On the application, reporting, and sharing of in silico simulations for genetic studies

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Abstract
In silico simulations play an indispensable role in the development and application of statistical models and methods for genetic studies. Simulation tools allow for the evaluation of methods and investigation of models in a controlled manner. With the growing popularity of evolutionary models and simulation-based statistical methods, genetic simulations have been applied to a wide variety of research disciplines such as population genetics, evolutionary genetics, genetic epidemiology, ecology, and conservation biology. In this review, we surveyed 1409 articles from five journals that publish on major application areas of genetic simulations. We identified 432 papers in which genetic simulations were used and examined the targets and applications of simulation studies and how these simulation methods and simulated data sets are reported and shared. Whereas a large proportion (30%) of the surveyed articles reported the use of genetic simulations, only 28% of these genetic simulation studies used existing simulation software, 2% used existing simulated data sets, and 19% and 12% made source code and simulated data sets publicly available, respectively. Moreover, 15% of articles provided no information on how simulation studies were performed. These findings suggest a need to encourage sharing and reuse of existing simulation software and data sets, as well as providing more information regarding the performance of simulations.

KEYWORDS
data sets, Genetic simulations, reproducibility

1 | INTRODUCTION

In silico genetic simulations—or computer modeling of genetic data under specified assumptions—and the software tools used to generate these simulations (which we define as genetic simulators) have played an important role in the development and applications of statistical methods for genetic studies in multiple...
Different applications of genetic simulations demand different designs and implementations. For example, simulations designed to validate a statistical method need to follow the assumptions of the method closely and often employ model-based simulations, whereas simulations designed to test real-world performance need to follow the properties observed in real data. The latter typically use sideway methods (i.e., a method that generates simulated data sets by using existing data and resampling it) and is also preferred for comparing performance across multiple statistical methods as it is not as likely to bias toward any particular method being compared. Due to these different requirements, the level of sophistication of genetic simulations inevitably varies (Dasgupta et al., 2011; Engelman et al., 2016; Fragoulakis et al., 2019), and dedicated computer programs have been developed to perform genetic simulations and generate simulated data sets designed with different modeling emphases (Peng et al., 2013).

To obtain a better understanding of how genetic simulations are being generated, used, reported, and shared, we conducted a review of the literature. In this review, we provide details from 423 articles from five journals that publish on major application areas of genetic simulations, such as, epidemiology, bioinformatics, biomedical discoveries, and evolution theory. In addition, we examined whether simulations were performed using pre-existing software and whether the data and/or code were publicly available.

## 2 | METHODS

We performed a review of the literature to examine the approaches used for genetic simulations. We focused on in silico simulations that used computers to generate “hypothetical” data, manipulated empirically collected data sets, such as those from genetic epidemiological studies, or used genetic computer simulations in other genetics studies, spanning a variety of disciplines related to genetics.

### 2.1 | Selection of journals

To select articles for this review, we identified all the journals that were included as either “citations” or “applications” in the Genetic Simulation Resource (GSR) catalog (Peng et al., 2013). These journals included *American Journal of Human Genetics (AJHG)*, *Bioinformatics, BMC Bioinformatics, BMC Genomics, Evolution, Frontiers in Genetics, Genetic Epidemiology, Genetics, Hereditary, Molecular Biology and Evolution, Molecular
Ecology Resources, Nature Communication, Nature Genetics, PLoS Genetics, PLoS One, Proceedings of Biological Sciences, Proceedings of the National Academy Sciences of the United States of America, and Scientific Reports. First, we selected one recent issue from each of the 19 journals and recorded the number of articles that reported using simulations. Next, we selected the five journals with the highest proportion of articles that included simulated data within distinct scientific topic areas (Table S1). For instance, BMC Bioinformatics and Bioinformatics both reported a relatively high fraction of articles using genetic simulations, but we randomly selected only Bioinformatics because of overlap in the content area with BMC Bioinformatics.

The five journals that we ultimately selected for detailed analysis were AJHG, Bioinformatics, Evolution, Genetic Epidemiology, and Nature Genetics. These journals represent major scientific areas of genetic simulations such as epidemiology, bioinformatics, biomedical research, and evolution theory. We searched these journals starting from the end date of July 2019 and reviewed all previous issues until we identified either 100 articles using simulated data (for journals with a large number of simulation papers) or up to 2 years of articles for journals that had published fewer than 100 articles using genetic simulations. This strategy was used to ensure a review of a sufficient, roughly equal number of articles to make meaningful conclusions.

