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Reproducible research practices and transparency across the biomedical
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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2015

Abstract

Reproducible research practices and transparency across the biomedical literature

By Shareen Iqbal, PhD

There is a growing movement to encourage reproducibility and transparency practices in the scientific community. With increased open access to protocols, analytical codes, and raw data, external researchers have the opportunity to evaluate possible weaknesses in the design, conduct, and analysis of studies. Furthermore, increased transparency will allow for external investigators to reproduce study results. In this survey, the current status of reproducibility and transparency in a random sample of published biomedical journal articles was assessed. By deriving empirical data on important monitoring indicators, this study highlights the need to further sensitize scientists, funders, and journals to the need of improving these indicators.

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Acknowledgements

I wish to express my sincere thanks to my advisor, Dr. Muin J. Khoury and my field advisors, Dr. John Ioannidis, Dr. Sheri Schully and Mr. Joshua Wallach, for providing valuable advice and encouragement.

I am also grateful to the Department of Epidemiology, Ms. Jena Black, and my practicum advisor, Dr. Adel Driss, for their guidance and support.

I also place on record, my sense of gratitude to all those who directly or indirectly, have aided in this project.

Lastly, I especially want to acknowledge the unconditional support and love from Drs. B. Iqbal, J. Iqbal, and Z. Iqbal.

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The inability to replicate published research has been an ongoing concern in the scientific community (1). There is disconcerting evidence from basic molecular and animal modeling research that a large portion of published articles lack reproducibility (2), which could potentially be related to the increase in lack of efficacy of clinical trials (3, 4). It has been suggested that the inability to replicate findings is due to lack of research transparency (5). Recently, there has been a growing movement to encourage making protocols, analytical codes, and data openly available (6-8). This study aimed to assess the current status of reproducibility and transparency in a random sample of published biomedical journal articles and derive empirical data on indicators that have been proposed as being important to monitor in this regard (9). To date, there has not been an unbiased evaluation of the proportion of studies sharing protocols and raw data, undergoing rigorous independent replication and reproducibility checks, and reporting conflicts of interest and sources of public and/or private funding, across a random sample from the entire biomedical field.

A sample of 500 English language journal articles published between 2000 and 2014 was chosen randomly based on Pubmed identification (PMID) numbers spanning from PMID # 10,000,000 to PMID # 25,000,000. InCites Essential Science Indicators was used to determine the field of study for each index paper. Two investigators (SI and JDW) independently extracted data and then compared their extractions from the 500 studies. Publications in research

fields not directly related to core biomedical research (Chemistry, Physics, Computer Science, Economics & Business, Engineering, Geosciences, Material Science, Mathematics, Physics, and Space Science) were further excluded from analysis. Please see the supplement for complete discussion of methods.

A total of 448 (89.6%), from the original randomly selected 500 articles were publications in research fields directly related to biomedicine. Of these, the majority were non-human articles with some form of empirical data (249 (56%)). Human studies, with empirical data, comprised 60 (13%) of the eligible articles, with 15 of those being randomized clinical trials. Articles without empirical data comprised 139 (31%) of the final dataset (Table 1).

Excluding articles without empirical data and case studies or case series, 272 (99.6%) of the 273 papers did not include a link to a full study protocol. Only one article had a protocol, in fact the article was the protocol itself of a trial and it was published in the open-access journal *Trials* (10). Another five studies either referenced their clinical trials identifier and included a link to ClinicalTrials.gov (A282, A434), provided only a Clinical Trials identifier (A477, A408), or stated that a Clinical Trials repository link was available on the journal website (262), but none of the articles contained information about a full protocol. One of the five studies referenced both a clinical trials identifier and an Eli Lilly and Company Clinical Trial Registry protocol identifier (A477).

There were eight other articles that had additional methods sections, figures, brief analytical plans and/or considerations, or supplementary materials either as a detailed appendix at the end of the paper (A434), or online via the

ACS Publications website <<http://pubs.acs.org>> (A35, A377), the journal website (A25, A175, A291 (supplemental material was not open access), A470), or on a scientific association website (A362 (contained an error message for page not found)). However, none of these supplementary materials fit the pre-specified definition of publicly available full or partial protocols.

Of the 273 articles with empirical data (excluding case studies and case series) none provided access to all the raw data involved in the study. There were 10 articles that either contained information on how to request a complete dataset (11), provided a program data base (PDB) online file, without referencing the format and the program to install it with (12), listed a non-functioning online link for supplementary data (13, 14), or had supplementary files or links to some absorption spectra figures and/or data (15-19), but not to the entire raw data used in the paper.

About half (51%) of the 448 biomedical articles did not include any information on funding and about a third (35%) were publically funded either alone or in combination with other funding sources. Of the 158 publically funded articles, 63 had NIH funding, six received NSF support, and 103 had other forms of public funding (Figure 1). There was no major change in the pattern of sources of funding over the 15-year period (supplementary Figure 1S).

Of the 273 biomedical articles with empirical data, excluding case studies and case series, systematic reviews/meta-analyses, and cost effectiveness/decision analysis studies, only 3 (1.1%) clearly claimed to be replication efforts trying to validate previous knowledge. Four index articles were

inferred to be replication efforts. Just under half (47.6%) of the studies claimed to present some novel findings and about a tenth (9.9%) had clear statements of both study novelty and some form of replication. There were 104 (38.1%) index articles that either had no statement or an unclear statement in the abstract and/or introduction about whether there were any novel findings or replication efforts.

For the 264 biomedical articles with empirical data, excluding case studies and case series, systematic reviews/meta-analyses, and cost effectiveness/decision analysis studies, it assessed whether any subsequently published papers had cited them mentioning that they were attempting to replicate part or all of their findings. Seven articles in the final data set had at least some portion of their findings replicated (A), while the remaining 254 articles had no citing article that claimed to be a replication. Of the replicating articles, one was unable to reproduce the results from the original article (A60), but mentioned that different definitions were used (B10). Two index articles had their results replicated through different methodology (B12 [A223], B14 [A408]). One index article (A11) had several studies that either confirmed portions of the original study [B15, B16], or failed to validate certain previous findings (B17). Two index studies developed new methodology that the replicating studies either confirmed (A286) by comparing to available methods (B18) or a newly developed method (B19 [A441]).

