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Reproducibility and transparency characteristics of oncology research evidence

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Title: Reproducibility and transparency characteristics of oncology research evidence

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Abstract

Objectives: As much as 50%-90% of research is estimated to be irreproducible, costing upwards of $28 billion in the United States alone. Reproducible research practices are essential to improving the reproducibility and transparency of biomedical research, such as including pre-registering studies, publishing a protocol, making research data and metadata publicly available, and publishing in open access journals. Here we report an investigation of key reproducible or transparent research practices in the published oncology literature.

Design: We performed a cross-sectional analysis of a random sample of 300 oncology studies published from 2014-2018. We extracted key reproducibility and transparency characteristics in a duplicative fashion by blinded investigators using a pilot tested Google Form.

Setting: N/A

Participants: N/A

Primary Outcome Measures: The primary outcome of this investigation is the frequency of key reproducible or transparent research practices followed in published biomedical and clinical oncology literature.

Results: Of the 300 studies randomly sampled, 296 studies were analyzed for study reproducibility characteristics. Of these 296 studies, 194 were contained empirical data that could be analyzed for reproducible and transparent research practices. Raw data was available for 9 studies (4.6%). Approximately 5 studies (2.6%) provided a protocol. Despite our sample including 15 clinical trials and 7 systematic reviews/meta-analyses, only 7 included a pre-registration statement. Less than 25% (65/194) of studies provided an author conflict of interest statement.

Conclusion: We found that key reproducibility and transparency characteristics were absent from a random sample of published oncology studies. We recommend required pre-registration for all eligible trials and systematic reviews, published protocols for all manuscripts, and deposition of raw data and metadata in public repositories.

Article Summary:

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- This investigation is an observational study using a cross sectional design based on a study examining reproducibility characteristics of social science publications with modifications.
- We extracted key reproducibility and transparency characteristics from a random sample of 300 biomedical and clinical oncology publications.
- The key reproducibility and transparency indicators extracted from each publication included: availability, raw data availability, analysis scripts, linkable protocol, trial pre-registration statements, author conflict of interest statement, funding source, and open access
- Publications were examined to verify if they had been replicated in other works or were included in future systematic reviews or meta-analyses.

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Introduction

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The ability to reproduce, or replicate, research results is a cornerstone of scientific advancement[1,2]. Absent efforts to advance the reproducibility of scientific research, advancements in patient care and outcomes may be delayed[3,4], in part due to a failure in the translation of evidence to practice[5]. Evidence may fail translation to practice owing to bias[6,7], lack of publication[4], or poor reporting[8]. Thus, it may not be surprising that recent estimates of irreproducible research span a range of 50%-90% of all articles, costing upwards of $28 billion in the United States alone[9]. Moreover, it may not be surprising that large-scale efforts to replicate (ie, re-enact or reconduct previously published research studies) have failed[10], in part due to an inability to navigate published methods. What is lost when scientific research fails to be reproducible carries significant weight; namely, the ability of science to be self-correcting[11] and produce trustworthy results[12].

It is commonly accepted that certain items are essential to improving the reproducibility of biomedical research. Examples of such items include pre-registering studies, publishing a protocol, making research data and metadata publicly available, and publishing in such a way to allow free access to the final manuscript. Pre-registering a study and publishing a protocol are important to prevent selective publication of studies with "positive" results[13] and preventing the reordering of endpoints based on statistical significance[14,15]. Providing access to one's raw research data, metadata, and analysis script allows independent researchers to computationally reproduce results, tailor results to specific patient populations, and determine the rigor of statistical analysis[16,17]. Publishing in open access journals or using preprint servers allows readers across economically diverse countries to access research articles that have implications for clinical practice[18]. Altogether, reproducible research practices aim to increase the efficiency, usefulness, and rigor of published research[5].

Despite a high rate of author endorsement of reproducible practices[19,20], some evidence suggests that authors infrequently implement them[21]. Absent such reproducible research practices, attempts to validate study findings may be thwarted. For example, Bayer and Amgen both attempted to replicate oncology research studies, with each failing to do so[22,23]. Bayer's attempt to reproduce prior research studies is especially significant because they attempted to reproduce internal studies. Other non-pharmaceutical entities have attempted to replicate cancer research studies with similar results[24]. One may hypothesize that improved use and reporting of key reproducible or transparent research practices would improve future efforts to reproduce oncology research studies and build trust in existing evidence. Building on recent, similar analyses[25–27], here we report an investigation of key reproducible or transparent research practices in the published oncology literature.

Methods

We performed an observational study using a cross sectional design based on methods developed by Hardwicke et. al.[25] with modifications. Our study employed best-practice design in accordance with published guidance, where relevant[28,29]. Study protocol, raw data, and other pertinent materials are available on the Open Science Framework (https://osf.io/x24n3/). This study did not meet U.S. regulation requirements to be classified as human research, therefore it is exempt from Institutional Review Board approval[30].