### 2.2 | Selection of articles

We defined an article to contain simulated data if the data were generated completely using in silico models or simulated from real data or parameters. We excluded studies that used empirical data sets (e.g., 1000 genomes; Auton et al., 2015) to validate or compare statistical methods although the difference between simulated and empirical data sets can be subtle. For example, a simulation study could ascertain random samples from empirical data sets, and some empirical data sets could be computationally enhanced (e.g., imputed against reference genome). We define simulation studies as the use of computers to manipulate data by the authors and consider random ascertainment of empirical data as simulations. Targets of simulations included genetic data (e.g., genetic markers and DNA sequences, RNA sequences and gene expressions, protein sequences, and protein abundances), observed characteristics associated with genetic data (e.g., qualitative and quantitative traits), the relationship between genetic data (e.g., pathways, networks, and phylogenetic trees), and mathematical models that describe genetic data. Other targets of simulations included were cells (type, shape, growth, etc.), drugs, and treatment effects, among others.

### 2.3 | Data collected

We abstracted information from the articles using simulated data, summarized in Table S2. The information collected included: date of publication, target of simulation, application of simulation, and how

#### SUMMARY BOX 1 Categories of applications of simulations

| Application | Characteristics |
|-------------|-----------------|
| Estimation of Type 1 error, sensitivity, specificity, or statistical power | Application of statistical methods on multiple replicates of simulated data sets to quantify success rate of detecting signals (or no signal) in the data sets |
| Validation of correctness or robustness of models | Application of statistical methods on data sets simulated according to or deviate from specific model assumptions |
| Statistical inference | Simulations of data with varying parameters and the identification of simulations (and therefore parameters) that best match empirical data |
| Comparison of performance of statistical methods | Application of multiple statistical methods on the same set of simulated data sets for the purposes of comparing results |
| Exploratory simulations | Exploration of results from simulations with varying parameters to observe possible outcomes associated with a parameter space |
simulations were conducted and reported. Any individual article may contain multiple simulations; therefore, several characteristics were not mutually exclusive. We consider a simulation to be developed using in-house methods if the script or software was developed by the article authors without using existing simulation software or simulated data sets, independent of whether such a method was later made publicly available. Other information abstracted included how the software was used, whether the simulations were conducted using particular software, and whether and where the data and the code for the simulation are available. Over 50% of the articles were quality controlled by a second reviewer.

We classify applications of simulations into five categories (Summary Box 1). We report multiple applications for articles that use more than one simulation studies for multiple purposes (e.g. for both validation and performance comparison).

3 | RESULTS

We included for review 423 articles with simulations from 1409 total articles surveyed from the five selected journals. The complete abstracted data are provided as supplementary material 2B. Genetic Epidemiology published the highest proportion of articles that utilize genetic simulations (72.4%), followed by Evolution (35.7%), Bioinformatics (31.6%), Nature Genetics (22.5%), and AJHG (12.4%; Table 1). Some characteristics were similar across all five journals. For example, the frequency of articles that reported using pre-existing methods ranged 25.6%–31.0%. However, other characteristics, such as the proportion of articles that provided details on the simulated data sets or provided source codes, varied by a journal. Specifically, out of the 423 articles, 49 (11.6%) provided publicly available simulated data sets and 82 (19.4%) provided source codes. When this data was examined by journal, most of these articles were from the journal Evolution; almost half of the articles reported details of simulations in the format of source code (N = 47) and almost a third of the articles provided simulated data sets (N = 28), in contrast to the other four journals.