In order to measure whether empirical studies are eventually integrated in systematic reviews, the 264 index articles with empirical data (again excluding

case studies and case series, systematic reviews/meta-analyses, and cost effectiveness/decision analysis studies) were assessed on whether they had been cited at least once in subsequent systematic reviews and/or meta-analyses. Empirical data from 16 (6.1%) index articles were utilized in a systematic review/meta-analysis (20-35). For another six of the articles, at least one systematic review/meta-analysis cited the index paper, but provided reasons for not including any of its data in a quantitative synthesis for any outcome (10, 33-37). Lastly, 26 (9.8%) articles were cited by systematic reviews/meta-analyses, but had no data used in quantitative syntheses for any outcome (30-34, 36-56). The remaining 228 articles (90.2%) were not cited in any systematic reviews/meta-analyses.

The large majority of the 448 articles had no conflict of interest statement (311 (69.4%)). Of the remaining, 111 (24.9%) did not report any conflicts of interest and only 26 (5.8%) reported conflicts of interest. Of the 171 human studies with empirical data, 103 (60.2%) papers had no statement, 51 (29.8%) papers reported no conflicts, and 17 (9.9%) papers had clear statements of conflict. For the 15 randomized clinical trials, eight articles (53.3%) reported no conflicts of interest, four (26.7%) articles had no statement of conflict, and three (20.0%) articles had a clear statement of conflict.

Between 2000 and 2014, the percentage of articles with no statement of conflict decreased substantially (94.4% in 2000 to 37% in 2014), whereas the number of articles reporting statements of conflicts or no conflicts increased

(conflicts: 0% in 2000 to 14.8% in 2014; no conflicts: 5.6% in 2000 to 48.1% in 2014) (Figure 2).

The empirical evaluation shows that the published biomedical literature lacks transparency. Only one full protocol was found in the sample. Previous evaluations have identified common inconsistencies between protocols and publications of randomized trials (57, 58). For other types of study designs, such research is hampered by the rare availability of protocols. Public protocol sharing not only provides external researchers ways to find possible discrepancies between final publications and research plans (B9); more importantly, it allows study designs and experiments to be reproduced by interested scientists.

Of the 273 biomedical articles with empirical data assessed, none had open access to all the raw data. A previous evaluation found 9% of articles published in the 50 journals with the highest impact factor in 2009 had deposited full primary data online (B22). The results may differ due to the fact that this study focused on the full spectrum of biomedical journals in Pubmed (median impact factor 3.1). Even though data sharing requirements have changed over the last few years, especially in high impact journals (B22, B27), high impact journals represent only a fraction of the journals studied in this paper. Although one article in this study claimed that the complete dataset was available upon request (A288), a statement of willingness to share may not guarantee that the data will be available to independently requesting scientists (B23). Sponsor priorities, lack of resources, personal investigator opinions, and proprietary perceptions all may influence raw data withholding (B24, B25). Seven other

articles included supplementary files or links with some additional data, but for two of them the links were non-functioning (A291, A362). Evidence exists that even the most prestigious journals have supplementary information that eventually became unavailable (59).

There were 130 papers that claimed to have novel discoveries. However, it is anticipated that the majority of index papers do not truly have new findings, but may be operating in knowledge space where other past studies may also have operated. Only three index articles had clear statements that they were replication attempts. Studies that explicitly describe themselves as replication attempts are rare across the biomedical literature. Moreover, none of the subsequently published papers that cited the index articles mentioning that they were attempting to replicate part or all of their finds were full study replication attempts. Replication has been accepted as a sine qua non in a few disciplines such as human genome epidemiology, but this is the exception. When done, investigators may still try to differentiate their replication study as being different from the original and thus make a case for novelty. It was also demonstrated that only a very small fraction of primary data are currently included in systematic reviews and meta-analyses. Despite the advent of evidence-based medicine, these data syntheses still cover only small fractions of the available evidence.

Previous studies have found that between 29 to 69% of published clinical research articles had some type of financial conflict (60, 61), and a survey of NIH funded life science researchers found that 43% of 2,167 respondents reported receiving research related contribution, such as reagents, equipment, travel

funds, or other (B31.). In this study, which covers a very wide range of research designs and types, only 5.8% had conflict of interest statements, and the percentage was still less than 10% for human studies. This is likely an underestimate of the prevalence of conflicts in biomedical research, and could be a result of the lack of conflict of interest disclosure policies among many journals (B32). However, this study also found that the number of statements reporting no conflicts of interest increased and, conversely, the number of articles without any statements decreased over time, perhaps due to strengthening of certain journal disclosure policies (62). The high prevalence of no statement of conflict is alarming considering that conflicted stakeholders can have a significant impact on the design, conduct, and analysis of biomedical studies (B1, B33, B34).

Slightly over half of the analyzed papers reported no funding. It is possible that some of them simply did not mention existing sponsors. Still, a large share of the published literature occurs without any support, and this should cause some concern. Public funding is listed for about a third of the biomedical literature and NIH accounts for a mere 15% of the biomedical literature with no major change over time.

This evaluation is limited to the published biomedical research information. In theory, one may be able to obtain additional raw data and protocols, and clarifications on conflicts or funding by communicating with the authors or sponsors. However, the yield would be uncertain and personal communications

should not be considered an alibi for lack of transparency in the published scientific record.

Hopefully this survey will sensitize further scientists, funders, journals and other science-related stakeholders to the need of improving these indicators. There are several efforts to improve reproducibility (*B37*). By continuing to monitor these indicators in the future it is possible to track any evidence of improvement in the design, conduct, and analysis of biomedical research over time.

Tables and Figures.