Journal Selection

We used the National Library of Medicine (NLM) catalog to search for all oncology journals using the subject terms tag Neoplasms[ST]. This search was performed on May, 29, 2019 which identified 344 journals. The inclusion criteria required that journals were both in "English" and "MEDLINE indexed". We extracted electronic ISSN (or linking if electronic was unavailable)for each journal to use in a PubMed search on May 31, 2019. The total list of publications was then limited to those from January 1, 2014 to December 31, 2018.From search returns, we selected a random sample of 300 publications using Excel's random number function (https://osf.io/wpev7/).

Data Extraction

We used a pilot-tested Google Form based on the one provided by Hardwicke et. al. [25] with modifications (https://osf.io/3nfa5/). The first modifications were extracting the 5-year impact factor and the date of the most recent impact factor, neither of which were extracted by Hardwicke, et. al. Second, additional study designs were added to include cohort, case series, secondary analyses, chart reviews, and cross-sectional studies. Third, funding options were expanded that allowed for greater specification of university, hospital, public, private/industry, or non-profit sources.

The Google Form contained questions for investigators aimed at identifying whether a study demonstrated the information necessary to be reproducible (Table 1, Supplement 1). Variations in study design changed the data that was extracted from each study. For example, studies with no empirical data (e.g. editorials, commentaries [without reanalysis], simulations, news, reviews, and poems) were unable to examined for reproducibility characteristics. However, for all publications, the following data were extracted: title of study, 5 year impact factor, impact factor of the most recent year, country of corresponding author and publishing journal, type of study participants (eg, human or animal), study design, author conflicts of interest, funding source, and whether the article was open access (Table 2). Studies with empirical data were examined for the following characteristics in addition to those stated above: material and data availability, analysis scripts, linkable protocol, and trial pre-registration statements. Together, the 8 key reproducibility and transparency indicators analyzed were as follows: material availability, raw data availability, analysis scripts, linkable protocol, trial pre-registration statements, author conflict of interest statement, funding source, and open access. Open access was determined using www.openaccessbutton.org. In the event a study could not be found, investigators performed a Google search to see if the study was available elsewhere. Web of Science was used to evaluate whether each examined publication 1) had been replicated in other works and 2) was included in future systematic reviews or meta-analyses.

Prior to data extraction, each investigator underwent a full day of training to increase the interrater reliability of the results between authors. This training consisted of an in-person session that reviewed study design, protocol, and Google Form. Investigators (C.G.W., N.V.) extracted data from 3 sample articles and differences were reconciled following extraction. A recording of this training session is available and listed online for reference (https://osf.io/tf7nw/). One investigator (C.G.W.) extracted data from all 300 publications. Z.J.H. extracted data for 200 publications and N.V. extracted data for 100 publications. C.G.W.'s data were compared to Z.J.H.'s and N.V.'s with discrepancies being resolved via group discussion.

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All authors were blinded to each other's results. A final consensus meeting was held by all authors to resolve disagreements. If no agreement could be made, final judgment was made by an additional author (D.T.). Our manuscript has been made available as a preprint, online at www.medRxiv.org (https://doi.org/10.1101/19001917).

Statistical Analysis
Descriptive statistics were calculated for each category using Microsoft Excel with 95% confidence intervals.

Results

The NLM search identified 344 journals but only 204 fit our inclusion criteria. Our initial search string retrieved 199,420 oncology publications, from which, 300 were randomly sampled. Approximately 296 publications were analyzed for study reproducibility characteristics; 4 studies were not accessible, thus they were excluded from our analysis. Of these 296 publications, 215 contained empirical data and 81 did not. Publications without empirical data were unable to be analyzed for study reproducibility characteristics. Additionally, 21 publications with empirical data were case studies or case series. These case studies and series are unable to be replicated, thus are excluded from the analysis of study characteristics. In total, we were able to extract study reproducibility characteristics for 194 oncology publications (Figure 1).

Study Characteristics
In our sample of oncology publications, the publishing journals had a median 5 year impact factor of 3.445 (IQR 2.27-5.95). The majority (156/296, 52.7%) of journals were located in the United States. Over half (165/296, 55.8%) of published studies were available for free via open access networks. The remaining 131 publications (44.2%) were located behind a paywall — making the studies inaccessible to the public — available only through paid reader access. Approximately 109 publications (36.8%) made no mention of funding source. Public funding (95/296, 32.1%), such as state or government institutions, comprised the next most prevalent source of study funding. Publication authors disclosed no conflict of interest more frequently than conflicts of interest (174/296, 58.8 vs. 57/296, 19.2%); however, 65 publications (22.0%) had no author conflict of interest statement. Human participants were the most common study population in sample (154/269, 52.0%). Citation rates of these 296 publications by systematic reviews and meta-analyses can be found in Table 2.