3.1 | Methods used to conduct simulations

Even though 67 (15%) articles provided little to no information on how the simulation studies were

| TABLE 1 Summary of articles using genetic simulations surveyed from five selected journals |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| Genetic Epidemiology                        | American Journal of Human Genetics         | Bioinformatics                              | Nature Genetics                             | Evolution                                   | Total                                      |
| Total articles surveyed                      | 134                                          | 354                                         | 364                                         | 280                                         | 1409                                       |
| Articles with genetic simulations           | 97 (72.4%)                                   | 44 (12.4%)                                  | 82 (22.5%)                                  | 100 (35.7%)                                 | 423 (30.0%)                                |
| Among the articles with genetic simulations and abstracted | 27 (27.8%)                                   | 13 (13.0%)                                  | 12 (22.3%)                                  | 21 (25.6%)                                  | 49 (11.6%)                                 |
| Articles that perform simulations with pre-existing software | 22 (2.1%)                                     | 18 (18.0%)                                  | 9 (11.0%)                                   | 10 (14.4%)                                  | 28 (6.7%)                                  |
| Articles that make simulated data set publicly available               | 0 (0%)                                        | 0 (0%)                                       | 0 (0%)                                       | 0 (0%)                                       | 8 (1.9%)                                   |
| Articles that make source code for simulations available                | 2 (2.1%)                                     | 2 (2.1%)                                    | 1 (1.3%)                                    | 0 (0%)                                       | 4 (0.9%)                                   |
| Articles that make use of existing simulated data sets                   | 0 (0%)                                        | 0 (0%)                                       | 0 (0%)                                       | 0 (0%)                                       | 0 (0%)                                     |

*For each of the five journals, we surveyed either 100 articles with genetic simulations or all articles with genetic simulations in the past 2 years. We were able to survey 100 articles in the journals of Bioinformatics and Evolution, but fewer than 100 articles from the other three journals.

The numbers include data sets and source code that were not immediately available (embargoed) but were available upon request. We did not contact the authors to confirm the availability of such data or source code.
performed, most articles described the methods used. The majority of the articles reported using in-house simulation methods (72% of 423), and the proportions were similar across the five journals (from 69% in *Evolution* to 74% in *Nature Genetics*). Many of the in-house methods were implemented using general-purpose scripting languages such as R, Python, and MATLAB and only one-fifth were made publicly available.

The remaining 117 (27%) articles (ranging from 12 in AHSG to 31 in *Evolution*, Table 1) reported using an existing simulator, which are listed in Table S2. Overall, COSI (*N* = 13, of which 11 in *Genetic Epidemiology*; Schaffner et al., 2005), HapGen2 (*N* = 8, all in *Genetic Epidemiology*; Su et al., 2011), and SLiM (*N* = 6, of which 4 in *Nature Genetics*; Haller & Messer, 2017, 2019) were the most commonly used simulators for the simulation of genotype data in this sample of articles, whereas PhyTools (Revell, 2012; *N* = 11, all in *Evolution*) was the most popular for the simulation of phylogenetic trees. Other tools were used sparsely for other specific applications, including GeneNetWeaver (Schaffer et al., 2011; *N* = 3 in *Bioinformatics*), DWGSIM, and ART (Huang et al., 2012; *N* = 2 in *Bioinformatics*). Other tools were only used once each (Huang et al., 2012; Schaffer et al., 2011).

Eight of the 423 articles (1.8% or 8 of 423, of which 7 in *Bioinformatics*, Table 1) used pre-existing simulated data sets. Out of the eight, three used DREAM Challenges data (Cao et al., 2019; Ghanbari et al., 2019; Zheng et al., 2019), one used the CAMI2 simulated human microbiome data sets (Shi et al., 2019), and the remaining four used simulated data sets from previously published papers (Caetano et al., 2018; Han et al., 2019; Kim et al., 2019; Yu et al., 2018).

### 3.2 Sharing of simulation programs and data sets

Among 49 articles with publicly available simulated data (11.3%), most simulated data sets were saved to repositories such as DRYAD (*N* = 22), GitHub (*N* = 6), GitBuckets (*N* = 1), FigShare (*N* = 1), and UniShare.nl (*N* = 1). Others were provided as supplementary material (*N* = 3), posted on authors’ personal websites (*N* = 2), and one was available upon request. The size of shared simulated data sets varied greatly, with the largest data sets saved to UniShare.nl (53 GB; Xu & Etienne, 2018) and DRYAD (23 GB; Culshaw et al., 2019 and 18 GB; Hvala et al., 2018). Similarly, among 82 articles with publicly available source codes for simulation studies, most were saved to code sharing platforms: 29 to DRYAD, 29 to GitHub, 2 to FigShare, 1 to GitBucket, and 1 to Zenodo. The source code was available as supplementary material in five articles and available upon request in two articles.