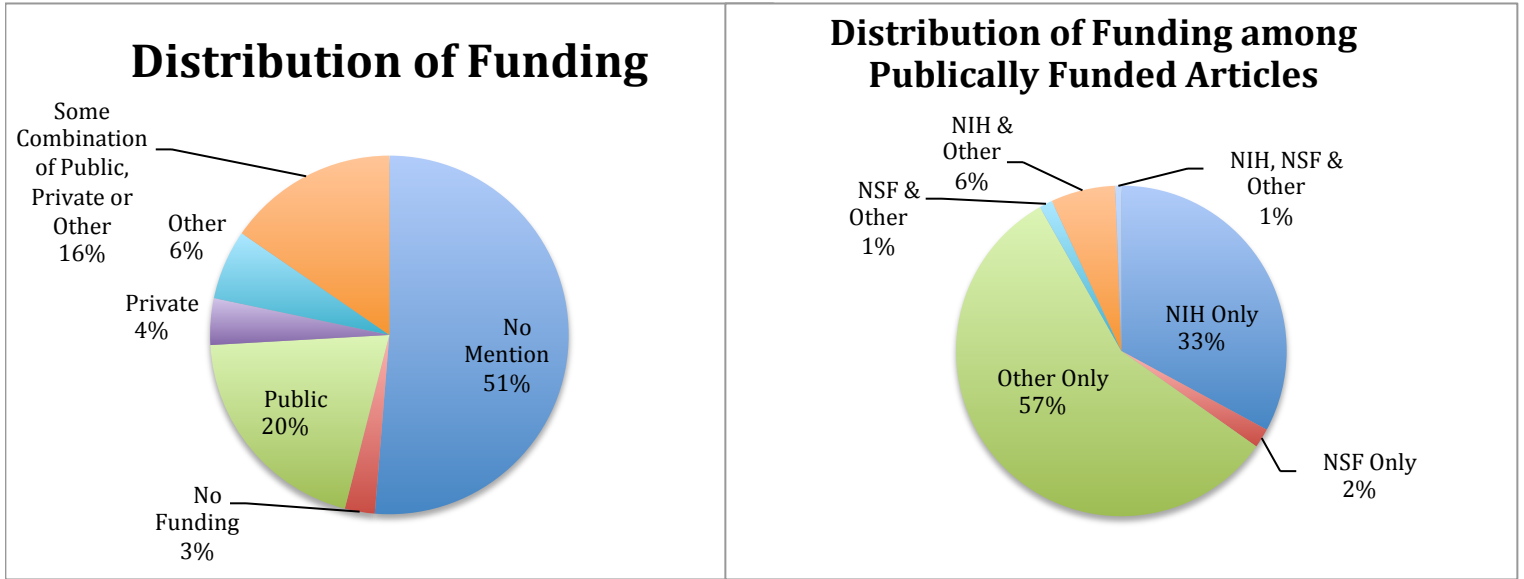


Figure 1: Distribution of Funding overall (a) or among publically funded articles (b).

Trends in Reporting Conflicts of Interest

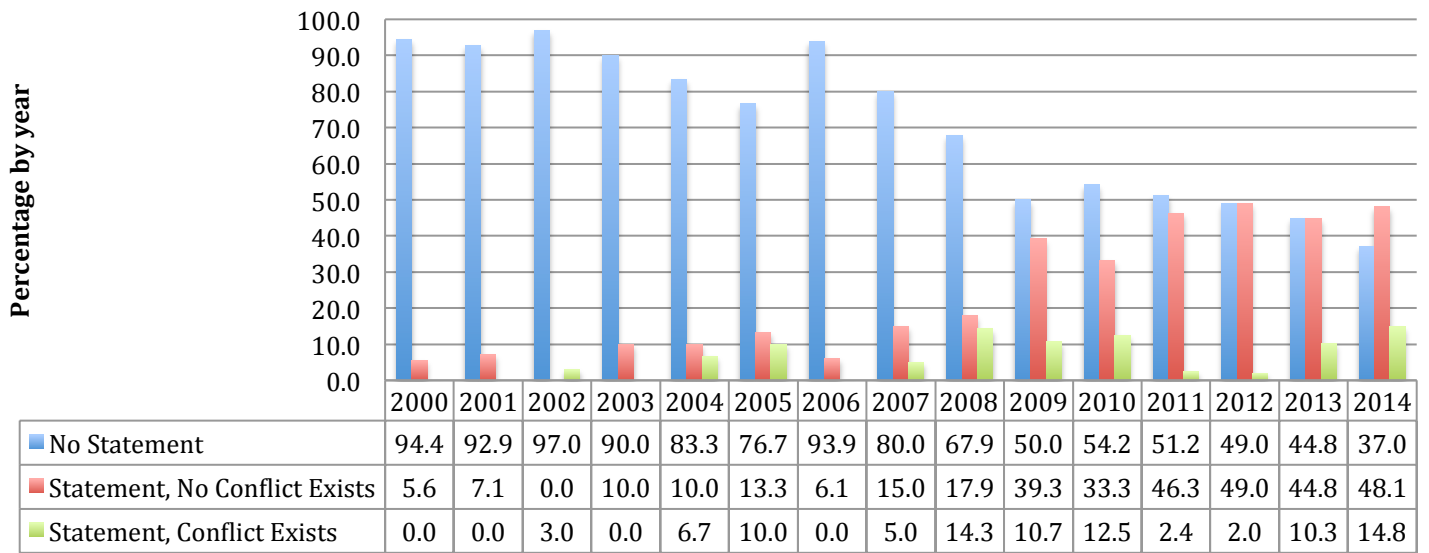


Figure 2: Trends in Reporting Conflicts of Interest.

Table 1. Distribution of 500 Randomly Selected Articles by Research Type.

Variables	n (%)
Articles in Medical Field	448 (89.6)
Research Type (Categorized)	
Research with Empirical Data (Human)	
Cost Effectiveness/Decision Analysis	4 (0.9)
Case Studies or Series	36 (8.0)
Randomized Clinical Trial	15 (3.4)
Systematic Review/Meta Analysis	5 (1.1)
Research with Empirical Data (Other)	249 (55.6)
Research without Empirical Data	139 (31.0)
No Research (Items with No Data)	135 (30.1)
Models/Modeling	4 (0.9)
Articles with Empirical Data by Type (Abstract only)	
Animal	48 (17.6)
Genes	9 (3.3)
Human	128 (47.1)
Clinical Trial	18
Animal and Genes	11 (4.0)
Genes and Human	7 (2.6)
Undefined in Abstract	65 (23.9)
No Abstract	4 (1.5)
Articles with Full Free Access	87 (19.4)
Article Study Field Distribution	
Agricultural Sciences	9 (2.0)
Biology and Biochemistry	39 (8.7)
Clinical Medicine	136 (30.4)
Environment/Ecology	9 (2.0)
Immunology	7 (1.6)
Microbiology	7 (1.6)
Molecular Biology and Genetics	12 (2.7)
Neuroscience and Behavior	27 (6.0)
Pharmacology and Toxicology	17 (3.8)
Plant and Animal Science	10 (2.2)
Psychiatry/Psychology	14 (3.1)
Social Sciences, General	14 (3.1)

Various	23 (5.1)
No Document on ESI	55 (12.3)
Not listed on ESI	69 (15.4)

Corresponding Author Distribution by Continent

Africa	6 (1.3)
Asia	91 (20.3)
Europe	138 (30.8)
North America	183 (40.8)
Oceania	3 (0.7)
South America	9 (2.0)
None Listed	18 (4.0)

Table 2. Distribution of Biomedical Article Research Claims of Research Originality, Novelty and Replication.