Reproducibility Characteristics
Only 21 publications (21/194, 10.8%) made their raw data available. Approximately 9 of these publications with available raw data were downloadable by readers, while the rest was available upon request from the corresponding author of the study. A complete description of study materials required to reproduce the study — laboratory instruments, stimuli, computer software — was provided in 6/194 studies (3.2%). Of those publications with available materials, most were only accessible to readers upon request to the corresponding author, rather than being listed in a protocol or methods section. None of the included studies made their analysis scripts accessible, which details the steps the authors used to prepare the data for interpretation. Only 5 (5/194, 2.6%) publications provided a protocol detailing the *a priori* study design, methods, and analysis plan. Seven publications (7/194, 3.6%) were pre-registered in trial databases, such as

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ClinicalTrials.gov, prior to commencement of the study, despite there being 15 clinical trials and 7 systematic reviews/meta-analyses included in our analysis. One publication (1/194, 0.05%) claimed to be a replication study; all remaining studies (193/194, 99.5%) claimed to be novel or did not provide a clear statement about being a replication study. A subgroup analysis of the 8 key reproducibility and transparency indicators demonstrated that 29 publications had 0 indicators, 62 publications had 1 indicator, 209 publications had 2 to 5 indicators, and 0 publications had 6 or more.

Discussion

Our cross-sectional investigation of a sample of the published oncology literature found that key reproducibility and transparency practices were lacking or entirely absent. Namely, we found that publications rarely pre-registered their methods, published their full protocol, or deposited raw data and analysis scripts into a publicly-accessible repository. Moreover, conflicts of interest were not discussed approximately 20% of the time and just over half of the included studies were not accessible due to journal paywalls. Given the challenges in understanding the molecular mechanisms that drive cancer, the continuum of research in the field of oncology is slow, laborious and inefficient[31]. To combat these inherent obstacles, transferring outcomes and information from preclinical to clinical research demands consistency and precision across the continuum. Otherwise, publications downstream in the cancer research continuum may be based on spurious results incapable of independent confirmation due to a lack of access to study data, protocols, or analysis scripts. Science advances more rapidly when people spend less time pursuing false leads[32], thus, for patients with cancer and for whom rapid scientific advancement is most significant, it is paramount that scientists, researchers and physicians advocate for an efficient research system that is transparent, reproducible, and free from bias.

Pre-registration of research study methods is a mechanism to improve the reproducibility of published results and prevent bias — either from selective reporting of outcomes or selective publication of a study[33]. Previously, it has been shown that the selective reporting of study endpoints affects the research portfolio of drugs or diseases[15,34,35]. For example, Wayant et. al found that 109 RCTs of malignant hematology interventions selectively reported their trial endpoints 118 times, with a significant portion doing so in a manner that highlighted statistically significant findings[34]. Were trial registries not available, these trials may have never been found to exhibit selective outcome reporting. Now, through trial registries, hematologists and other interested researchers are able to independently assess the robustness of not only study rationale and results, but also study rigor and reporting. The present study indicates that pre-registration of study methods was rare, even among trials and systematic reviews that have available registries. The importance of preregistration across the continuum of cancer research cannot be understated. For example, preclinical animal models serve as the foundation for clinical trials, but have exhibited suboptimal methods[36], which may explain why animal study results fail to successfully translate to clinical benefit. In fact, it was recently shown that many phase 3 trials in Oncology are conducted despite no significant phase 2 results[37]. One possible explanation for why phase 3 trials proceed despite nonsignificant phase 2 results is the strong bioplausibility demonstrated in preclinical studies. If it is true that preclinical studies exhibit poor research methods, it is not unlikely that they are affected by selective outcome reporting bias, just like clinical research

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studies. Thus, to strengthen oncology research evidence — from foundational, preclinical research to practice-changing trials — we recommend either the creation of relevant study registers or the adherence to existing registration policies. In so doing, one key aspect of research — the accurate reporting of planned study endpoints — could be monitored, detected, and mitigated.

Equally important to self-correcting, rigorous cancer research is the publication of protocols, raw data, and analysis scripts. Protocols include much more information than study outcomes — they may elaborate on statistical analysis plans or decisions fundamental to the critical appraisal of study results[38]. It is unlikely that anyone would be able to fully appraise a published study without access to a protocol, and far less likely that anyone would be capable of replicating the results independently. In fact, two recent efforts to reproduce preclinical studies revealed extant barriers to independent verification of published findings[20,39], including the absence of protocols, data, and analysis scripts. Our present investigation found that only 5 (2.6%) studies published a protocol, 9 (4.6%) fully published their data, and none published their analysis scripts. In the context of the recent failures to reproduce cancer research studies, one may reasonably conclude that our study corroborates the belief that oncology research is not immune to the same shortcomings that contribute to an ever-expanding cohort of irreproducible research findings[40]. Oncology research, like all biomedical research, is at an inflection point, wherein it may progress toward more transparent, reproducible, efficient research findings. However, in order to do so, the availability of protocols, data, and analysis scripts should be considered fundamental.

