Outcomes of Hospitalized Patients With Chronic Obstructive Pulmonary Disease: A Randomized Clinical Trial. JAMA. 2018;320(22):2335-2343.

To the Editor On behalf of our coauthors, we write to report a programming error and other errors that affected the results in our article, “Effect of a Program Combining Transitional Care and Long-term Self-management Support on Outcomes of Hospitalized Patients With Chronic Obstructive Pulmonary

Disease: A Randomized Clinical Trial” published in the December 11, 2018, issue of *JAMA*.¹ We write to explain what happened and to request retraction of this article.

In this study, we had tested a 3-month hospital-initiated program that combined transition and long-term management support for patients hospitalized for chronic obstructive pulmonary disease (COPD). We had originally reported that the intervention, compared with usual care, resulted in a fewer number of mean COPD-related hospitalizations and emergency department visits at 6 months per participant (0.72 [95% CI, 0.45-0.97] vs 1.40 [95% CI, 1.01-1.79]) and an adjusted difference in the 100-point St George's Respiratory Questionnaire (SGRQ) score between groups of -6.69 (95% CI, -12.97 to -0.40; $P = .04$). The correct results reverse the main finding to more COPD-related hospitalizations and emergency department visits in the intervention group vs the usual care group (1.40 [95% CI, 1.10-1.79] vs 0.72 [95% CI, 0.46-0.97]) and an adjusted difference in the SGRQ score that is no longer statistically different (5.18 [95% CI, -2.15 to 12.51]; $P = .11$). Here we describe the detected errors and the additional analyses that have been conducted.

The identified programming error was in a file used for preparation of the analytic data sets for statistical analysis and occurred while the variable referring to the study “arm” (ie, group) assignment was recoded. The purpose of the recoding was to change the randomization assignment variable format of “1, 2” to a binary format of “0, 1.” However, the assignment was made incorrectly and resulted in a reversed coding of the study groups. Even though the data analyst created and conducted some test analysis programs, they were of the type that did not show any labeling of the arm categories, only the “arm” variable in a regression, for example. After detecting this error, we promptly reported it to our institutional review board and appropriate offices within our university, alerted *JAMA*, and proceeded to confirm whether the error had affected the analytic data sets, which we found to be the case. We therefore started a complete data reanalysis, with 2 biostatisticians performing double programming and an independent analysis of study primary outcomes to ensure the validity of the reported results. As noted here, this reanalysis showed reversed study findings, with a higher number of hospitalizations and emergency department visits in the intervention compared with the usual care group.

All study data were subsequently reanalyzed to detect any other errors. This included data review, repeating all the data preparation and programming, and full reanalysis. Over the course of this reanalysis, we detected an error in imputing missing values for the SGRQ, whereby the worst possible score (100) was incorrectly imputed for missing values of participants who had died beyond the 6-month study period. The correct approach would have been to classify those values as missing because those participants had not died by the 6 months after discharge study end point. As noted here, after correction of this error, we found no significant difference in the co-primary outcome of change in health-related quality of life as measured by the SGRQ between the intervention and usual care groups. We also

detected an error in summarizing the baseline medication classes in Table 1, and 2 hospitalizations that were not counted in the initial analysis.

To reduce the occurrence of future similar programming errors, the Johns Hopkins Biostatistics Center has instituted a new standard operating procedure for checking randomization assignment to be followed in all trial analyses. To ensure that the group assignment used in any of the trial analyses is correct, a verification process will be included at the beginning and end of each analysis program. This process is intended to confirm that the group assignment separately provided by the trial team matches the group assignment used in the analysis program. The matching confirmation is reviewed by a second biostatistician/analyst before its use in the results.

With this notice of retraction, we are publishing a new article with complete corrected findings.² Given the corrected finding of a paradoxical increase in acute care use in the intervention group, we conducted a post hoc exploratory analysis to evaluate the difference in treatment effect between the study groups in subgroups of patients whose characteristics might affect the primary acute care visits outcome. The results of this additional analysis are included in the new article.

We apologize to the readers and editors of *JAMA* for any confusion caused by these errors and the erroneous original report of the trial findings and this subsequent retraction of the article. We appreciate the opportunity to publish a new article with the correct findings and an additional analysis. All of our coauthors agree with this retraction notice.

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1. Aboumatar H, Naqibuddin M, Chung S, et al. Effect of a program combining transitional care and long-term self-management support on outcomes of hospitalized patients with chronic obstructive pulmonary disease: a randomized clinical trial. *JAMA*. 2018;320(22):2335-2343. doi:10.1001/jama.2018.17933

2. Aboumatar H, Naqibuddin M, Chung S, et al. Effect of a hospitalized-initiated program combining transitional care and long-term self-management support on outcomes of patients hospitalized with chronic obstructive pulmonary disease: a randomized clinical trial [published October 8, 2019]. *JAMA*. doi:10.1001/jama.2019.11982