Categories	n (%)
Novel Findings	130 (47.6)
Replication	3 (1.1)
Replication (Unclear Abstract)	4 (1.5)
Unclear or No Statement	104 (38.1)
Novel and Replication	27 (9.9)
No Abstract and Introduction	5 (1.8)

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SUPPLEMENTAL MATERIALS:

Methods:

The inability to replicate published research has been an ongoing concern in the scientific community (1). There is disconcerting evidence from basic molecular and animal modeling research that a portion of published articles lack reproducibility (2), which could potentially be related to the increase in lack of efficacy of clinical trials (3, 4). It has been suggested that the lack of transparency of the data is linked to the inability to replicate findings (5). Although previous publications have reported on the lack of reproducibility and transparency in published data, a detailed identification of their predictive indicators has not been developed.

Aims: To evaluate the trend in reproducibility and transparency in a random sample of published biomedical journal articles. Additionally, the project aims to identify predictors for reproducibility and transparency through study characteristics. The plan is to derive empirical data on indicators of transparency and reproducibility that have been proposed in the Lancet series on increasing value and reducing waste in research by Ioannidis et al. (Lancet, 2014).

Objective1: Measure a sample of 500 biomedical journal articles, chosen randomly based on Pubmed Identification (PMID) numbers spanning from PMID # 10,000,000 to PMID # 25,000,000. The random sample will include English language articles published between 2000 and 2014.

Methodology overview: PMID numbers, ranging from 10,000,000 to 25,000,000 were inputted into OpenEpi (version 3.02) random number generator to select a random sample of 750 PMID numbers (Table 1). Beginning from the first number generated (number 1 in column 1, row 1, Table 1), numbers were verified for eligibility in sequence until 500 eligible PMID numbers were chosen (Table 2). Of the original 750 numbers, 742 were checked, with 242 being ineligible (54 unfound, 100 before year 2000, 35 not in English, and 53 not in English and before year 2000). The selected article distribution of PMID numbers (by year) was compared to the overall distribution of PMID numbers by year for English articles. The sample was found to be representative of the overall distribution, χ^2 (df=14), $p>0.05$. The sample was independently characterized and cross-compared by two investigators (SI and JDW) into 7 study characteristic categories (supplemental Table A): 1. no research (items with no data such as editorials, commentaries, news, comments and non-systematic expert reviews, 2. models/modeling or software or script or methods without empirical data (other than simulations), 3. case report or series (humans only, with or without review of the literature) 4. randomized clinical trials (humans only) 5. systematic reviews and/or meta-analyses (humans only) 6. cost effectiveness or decision analysis (humans only), and 7. other (empirical data that includes uncontrolled study (human),

controlled non-randomized study (human) or basic science studies). A third reviewer (JPAI) reassessed articles with arbitration discrepancies.

The sample was found to be primarily composed of articles with empirical data (70%), with the majority of those articles consisting of uncontrolled or controlled non-randomized human studies or basic science research (Figure 1).

InCites Essential Science Indicators was used to determine the field of study. Briefly, the journal for each index paper was first selected in InCites Essential Science Indicators. Then utilizing the documents tab, the Highly Cited Papers for each journal were examined. Data extracted were as follows, for articles with one field listed under the Research Fields for each of the Highly Cited Papers, the type of field was recorded. Articles with more than one research fields were listed as VARIOUS. If the journal for an index article had no results when selecting the documents tab, NODOC was recorded. If the journal was not found on InCites, then NOESI was listed as field of study. Publications in research fields not directly related to biomedical research (Chemistry, Physics, Computer Science, Economics & Business, Engineering, Geosciences, Material Science, Mathematics, Physics, and Space Science) were further excluded from analysis. For this sample, a total of 52 articles were excluded due to field of study (Table 3).

Based on the initial article characteristic classification, publications with data and analyses (classification categories 4-7, Table A), will be assessed for publically available full protocols and datasets, conflict of interests, and patterns of reproducibility. For the items that do not include data and analyses, categories 1-3, only statements of conflict will be investigated, since protocols, datasets, and reproducibility are not relevant.

1. To assess the proportion of publications that have publically available protocols, the methods sections will be reviewed for direct protocol listing or reference to the source for available protocol. For the studies that have publically available protocols, a report will be made on whether or not the available protocols cover all or part of the presented analyses. Data extracted: 0=no protocols, 1=partial coverage, 2=full coverage
2. To identify the proportion of publications that have publically available datasets, chosen manuscripts will be examined for access to the datasets that stand behind the analyses presented in the paper. If so, it will also be recorded whether the available datasets cover all or part of the presented analyses. Data extracted: 0=no datasets, 1=partial coverage, 2=full coverage
3. To identify reported conflict of interests, the proportion of publications that state that none of the authors have any conflicts of interest, as attested by declaration statements and checked by reviewers, will be

identified. Each article will be noted whether it includes a statement on conflict of interest disclosures or not; and, if yes, whether any conflicts of interest are disclosed. Data extracted: 0=no statement, 1=statement exists, conflicts present, 2=statement exists, no conflicts

4. To determine reproducibility patterns, the proportion of publications whose findings have been replicated will be measured. Web of Knowledge (v 5.14) will be utilized to identify the number of citations to each of the index papers of interest as of mid-2014. Furthermore, the citing papers of each index paper will be examined to identify systematic reviews and/or meta-analyses and/or studies that claim to try to replicate findings from the index paper. The citing papers will be screened at the title level, and those that seem potentially relevant will also be screened at the abstract and possibly full-text level. Eligible citing papers that are systematic reviews and/or meta-analyses and/or replications will be downloaded in full text starting with the one that is published earlier.