In summary, we found that key reproducibility and transparency characteristics were absent from a random sample of published oncology studies. The implication of this finding is a research system that is incapable of rapid self-correction, or a research system that places a stronger emphasis on what is reported rather than what is correct. We recommend three key action items which we believe benefit oncology research and all its stakeholders. First, require pre-registration for eligible trials and systematic reviews, since these study designs have existing registries available, and support the development of registries for preclinical studies. Second, understand that published reports are snapshots of a research study, and require protocols be published. Last, encourage a scientific culture that relies on data that is true and robust, rather than author reports of their data, by requiring the deposition of raw data, meta data, and analysis scripts in public repositories.

This study has several strengths and limitations. First, for strengths, we sampled 300 published oncology articles indexed in PubMed. In doing so we captured a diverse array of research designs in an even more diverse range of journals. As such, all oncology researchers can read our paper and glean useful information and enact changes to improve the reproducibility of new evidence. With respect to our limitations, our study is too broad to make absolute judgments about specific study designs. All signals that suggest irreproducible research practices from our study fall in line with prior data in other areas of medicine[25–27], but are nonetheless signals rather than answers. We suggest more narrow investigations of the reproducibility of specific study designs and suggest trials and animal studies be prioritized due to their potential influence (present or future) on patient care. Moreover, we do not suggest that irreproducible research findings are false; however, the trust in the results may be blunted. Further, replicating (ie, reconducting) a study is not necessary in all cases to assess the rigor of the results. If a protocol,

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statistical analysis plan, and raw data (including metadata) are available, one fundamental pillar of science would be reinforced: self-correction.

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Competing Interest: The authors have no conflicts of interest.

Author Contributions: DT and MV developed the protocol and conceptualized the study. CWalt, ZJH, CWay, NV, MW, JC, DT, and MV will conduct all literature searches. CWalt, ZJH, CWay, and NV will conduct all statistical analyses. CWalt and DT will manage all data, including the management of the OSF repository. CWalt, ZJH, CWay, NV, CWay, MW, JC, DT, and MV will participate in all writing. CWalt, ZJH, CWay, NV, CWay, MW, JC, DT, and MV are equally the guarantors of the study and the integrity of the data.

Material and Data Availability: All datasets, materials, and the protocol are available online at https://doi.org/10.1101/19001917.

Patient and Public Involvement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research

Word Count: 2668 words

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Legends:

Figure 1: PRISMA Diagram of Included Studies

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Table 1: Reproducibility Characteristics of Oncology Studies

Table 2: Characteristics of Oncology Studies

Supplementary Table 1: Additional Reproducibility Characteristics

Table 1: Reproducibility Characteristics of Oncology Studies			
Characteristics (N=194 studies)		**Variables**	
		N (%)	**95% CI**
Data Availability	Statement, some data are available	21 (10.8)	7.80-14.90
	Statement, data are not available	0	0
	No data availability statement	173 (89.2)	85.10-92.20
Material Availability	Statement, some materials are available	6 (3.2)	1.20-5.20
	Statement, materials are not available	0	0
	No materials availability statement	181 (96.8)	94.80-98.80
Protocol Available	Full Protocol	5 (2.6)	0.80-4.40
	No Protocol	189 (97.4)	95.60-99.20
Analysis Scripts	Statement, some analysis scripts are available	0	0

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	Statement, analysis scripts are not available	0	0
	No analysis script availability statement	194	1
Replication Studies	Novel study	193 (99.5)	98.70-100.30
	Replication	1 (0.05)	-0.30-1.30
Pre-registration	Statement, says was pre--registration	7 (3.6)	1.50-5.72
	Statement, was not pre--registration	0	0
	No - there is no pre--registration statement	187 (96.4)	94.28-98.50

Table 2: Characteristics of Oncology Studies

Characteristics (N=296 studies)		**Variables**	
		N (%)	**95% CI**
Test Subjects	Animals	25 (8.5)	5.30-11.60
	Humans	154 (52.0)	46.40-57.70
	Both	0	0
	Neither	117 (39.5)	34.00-45.10
Country of journal publication	US	156 (52.7)	47.05-58.35
	UK	71 (24.0)	19.15-28.82
	Greece	18 (6.1)	3.38-8.79