### 3.3 Targets and applications of simulations

Overall, genetic simulations have simulated a wide array of data and processes (targets), played many roles (applications) in genetic studies, and the distributions of targets and applications varied from journal to journal (Tables 2 and 3). Many studies simulated multiple targets for multiple applications. For example, many genetic epidemiological studies simulated both genotype and phenotype data estimated the power (and Type-I error, etc.) of a new genetic association test, and compared its performance with existing methods.

### Table 2 Number and proportion of articles by targets of genetic simulations by journal

| Target of genetic simulation | Genetic Epidemiology | Bioinformatics | American Journal of Human Genetics | Nature Genetics | Evolution |
|-----------------------------|----------------------|----------------|-----------------------------------|----------------|-----------|
| Genotype                    | 88 (90.7%)           | 71 (71.0%)     | 32 (72.7%)                        | 64 (78.0%)     | 20 (20.0%)|
| Phenotype                   | 87 (89.7%)           | 30 (30.0%)     | 17 (38.6%)                        | 36 (42.7%)     | 24 (24.0%)|
| Relationship                | 35 (36.1%)           | 21 (21.0%)     | 13 (29.5%)                        | 16 (19.5%)     | 32 (32.0%)|
| Mathematical models         | 5 (5.2%)             | 11 (11.0%)     | 8 (20.5%)                         | 10 (12.2%)     | 11 (11.0%)|
| Others                      | 1 (1.0%)             | 8 (8.0%)       | 2 (4.5%)                          | 5 (6.1%)       | 39 (39.0%)|

*Number of articles does not add up to the total due to multiple types of data simulated in each article.*

*Proportion of articles do not add to 100%.*

*Target of genetic simulation are defined in Section 2.*
The targets of simulation studies reflected the scope of the articles that the journals publish. As the field of genetic epidemiology focuses largely on deciphering genetic causes of human diseases and traits, it is not surprising that 90% of simulation studies in this journal simulated genotypes and phenotypes. Upon closer examination, 86.4% of these articles simulated DNA (markers, sequences, and sequencing reads) while the remainder simulated RNA and other types of genetic data such as gene expression (see Table S2 for details). Compared with Genetic Epidemiology, the journals Bioinformatics, AJHG, and Nature Genetics place less emphasis on phenotypes and included a broader range of genetic studies. Although genotypes remained the most common targets for simulations performed in these journals, around half of the studies published simulated RNA and corresponding expressions, microbiome, summary statistics, and annotations. A large portion of articles in Evolution simulated phylogenetic trees to study the relationship among species and genes. Articles in this journal also simulated targets that are less commonly studied in the other four journals, such as mating patterns and seed banking strategies (McCullough et al., 2018).

Likewise, the types of applications varied by journal, where 70% of articles in Genetic Epidemiology used genetic simulations to evaluate the performance of statistical methods. The proportion of published articles that evaluated the performance of statistical methods were substantially lower in the other journals, especially Evolution. Similarly, we observed differences in the percentages of papers published by journal that compared the performance of existing statistical methods. For this application type, Bioinformatics published the largest proportion of such articles. This finding is consistent with its aims where studies published in Bioinformatics often focus on identifying the best methods to address specific bioinformatic challenges, rather than on developing new methods. Finally, not surprisingly, simulations used for the purposes of statistical inference were most frequently observed in Evolution followed by Nature Genetics, as the aim of these journals is to draw conclusions from genetic data.

4 | DISCUSSION

We surveyed 1409 articles from journals and identified 423 (30%) articles that utilized genetic simulations. Based on our abstraction of these 423 articles, we observed less than onethird of these publications reported using pre-existing simulation methods and only eight used pre-existing data sets. About 15% of articles provided no information about how simulations were performed. In addition, the proportion of articles that shared data (11.6%) or source code (19.4%) was limited. We also observed variability across journals in the proportion of articles that utilized genetic simulations, where 72% of articles in the journal of Genetic Epidemiology used genetic simulations compared with 12.4% of articles in AJHG. Furthermore, we observed differences in patterns of targets and applications that were simulated across the journals, likely reflecting differences in the aim and scope of each journal. For example, 70% of the articles in Genetic Epidemiology that reported using genetic simulations were for the validation and comparison of performance of statistical methods compared with journals that focus more on applications of genetic studies, such as AJHG and Nature Genetics.