1. To measure research originality, abstracts from papers that include data and analyses (classification categories 4-7, Table A) will be examined for clear statements for study novelty or replication.

Data extracted D1: 0=based on the abstract and/or introduction, the index paper claims that it presents some novel findings, 1=based on its abstract, the

index paper clearly claims that it is a replication effort trying to validate previous knowledge, 1.5=unclear statement in the abstract, but based on its introduction, it is inferred that the index paper is a replication trying to validate previous knowledge, 2=based on the abstract and/or introduction, it claims to be both novel and replicate previous findings, 3=no statement or unclear statement in the abstract and/or introduction about whether the index paper presents a novel finding or replication, 4=no abstract and introduction

2. Randomized clinical trials and other empirical data publications (classification categories 4 and 7, Table A) will further be assessed for articles citing the sample publication in an English language systematic reviews and/or meta-analysis (variable D2) and for articles replicating the sample publication (variable D3).

Data extracted D2: 0=no systematic review and/or meta-analysis has ever cited the index paper, 1=at least one systematic review and/or meta-analysis has cited the index paper but none has included any of its data in quantitative syntheses for any outcome, 1.5 = at least one systematic review and/or meta-analysis

has cited the index paper but has provided reasons for not including any of its data for quantitative syntheses for any outcome, 2=at least one systematic review and/or meta-analysis has cited the index paper and has included some of its data in quantitative synthesis for at least one outcome.

For studies with more than one type of systematic review and/or meta-analysis, combinations of the three possible categories (1, 2, 1.5) will be extracted.

Data extracted D3: 0=no citing article identified claiming to be a replication attempt of the index paper, 1=at least one citing article identified claiming to be a replication attempt of the index paper.

Detailed results of the systematic reviews, meta-analyses, and replication studies will not be focused upon, since this sample is expected to be underpowered and inefficient to detect whether specific results are indeed replicated or not. This study will focus simply on whether replication and integration in systematic reviews/meta-analyses of multiple studies has been considered and

performed or not. Moreover, it is anticipated that the majority of index papers will not have truly new discoveries, but may be operating in a knowledge space where other past studies may also have operated. Studies will be considered novel if the abstract and/or introduction a) claim to investigate new hypotheses, b) claim to develop and test new methods, c) claim to be the first to investigate something that has not been examined before, or d) include any statement about new insights. For index papers, the aim is not to decipher which of these index studies are indeed proposing entirely new discoveries, or making claims for some novel findings without these actually being novel.

Objective2: Create multivariate models that utilize study characteristics for predictors of whether a publication will have adequate information on transparency and reproducibility aspects.

Methodology Overview: Predictor variables will include the year of publication, human study (yes/no), animal study (yes/no), clinical trial (yes/no), mention of genes or genotype at the abstract level (yes/no), country of corresponding author (USA, Europe, other), 2013 InCites journal impact factor (including journal self cites), and availability of free access in PubMed Central based on assignment of a PCMID (yes/no). Study and individual researcher funding will also be assessed (0=no

mention, 1=no funding, 2=public, 3=private industry, 4=other, 5=combination of 2&3; 6=combination of 2&4; 7=combination of 3&4, 8=combination of 2-4). All of the studies with public funding were then examined to determine whether they had NIH(or any of the 27 separate NIH institutes or centers) funding (1=yes, 0=no), NSF funding (1=yes, 0=no), or Other public funding (1=yes, 0=no) Individual investigator funding will be excluded from this assessment if listed under possible conflicts of interest. Field of study will also be determined for each article utilizing InCites Essential Science Indicators as described in Objective 1 methodology.

Tables

Table 1: Random Sampling of 750 PMID numbers between 10-25 million

1. 17221499	151. 13391880	301. 10495830	451. 22655006	601. 21116942
2. 17467223	152. 15794343	302. 10899442	452. 11887089	602. 19114960
3. 22349201	153. 13623619	303. 21852490	453. 24328800	603. 16463060
4. 20566118	154. 24509220	304. 19051334	454. 13869388	604. 24307012
5. 22402381	155. 21777870	305. 24629269	455. 21151244	605. 24625699
6. 10755285	156. 24697300	306. 18452984	456. 15908535	606. 21145441
7. 19762479	157. 19364123	307. 23669047	457. 22173573	607. 18375142
8. 12140369	158. 23132104	308. 18917072	458. 22432794	608. 11716869
9. 17155884	159. 24188923	309. 17314962	459. 21827945	609. 13179795
10. 12905220	160. 24848787	310. 24582048	460. 12353298	610. 11315136
11. 11570872	161. 15420017	311. 11443035	461. 17170461	611. 24156623
12. 15852141	162. 12962197	312. 11258324	462. 21011460	612. 14479408
13. 10332964	163. 16791592	313. 15500907	463. 20688609	613. 16504851
14. 23048646	164. 20386259	314. 18756556	464. 17142822	614. 11324818
15. 16014249	165. 20196510	315. 22730448	465. 21950181	615. 15580405
16. 10788232	166. 11439346	316. 18538496	466. 11238717	616. 18739472
17. 14345855	167. 12797390	317. 20237113	467. 18154596	617. 16501348
18. 11035971	168. 16156622	318. 23588459	468. 23944022	618. 17257304
19. 20569066	169. 20396033	319. 13645566	469. 21725778	619. 21004937
20. 11207185	170. 10370148	320. 16850500	470. 14948903	620. 11914670
21. 15420359	171. 14374101	321. 24523190	471. 19446026	621. 22060480
22. 15836815	172. 15353349	322. 24045672	472. 22675040	622. 22970304
23. 22996984	173. 11784342	323. 12550227	473. 21575746	623. 16500254
24. 23834563	174. 13623500	324. 15699395	474. 18736495	624. 24387237
25. 11668675	175. 10673754	325. 11421246	475. 21555541	625. 16481151
26. 20079366	176. 18151469	326. 23169152	476. 20159571	626. 19439710
27. 15003652	177. 15613125	327. 18900919	477. 24880519	627. 22561928
28. 15274701	178. 19741212	328. 23884430	478. 24743622	628. 18303555
29. 17906692	179. 11519166	329. 14239947	479. 14732097	629. 24373224
30. 10747129	180. 16350274	330. 10566157	480. 10605859	630. 11918964
31. 13708517	181. 19577987	331. 10665622	481. 12479497	631. 11922580
32. 20950261	182. 20843821	332. 16413074	482. 14098542	632. 20729984
33. 12035268	183. 13632085	333. 21411802	483. 14767578	633. 18037441
34. 13388210	184. 24080467	334. 12619433	484. 19813929	634. 21804977
35. 10806516	185. 13294531	335. 21139778	485. 12734514	635. 13861569
36. 17591881	186. 14561913	336. 23193508	486. 16251691	636. 15714066
37. 15316506	187. 12972505	337. 12532543	487. 11893586	637. 20258683
38. 18625144	188. 23569200	338. 14931715	488. 18047023	638. 22931120
39. 23359937	189. 13273257	339. 21963068	489. 11731360	639. 23494105