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	Netherlands	11 (3.7)	1.58-5.86
	Ireland	11 (3.7)	1.58-5.86
	South Korea	6 (2.0)	0.43-3.62
	India	4 (1.4)	0.44-2.66
	Italy	2 (0.7)	-0.25-1.60
	Japan	2 (0.7)	-0.25-1.60
	Germany	1 (0.3)	-0.32-0.99
	Unclear	9 (3.0)	1.97-4.98
	Other	5 (1.7)	0.23-3.15
Country of corresponding author	US	87 (29.4)	24.24-34.55
	China	52 (17.6)	13.26-21.87
	Japan	19 (6.4)	3.65-9.19
	Germany	16 (5.4)	2.85-7.96
	South Korea	13 (4.4)	2.07-6.71
	UK	12 (4.0)	1.82-6.29
	Italy	10 (3.4)	1.33-5.42
	Canada	7 (2.4)	0.65-4.08
	France	6 (2.0)	0.43-3.62
	India	6 (2.0)	1.33-5.42
	Unclear	8 (2.7)	0.87-4.54
	Other	60 (20.3)	15.72-24.82
Funding	University	32 (10.8)	7.30-14.30
	Hospital	8 (2.7)	0.90-4.50
	Public	95 (32.1)	26.80-37.40

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	Private/Industry	6 (2.0)	0.40-3.60
	Non-profit	7 (2.4)	0.60-4.10
	No statement listed	109 (36.8)	31.40-42.30
	No funding received	18 (6.1)	3.40-8.80
	Mixed	21 (7.1)	4.19-10.0
Conflict of Interest statement	Statement, one or more conflicts of interest	57 (19.2)	14.79-23.72
	Statement. no conflict of interest	174 (58.8)	53.21-64.35
	No conflict of interest statement	65 (22.0)	17.27-26.64
Open Access	Yes - found via Open Access Button	139 (47.0)	40.69-51.97
	Yes - found article via other means	26 (8.8)	5.48-11.85
	No Could only access through paywall	131 (44.2)	38.05-49.28
5 Year Impact Factor	Median	3.445	-
	1st quartile	2.2705	-
	3rd quartile	5.95	-
	Interquartile range	2.2705-5.95	-
Most Recent	2014	4 (1.4)	-

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Impact Factor Year	2015	0	-
	2016	4 (1.4)	-
	2017	271 (91.5)	-
	2018	1 (0.3)	-
	Not Found	16 (5.4)	-
Most Recent Impact Factor	Median	3.346	-
	1st quartile	2.37375	-
	3rd quartile	6.471	-
	Interquartile range	2.37375-6.471	-
Cited by Systematic Review N=296 (a)	No Citations	279 (94.3)	91.60-96.90
	A Single Citation	9 (3.0)	1.10-5.00
	One to Five Citations	8 (2.7)	0.90-4.50
	Greater than Five Citations	0	0
Cited by Meta-Analysis N=296 (b)	No Citations	274 (92.6)	89.60-95.50
	A Single Citation	13 (4.4)	2.10-6.70
	One to Five Citations	9 (3.0)	1.10-5.00
	Greater than Five Citations	0	0

Abbreviations: CI, Confidence Interval. a - Two studies were explicitly excluded from the systematic reviews that cited the original article. b - Three studies were explicitly excluded from the meta-analysis that cited the original article