| Applications of genetic simulation | Genetic Epidemiology | Bioinformatics | American Journal of Human Genetics | Nature Genetics | Evolution |
|-----------------------------------|----------------------|----------------|------------------------------------|----------------|-----------|
| Type-1 error, power, and sensitivity | 68 (70.1%) | 23 (23.0%) | 19 (43.2%) | 30 (36.6%) | 9 (9.0%) |
| Comparison of statistical methods performance | 84 (86.6%) | 69 (69.0%) | 20 (45.5%) | 21 (25.6%) | 4 (4.0%) |
| Validation/robustness | 31 (32.0%) | 50 (50.0%) | 13 (29.5%) | 33 (40.2%) | 19 (19.0%) |
| Exploratory analysis | 3 (3.1%) | 0 (0%) | 2 (4.5%) | 5 (6.1%) | 32 (32.0%) |
| Statistical inference | 0 (0%) | 2 (2.0%) | 10 (22.7%) | 24 (29.3%) | 57 (57.0%) |
| Total number of articles reviewed | 97 | 100 | 44 | 82 | 100 |

*aNumber of articles does not add up to the total due to genetic simulations being used for multiple applications.

*bProportion of articles do not add to 100%.

*cDefinitions for applications of genetic simulation are provided in Section 2.
Approximately 70% of the publications surveyed used in-house genetic simulations methods, of which only around 20% were made publicly available. Although it is too early to predict how many of these in-house methods will be reused in the future, we observed that only three articles from our review used in-house methods previously published (Mak et al., 2017; Wainberg et al., 2019; Wang et al., 2017), possibly indicating that most in-house methods are rarely reused. A large number of in-house simulation methods and their limited sharing and reuse are likely due to multiple reasons. Some of the genetic studies used simple simulations for one-time use only; these were based on general-purpose scripting languages, such as the use of random number generators to generate phenotypes with certain distributions or random sampling process to ascertain samples from a pool of data sets. Researchers may prefer to develop their own in-house methods to more readily control all aspects relevant to the specific research requirements (Chen et al., 2015). Unlike data sets generated carefully by organizations such as the Genetic Analysis Workshop (Blangero et al., 2016) and DREAM (Lee et al., 2018; Marbach et al., 2012), simulations designed for a specific research paper often have nonstandard formats, less documentation, and are difficult to reuse. Researchers may also choose to create their own simulation code rather than search for available software especially when the simulations are not very complicated. In addition, simulations created for other statistical methods are likely based on specific assumptions that provide important performance information for those scenarios, and they may not be suitable for evaluating or comparing the power of methods based on different assumptions.

Additional reasons that may have contributed to the underutilization of existing tools include a lack of detailed description of simulations (e.g., source code and parameters used) and the unavailability of simulated data sets leading to the high proportion of in-house simulations observed. The National Cancer Institute created the GSR website with the intent of increasing awareness of existing tools; however, more needs to be done to address the availability of data and source code (Chen et al., 2015; Peng et al., 2013). Reusing existing data and software would maximize the utility of existing resources and should be encouraged to limit potential replication of effort and redundancy of tools. Comparison and evaluation of different simulators are also needed to identify the strengths and weaknesses of available methods (Chen et al., 2015). Furthermore, creating in-house methods that are tailored to answer a particular research question may lead to an optimistic interpretation of results (Chen et al., 2015; Mechanic et al., 2012). For example, in genetic simulation of rare genetic variants, many models assume a large percentage of highly penetrant mutations, resulting in optimistic power assumptions. Therefore, the use of common simulation programs or data sets has been encouraged. Due to the wide range of applications for which genetic simulations can be used, it is not feasible to have a single dedicated simulation program for all possible applications and the development of new simulation methods may be necessary.

Among the five journals surveyed, articles published in *Evolution* most consistently deposited simulated data sets and related source code. Although Figshare and some other (e.g., university) file-sharing mechanisms were occasionally used, almost all articles published in *Evolution* deposited data in DRYAD (Khan & Weeks, 2015), which is a data repository funded by multiple publishers and supported by multiple institutions. We attribute this observation to the *Evolution* journal’s policies, which states “Authors must make their empirical raw data and analytic methods available to other researchers and must specify where that material is available.” Moreover, its guidelines to authors explicitly require, “as a condition for publication, that data supporting the results in the paper should be archived in an appropriate public archive, such as DRYAD, Figshare, GenBank, TreeBASE, the Knowledge Network for Biocomplexity, or other suitable long-term and stable public repositories.” The other four journals surveyed did not explicitly require authors to share data or source codes, which may account for part of the differences observed. The policy adopted by *Evolution* originated from a Transparency and Openness Promotion framework that contains editorial guidelines for journals. The purpose of this policy is to help achieve data and material transparency such that other researchers can replicate the procedure and reproduce results (Nosek et al., 2015). It is highly recommended that disciplines such as genetics and bioinformatics follow these guidelines.