40. 22778772	190. 21684540	340. 21260701	490. 10752330	640. 10273412
41. 11353767	191. 24230843	341. 11720610	491. 22642145	641. 14969306
42. 20633936	192. 19355891	342. 24422544	492. 20147811	642. 15247411
43. 19189154	193. 12841824	343. 20469608	493. 11239814	643. 13198290
44. 15378498	194. 23930656	344. 17302485	494. 17005538	644. 13003837
45. 13984122	195. 17949899	345. 12502615	495. 16114396	645. 22307414
46. 22744898	196. 13287034	346. 20446052	496. 19627661	646. 18862864
47. 15341661	197. 15590859	347. 24601975	497. 15776026	647. 20719603
48. 17541669	198. 15823379	348. 24609705	498. 15034836	648. 19710198
49. 14436100	199. 20157910	349. 21285628	499. 12991433	649. 11923688
50. 13389745	200. 21819248	350. 22545948	500. 21508095	650. 19008705
51. 22856313	201. 17513835	351. 11615282	501. 12300585	651. 15255597
52. 18304443	202. 19746724	352. 15911863	502. 15522845	652. 12445353
53. 19930443	203. 15762649	353. 15099778	503. 14282890	653. 20733120
54. 23920060	204. 12872323	354. 21889689	504. 15839897	654. 14536278
55. 13518638	205. 18563731	355. 12644405	505. 12127510	655. 10525554
56. 20239860	206. 24213899	356. 17073634	506. 24624290	656. 24264977
57. 17774525	207. 14869533	357. 13288776	507. 10012931	657. 22304654
58. 22525923	208. 17373341	358. 13274043	508. 12534561	658. 19702778
59. 21168184	209. 20143627	359. 11007203	509. 22590901	659. 14025115
60. 15346464	210. 17393762	360. 19665358	510. 23413181	660. 16748035
61. 12974476	211. 16376652	361. 12443277	511. 20182785	661. 19032132
62. 19885199	212. 12949370	362. 22036530	512. 16988585	662. 22488610
63. 10936361	213. 13698455	363. 17215498	513. 22572629	663. 12208796
64. 20390172	214. 15097753	364. 23369776	514. 21405595	664. 19019474
65. 18134351	215. 14580252	365. 18929787	515. 11492834	665. 15839136
66. 12415524	216. 11756495	366. 18784538	516. 21504058	666. 19500286
67. 15351035	217. 12038089	367. 14286955	517. 12652399	667. 16051745
68. 20424863	218. 23786186	368. 11053721	518. 24187687	668. 22445326
69. 23529422	219. 15259403	369. 22204470	519. 22176668	669. 10219235
70. 21992636	220. 17139556	370. 11262088	520. 21720135	670. 11959368
71. 10797007	221. 12074782	371. 11099892	521. 10242406	671. 14025309
72. 11116889	222. 15262923	372. 16552123	522. 11022739	672. 16089518
73. 22914732	223. 15820264	373. 12919547	523. 16699766	673. 10213525
74. 20450536	224. 20470882	374. 16445269	524. 15793201	674. 11961616
75. 22624652	225. 11030722	375. 14545945	525. 10619634	675. 14000601
76. 19080039	226. 21306373	376. 19789670	526. 12341484	676. 20134924
77. 19223875	227. 21740615	377. 24834474	527. 12843471	677. 12973082
78. 17590930	228. 16662793	378. 15841663	528. 18894041	678. 19342235
79. 15534605	229. 24936990	379. 16210130	529. 17004526	679. 15721238
80. 20086276	230. 22638695	380. 22155803	530. 11901867	680. 21334298
81. 13007787	231. 14042300	381. 13124627	531. 23880939	681. 13565813
82. 10041757	232. 12488208	382. 24508130	532. 22098088	682. 12747949