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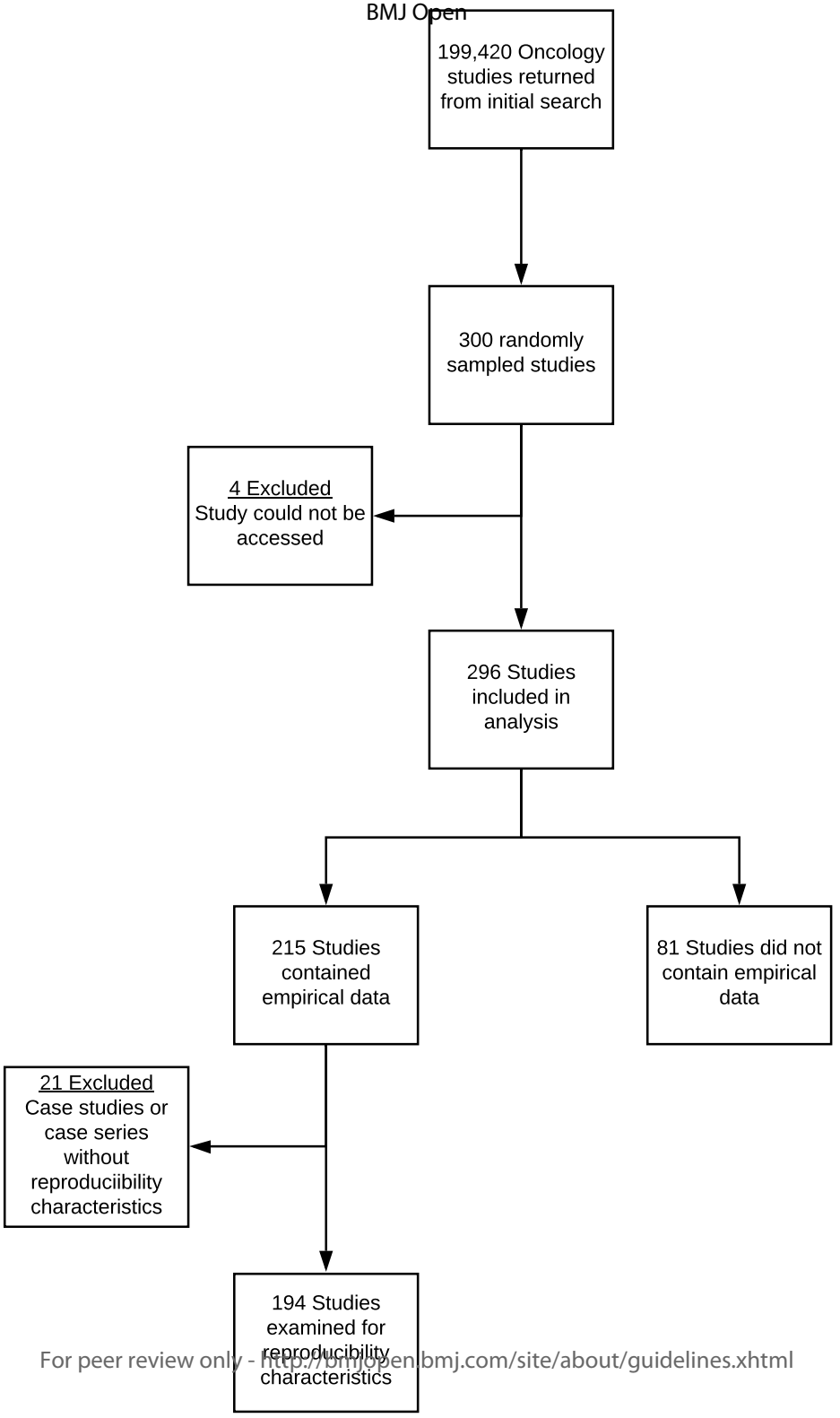

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Supplemental Table 1: Additional Reproducibility Characteristics[a]		
Characteristics		**Variables**
		No.
Type of Study N=296	No empirical	81
	Meta-analysis	7
	Observation	10
	Cross-Sectional	5
	Clinical Trial	15
	Case study	14
	Case Series	7
	Cohort	44
	Chart Review	7
	Case Control	8
	Survery	6
	Laboratory	79
	Multiple	9
	Other	4
Material availability	Personal or institutional	1
	Supplementary information hosted by the journal	1
	Online third party	0
	Upon Request	4

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	Yes, material was accessible	2
	No, material was not accessible	4
Data availability	Personal or institutional	1
	Supplementary information hosted by the journal	8
	Online third party	1
	Upon Request	10
	Yes, data could be accessed and downloaded	9
	No, data count not be accessed and downloaded	12
	Yes, data files were clearly documented	8
	No, data files were not clearly documented	1
	Yes, data files contain all raw data	3
	No, data files do not contain all raw data	4
	Unclear if all raw data was available	2

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Pre-registration	Pre-registered on ClinicalTrials.gov	6
	Yes, pre-registration was accessible	6
	No, pre-registration was not accessible	1
	Hypothesis was pre-registered	3
	Methods were pre-registered	6
	Analysis plan was pre-registered	1
Protocol	Hypotheses was included in the protocol	1
	Methods were included in the protocol	4
	Analysis plan was included in the protocol	2
a - additional analysis script characteristics were excluded because none were found in the analyzed journals		

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Do oncology researchers adhere to reproducible and transparent principles? : A cross-sectional survey of published oncology literature

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Manuscripts

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Title: Do oncology researchers adhere to reproducible and transparent principles? : A cross-sectional survey of published oncology literature

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Abstract

Objectives: As much as 50%-90% of research is estimated to be irreproducible, costing upwards of $28 billion in the United States alone. Reproducible research practices are essential to improving the reproducibility and transparency of biomedical research, such as including pre-registering studies, publishing a protocol, making research data and metadata publicly available, and publishing in open access journals. Here we report an investigation of key reproducible or transparent research practices in the published oncology literature.

Design: We performed a cross-sectional analysis of a random sample of 300 oncology publications published from 2014-2018. We extracted key reproducibility and transparency characteristics in a duplicative fashion by blinded investigators using a pilot tested Google Form.