There are several public repositories available for the deposit of research data sets and source code. Although some, like DRYAD, collect a service fee or is subscription based (which is often paid by institutions), services such as Figshare and Zenodo are available free of charge (with some restrictions). Due to the popularity of Git repository hosting services, websites such as GitHub and BitBucket are frequently used to store source code, and, in some cases, simulated data sets (da Fonseca et al., 2019). However, source code repositories are not designed for
the storage of data sets and have restrictions on file size (e.g., GitHub limits files to those less than 100 MB). In addition, these general-purpose data repositories may exacerbate the reusability problem by accepting a wide range of data types in a wide variety of formats (Wilkinson et al., 2016). Previously, in some instances, simulated data sets have been deposited to the National Institutes of Health (NIH)-funded repositories such as dbGaP (e.g., simulated data sets for the Framingham Heart Study; Cupples et al., 2009). For simulated data sets not generated from identifiable human subjects, other alternative NIH repositories without requirements for controlled access could be explored to promote the sharing of these data sets.

In addition to public repositories, other common ways for storing data and source code related to research articles include personal, institutional, and journal websites. Compared with public repositories that are designed for the storage, display, and retrieval of research data for a prolonged period of time, data stored on personal, institutional, and journal websites are less organized and sometimes inaccessible. For example, the website that hosts data and code for one of the articles was temporarily unavailable during our review. For these reasons, journals often recommend using public repositories for the deposit of research code and data.

This survey has some limitations. One limitation is that the survey was restricted to five journals that were selected for inclusion. Narrowly defining the inclusion criteria provides only a snapshot of the field. However, the included journals represent major application areas of genetic simulations and our observations are consistent with what has been reported previously, suggesting that expanding the scope of journals would not substantially change our results (Peng et al., 2015). Another limitation is that we did not evaluate the in-house methods to see whether the simulations could be performed, and hence, could not determine the quality of the description of the in-house methods. This is an important open question that should be addressed in future studies.

A large number of papers using genetic simulations for a variety of purposes and the limited observed use of existing simulation tools/data sets as well as sharing of these, suggest the need for best practices for reporting and sharing of these data sets, as was discussed previously (Chen et al., 2015). Although efforts have been made to facilitate the sharing of data sets and software, additional efforts are needed by journals and funding agencies to encourage the reuse of these resources to extract maximum benefit from research investments. We have summarized the key findings and suggest recommendations based on these findings to facilitate research in this area (Summary Box 2). Because genetic simulations are essential for the study of genetics of complex diseases, greater sharing of simulated data sets and related source code could help accelerate the development and application of statistical methods for genetic studies in multiple disciplines benefiting the scientific community.

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SUMMARY BOX 2  Key messages and recommendations

Key messages
• 30% of articles in surveyed journals utilized genetic simulations, depending on discipline and journal (range, 12.4%–72.0%).
• 15% of articles provided no information on how the simulation studies were performed.
• 70% of articles surveyed used in-house simulation methods. About 28% of articles used existing simulation software and 2% used existing simulated data sets.
• 12% of articles made simulated data sets and 19% of articles made source code for simulation studies publicly available.

Recommendations based on these findings
• The scientific community should encourage reuse of existing simulation software and/or data sets to facilitate fair comparison between statistical methods and to maximize benefit from research investment.
• Research articles should report complete information on how simulations were performed.
• Source code and simulated data sets should be deposited and shared in public repositories to facilitate reuse and reproducibility.
• Journal offices and funding agencies could encourage proper reporting and sharing of simulation studies by establishing guidelines and policies.
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CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT
The data that supports the findings of this study are available in the supplementary material of this article.

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**SUPPORTING INFORMATION**
Additional supporting information may be found online in the Supporting Information section.