83. 19218230	233. 10016385	383. 10557870	533. 21338070	683. 21345132
84. 19882067	234. 17499754	384. 19607044	534. 23714371	684. 19929994
85. 11126131	235. 15089009	385. 20814100	535. 20292056	685. 21345133
86. 18701402	236. 11363099	386. 23393528	536. 14339400	686. 20910396
87. 19880938	237. 14967987	387. 11062883	537. 10418134	687. 20631536
88. 24485116	238. 23245650	388. 22251977	538. 21787166	688. 15872224
89. 20349343	239. 20573849	389. 11201420	539. 12524609	689. 12090368
90. 20901025	240. 18839516	390. 19434720	540. 18258861	690. 15769648
91. 16964615	241. 22078487	391. 20388435	541. 12119800	691. 13798751
92. 15711980	242. 23951529	392. 18100492	542. 15639101	692. 12576555
93. 14010476	243. 22463266	393. 23551804	543. 12314829	693. 13214108
94. 23798245	244. 17890680	394. 13797247	544. 21311092	694. 13227543
95. 20286732	245. 17394056	395. 23977311	545. 23637984	695. 12083064
96. 23615987	246. 20897189	396. 18521688	546. 16697924	696. 19317902
97. 21942227	247. 13279492	397. 12556780	547. 22334939	697. 21388740
98. 24947539	248. 13152648	398. 24924783	548. 21839589	698. 15893508
99. 22166884	249. 13452510	399. 20596287	549. 20258168	699. 12861225
100. 11947480	250. 18752476	400. 18484917	550. 12475314	700. 15897045
101. 10024412	251. 16391363	401. 21511401	551. 22560018	701. 12076871
102. 13800493	252. 12473404	402. 24306712	552. 14120361	702. 11611086
103. 24859500	253. 20688003	403. 11095370	553. 24243477	703. 15904649
104. 17518445	254. 19690666	404. 16709823	554. 17125842	704. 22127457
105. 12821058	255. 12633474	405. 16966231	555. 14744095	705. 14350792
106. 13716614	256. 21453382	406. 14608100	556. 13466919	706. 14039788
107. 13827809	257. 24223392	407. 24890534	557. 24778596	707. 21098937
108. 16006233	258. 22041029	408. 18425350	558. 11241058	708. 19177880
109. 24941466	259. 10137351	409. 13962290	559. 13499113	709. 21395605
110. 17107901	260. 17337370	410. 18413068	560. 24120809	710. 13459374
111. 15240255	261. 14278780	411. 15171622	561. 23518874	711. 12866940
112. 12325011	262. 16714398	412. 20317107	562. 15430181	712. 12015495
113. 15744710	263. 24447322	413. 22183776	563. 11654612	713. 10028717
114. 17994599	264. 16564837	414. 11706932	564. 17214376	714. 20951698
115. 21381345	265. 13597083	415. 24343247	565. 23510502	715. 21354130
116. 10298218	266. 12455123	416. 18115639	566. 12066058	716. 12010930
117. 12641861	267. 10387752	417. 24000752	567. 24875287	717. 19502191
118. 11801543	268. 18541463	418. 12660203	568. 15129540	718. 17908083
119. 16537947	269. 11732882	419. 11907511	569. 22601902	719. 22126415
120. 11591566	270. 23139447	420. 21013892	570. 19115167	720. 16025326
121. 23370674	271. 10062653	421. 14709978	571. 15133172	721. 24075804
122. 14943529	272. 21152650	422. 19613608	572. 10283992	722. 15551653
123. 17475505	273. 15656611	423. 14745864	573. 21629745	723. 17758986
124. 18050965	274. 11679892	424. 16838146	574. 10673897	724. 17585649
125. 24664042	275. 22224476	425. 22996987	575. 11730444	725. 20344636

126. 12984467	276. 23918719	426. 14069977	576. 22141682	726. 19174516
127. 20629267	277. 16216925	427. 21549194	577. 18401690	727. 20614107
128. 14291052	278. 15425272	428. 22736545	578. 19611987	728. 10273369
129. 11927861	279. 12319418	429. 20093909	579. 15496969	729. 20953679
130. 13541851	280. 19429392	430. 20094080	580. 13315932	730. 24554181
131. 12781759	281. 21103071	431. 21577214	581. 11307834	731. 20922103
132. 19848053	282. 11963753	432. 18285063	582. 16685302	732. 22130044
133. 10912709	283. 15755103	433. 12053929	583. 22045399	733. 12005548
134. 15240386	284. 13032668	434. 10603127	584. 20971890	734. 15623168
135. 11158473	285. 18440207	435. 16449812	585. 18114016	735. 11968902
136. 14662594	286. 11856509	436. 22850023	586. 23393680	736. 24312511
137. 19834284	287. 17336812	437. 13141094	587. 13822251	737. 24197879
138. 15816788	288. 22545142	438. 16864888	588. 10241404	738. 12550665
139. 22184384	289. 10987165	439. 15766984	589. 11309466	739. 24224134
140. 18187080	290. 21960570	440. 22718035	590. 19249517	740. 13932365
141. 14198753	291. 22838749	441. 21075107	591. 16517111	741. 10058109
142. 12972256	292. 21307395	442. 17236083	592. 23449402	742. 20419484
143. 13630294	293. 23763414	443. 15191577	593. 10491560	743. 22562973
144. 22756720	294. 17318980	444. 15310796	594. 11639812	744. 24286993
145. 19924957	295. 18790507	445. 12570214	595. 10125878	745. 16966440
146. 23267827	296. 21440001	446. 16460580	596. 18098489	746. 10755151
147. 11784578	297. 13235647	447. 22430022	597. 24260308	747. 17845991
148. 15042988	298. 23448701	448. 10291915	598. 14005621	748. 15968961
149. 22937664	299. 10072238	449. 24030913	599. 12266381	749. 23885219
150. 11345261	300. 19858589	450. 17002004	600. 16504852	750. 17697393

Table 2: Sampling of 500 PMID numbers for English articles published between 2000-2014 with PMID numbers between 10-25 million

10665622	12949370	16850500	20086276	22545142
10673754	12962197	16864888	20093909	22545948
10747129	12972256	16964615	20094080	22560018
10755285	12972505	16966231	20147811	22561928
10797007	12973082	16988585	20157910	22572629
10899442	12974476	17002004	20159571	22590901
10912709	14561913	17004526	20182785	22624652
10936361	14580252	17005538	20237113	22638695
10987165	14608100	17073634	20349343	22642145
11007203	14662594	17107901	20386259	22655006
11030722	14709978	17125842	20390172	22675040
11035971	14744095	17139556	20424863	22718035
11053721	14745864	17142822	20469608	22730448
11062883	14767578	17155884	20470882	22736545
11095370	14967987	17170461	20566118	22744898
11099892	15003652	17214376	20569066	22778772
11126131	15034836	17215498	20573849	22856313
11158473	15089009	17302485	20596287	22914732
11201420	15099778	17314962	20614107	22931120
11207185	15129540	17318980	20631536	22970304
11238717	15133172	17336812	20633936	22996984
11239814	15171622	17337370	20688609	22996987
11241058	15191577	17373341	20729984	23132104
11262088	15240255	17393762	20733120	23139447
11307834	15240386	17394056	20814100	23169152
11309466	15247411	17467223	20843821	23193508
11315136	15255597	17475505	20922103	23245650
11324818	15259403	17499754	20950261	23267827
11345261	15262923	17513835	20951698	23359937
11353767	15274701	17518445	20953679	23369776
11421246	15310796	17541669	20971890	23370674
11439346	15316506	17591881	21075107	23393528
11443035	15341661	17890680	21098937	23393680
11570872	15351035	17906692	21103071	23448701
11591566	15353349	17949899	21116942	23449402
11668675	15378498	17994599	21139778	23494105
11706932	15496969	18037441	21145441	23510502
11716869	15500907	18047023	21152650	23518874
11730444	15522845	18154596	21168184	23529422
11731360	15534605	18187080	21306373	23551804