Setting: N/A

Participants: N/A

Primary Outcome Measures: The primary outcome of this investigation is the frequency of key reproducible or transparent research practices followed in published biomedical and clinical oncology literature.

Results: Of the 300 publications randomly sampled, 296 were analyzed for reproducibility characteristics. Of these 296 publications, 194 were contained empirical data that could be analyzed for reproducible and transparent research practices. Raw data was available for 9 studies (4.6%). Five publications(2.6%) provided a protocol. Despite our sample including 15 clinical trials and 7 systematic reviews/meta-analyses, only 7 included a pre-registration statement. Less than 25% (65/194) of publications provided an author conflict of interest statement.

Conclusion: We found that key reproducibility and transparency characteristics were absent from a random sample of published oncology publications. We recommend required pre-registration for all eligible trials and systematic reviews, published protocols for all manuscripts, and deposition of raw data and metadata in public repositories.

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Strengths and Limitations:

- This investigation is an observational study using a cross sectional design based on a study examining reproducibility characteristics of social science publications with modifications.
- We extracted key reproducibility and transparency characteristics from a random sample of 300 biomedical and clinical oncology publications.
- The key reproducibility and transparency indicators extracted from each publication included: material availability, raw data availability, analysis scripts, accessible protocol, trial pre-registration statements, author conflict of interest statement, funding source, and open access
- Publications were examined to verify if they had been replicated in other works or were included in future systematic reviews or meta-analyses.
- The number of publications providing author conflict of interest statements was assessed.

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Introduction

The ability to reproduce, or replicate, research results is a cornerstone of scientific advancement[1,2]. Absent efforts to advance the reproducibility of scientific research, advancements in patient care and outcomes may be delayed[3,4], in part due to a failure in the translation of evidence to practice[5]. Evidence may fail translation to practice owing to bias[6,7], lack of publication[4], or poor reporting[8]. Thus, it may not be surprising that recent estimates of irreproducible research span a range of 50%-90% of all articles, costing upwards of $28 billion in the United States alone[9]. Moreover, it may not be surprising that large-scale efforts to replicate (ie, re-enact or reconduct previously published research studies) have failed[10], in part due to an inability to navigate published methods. What is lost when scientific research fails to be reproducible carries significant weight; namely, the ability of science to be self-correcting[11] and produce trustworthy results[12].

It is commonly accepted that certain items are essential to improving the reproducibility of biomedical research. Examples of such items include pre-registering studies, publishing a protocol, making research data and metadata publicly available, and publishing in such a way to allow free access to the final manuscript. Pre-registering a study and publishing a protocol are important to prevent selective publication of studies with "positive" results[13] and preventing the reordering of endpoints based on statistical significance[14,15]. Providing access to one's raw research data, metadata, and analysis script allows independent researchers to computationally reproduce results, tailor results to specific patient populations, and determine the rigor of statistical analysis[16,17]. Publishing in open access journals or using preprint servers allows readers across economically diverse countries to access research articles that have implications for clinical practice[18]. Altogether, reproducible research practices aim to increase the efficiency, usefulness, and rigor of published research[5].

Despite a high rate of author endorsement of reproducible practices[19,20], some evidence suggests that authors infrequently implement them[21]. Absent such reproducible research practices, attempts to validate study findings may be thwarted. For example, Bayer and Amgen both attempted to replicate oncology research studies, with each failing to do so[22,23]. Bayer's attempt to reproduce prior research studies is especially significant because they attempted to reproduce internal studies. Other non-pharmaceutical entities have attempted to replicate cancer research studies with similar results[24]. One may hypothesize that improved use and reporting of key reproducible or transparent research practices would improve future efforts to reproduce oncology research studies and build trust in existing evidence. Building on recent, similar analyses[25–27], here we report an investigation of key reproducible or transparent research practices in the published oncology literature as part of a larger initiative to examine reproducible and transparent research practices across medical specialties

Methods

We performed an observational study using a cross sectional design based on methods developed by Hardwicke et. al.[25] with modifications. Our study employed best-practice design in accordance with published guidance, where relevant[28,29]. Study protocol, raw data, and other pertinent materials are available on the Open Science Framework (https://osf.io/x24n3/). This

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study did not meet U.S. regulation requirements to be classified as human research, therefore it is exempt from Institutional Review Board approval[30].