11732882	15551653	18258861	21311092	23588459
11756495	15580405	18303555	21334298	23615987
11784342	15590859	18375142	21338070	23637984
11784578	15613125	18401690	21345132	23669047
11801543	15623168	18413068	21345133	23714371
11887089	15639101	18425350	21354130	23763414
11893586	15656611	18440207	21388740	23786186
11907511	15699395	18452984	21395605	23798245
11914670	15711980	18484917	21405595	23834563
11918964	15714066	18521688	21411802	23880939
11922580	15721238	18538496	21440001	23884430
11923688	15744710	18541463	21453382	23918719
11927861	15755103	18563731	21504058	23920060
11959368	15762649	18625144	21508095	23930656
11961616	15766984	18701402	21511401	23951529
11968902	15769648	18752476	21549194	23977311
12005548	15793201	18756556	21555541	24000752
12010930	15794343	18784538	21575746	24045672
12015495	15816788	18790507	21577214	24075804
12035268	15820264	18929787	21629745	24080467
12038089	15823379	19008705	21684540	24120809
12053929	15836815	19019474	21725778	24156623
12066058	15839136	19032132	21740615	24187687
12074782	15839897	19051334	21777870	24188923
12076871	15841663	19080039	21787166	24197879
12083064	15852141	19114960	21804977	24223392
12090368	15872224	19115167	21819248	24260308
12119800	15893508	19174516	21827945	24264977
12127510	15897045	19177880	21839589	24306712
12140369	15904649	19218230	21852490	24312511
12208796	15908535	19249517	21889689	24328800
12325011	15911863	19317902	21960570	24343247
12353298	16006233	19342235	21963068	24373224
12415524	16025326	19355891	21992636	24387237
12443277	16051745	19364123	22036530	24422544
12445353	16089518	19429392	22041029	24447322
12473404	16156622	19434720	22045399	24485116
12475314	16210130	19439710	22060480	24508130
12479497	16216925	19446026	22078487	24509220
12488208	16350274	19500286	22098088	24523190
12502615	16376652	19502191	22125952	24582048
12524609	16391363	19577987	22126415	24601975
12534561	16413074	19627661	22127457	24609705

12556780	16445269	19665358	22130044	24624290
12570214	16449812	19690666	22155803	24625699
12576555	16460580	19710198	22173573	24629269
12619433	16463060	19741212	22176668	24664042
12633474	16481151	19746724	22183776	24697300
12641861	16500254	19762479	22184384	24743622
12644405	16501348	19789670	22224476	24778596
12660203	16504851	19834284	22304654	24834474
12734514	16504852	19848053	22334939	24848787
12747949	16517111	19858589	22349201	24859500
12781759	16537947	19880938	22402381	24875287
12797390	16685302	19882067	22430022	24880519
12821058	16697924	19885199	22432794	24890534
12841824	16699766	19924957	22445326	24924783
12861225	16709823	19929994	22463266	24936990
12866940	16714398	19930443	22488610	24941466
12872323	16791592	20079366	22525923	24947539

Table 3. Articles, by PMID, Excluded from Data Analysis Based on Field of Study.

11062883	16350274	20614107	22655006
11262088	17005538	20729984	22931120
11345261	17302485	20814100	23267827
12127510	17499754	21098937	23448701
12443277	17541669	21152650	23510502
12475314	17994599	21311092	23930656
12633474	18541463	21338070	24080467
15171622	18701402	21405595	24188923
15656611	18756556	21504058	24422544
15755103	19364123	22060480	24508130
15852141	20094080	22098088	24664042
16089518	20390172	22463266	24697300
16156622	20596287	22561928	24875287

Supplemental Figures:

Number	Description
1	No research (items with no data such as editorials, commentaries, news, comments and non-systematic expert reviews)
2	Models/modeling or software or script or methods without empirical data (other than simulations)
3	Case report or series (humans only, with or without review of the literature)
4	Randomized clinical trials (humans only)
5	Systematic reviews and/or meta-analyses (humans only)
6	Cost effectiveness or decision analysis (humans only)
7	Other (empirical data that includes uncontrolled study (human), controlled non-randomized study (human) or basic science studies)

Table A: Sample articles were categorized into 7 different categories based on article characteristics.

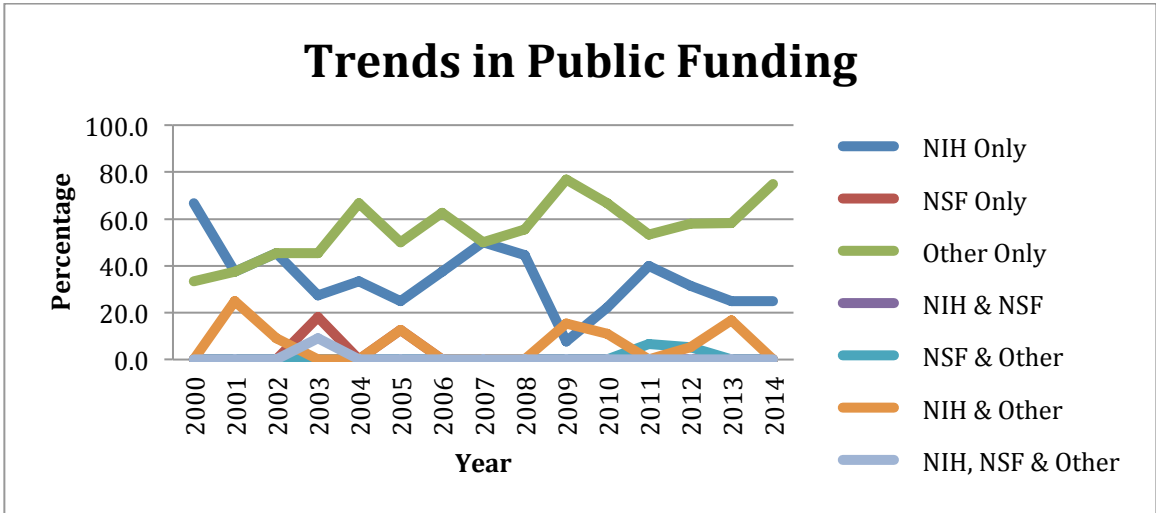


Figure 1S.

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