Journal Selection

We used the National Library of Medicine (NLM) catalog to search for all oncology journals using the subject terms tag Neoplasms[ST]. This search was performed on May, 29, 2019 which identified 344 journals. The inclusion criteria required that journals were both in "English" and "MEDLINE indexed". We extracted electronic ISSN (or linking if electronic was unavailable)for each journal to use in a PubMed search on May 31, 2019. We selected publications between January 1, 2014 to December 31, 2018. This date range is consistent with Hardwicke et. al. (2014-2017), but we chose to also include the most current year (2018) at the time of data extraction and was expanded to include 2018. Publications were evenly distributed across years. From search returns, we selected a random sample of 300 publications using Excel's random number function (https://osf.io/wpev7/).

Data Extraction

We used a pilot-tested Google Form based on the one provided by Hardwicke et. al. [25] with modifications (https://osf.io/3nfa5/). The first modifications were extracting the 5-year impact factor and the date of the most recent impact factor, neither of which were extracted by Hardwicke, et. al. Second, additional study designs were added to include cohort, case series, secondary analyses, chart reviews, and cross-sectional studies. Third, funding options were expanded that allowed for greater specification of university, hospital, public, private/industry, or non-profit sources.When screening studies, we relied on the authors' descriptions of their study designs.

The Google Form contained questions for investigators aimed at identifying whether a study demonstrated the information necessary to be reproducible (Table 1, Supplementary Table 1). Variations in study design changed the data that was extracted from each study. For example, publications with no empirical data (e.g. editorials, commentaries [without reanalysis], simulations, news, reviews, and poems) were unable to examined for reproducibility characteristics. However, for all publications, the following data were extracted: title of publication, 5 year impact factor, impact factor of the most recent year, country of corresponding author and publishing journal, type of study participants (eg, human or animal), study design, author conflicts of interest, funding source, whether the publication claimed to be novel or a replication study, and whether the article was open access (Table 2). Publications with empirical data were examined for the following characteristics in addition to those stated above: material and data availability, analysis scripts, and linkable protocolPre-registration statements were further assessed in publications for which pre-registration through trial databases, such as ClinicalTrials.gov, is the norm. Observational designs may also be registered on clinical trial registries. Systematic reviews and meta-analyses may be pre-registered through PROSPERO. Pre-registration for chart reviews and case studies and series is not typically performed. As, to our knowledge, there is not currently a registration site for preclinical studies[31], thus we have excluded these publications from examination of pre-registration statements.Together, the 8 key reproducibility and transparency indicators analyzed were as follows: material availability, raw data availability, analysis scripts, linkable protocol, trial pre-registration statements, author conflict of interest statement, and funding source. Open access was determined using

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www.openaccessbutton.org, an online service that searches for open access publications freely available to the public without a journal subscription. In the event a publication could not be found, investigators performed a Google search to see if the publication was freely available elsewhere. Novelty was assessed by searching each publication for whether the publication claimed to be novel, a replication study, or provided no statement related to study novelty. Web of Science was used to evaluate whether each examined publication 1) had been replicated in other works and 2) was included in future systematic reviews or meta-analyses.

Prior to data extraction, each investigator underwent a full day of training to increase the interrater reliability of the results between authors. This training consisted of an in-person session that reviewed study design, protocol, and Google Form. Investigators (C.G.W., N.V.) extracted data from 3 sample articles and differences were reconciled following extraction. A recording of this training session is available and listed online for reference (https://osf.io/tf7nw/). One investigator (C.G.W.) extracted data from all 300 publications. Z.J.H. extracted data for 200 publications and N.V. extracted data for 100 publications. C.G.W.'s data were compared to Z.J.H.'s and N.V.'s with discrepancies being resolved via group discussion. All authors were blinded to each other's results. A final consensus meeting was held by all authors to resolve disagreements. If no agreement could be made, final judgment was made by an additional author (D.T.). Our manuscript has been made available as a preprint, online at www.medRxiv.org (https://doi.org/10.1101/19001917).

Statistical Analysis

Descriptive statistics were calculated for each category with 95% confidence intervals using the Wilson formula for binomial proportions[32]. The total number of each data point present in the publications was presented in addition to the proportion of the whole sample.

Results

The NLM search identified 344 journals but only 204 fit our inclusion criteria. Our initial search string retrieved 199,420 oncology publications, from which, 300 were randomly sampled. Approximately 296 publications were analyzed for study reproducibility characteristics; 4 publications were not accessible, thus they were excluded from our analysis. Of these 296 publications, 215 contained empirical data and 81 did not. Publications without empirical data were unable to be analyzed for study reproducibility characteristics. Additionally, 21 publications with empirical data were case studies or case series. These case studies and series are unable to be replicated, thus are excluded from the analysis of reproducibility characteristics. In total, we were able to extract study reproducibility characteristics for 194 oncology publications (Figure 1).

Study Characteristics

In our sample of oncology publications, the publishing journals had a median 5 year impact factor of 3.445 (IQR 2.27-5.95). The majority (156/296, 52.7%) of journals were located in the United States. Over half (165/296, 55.8%) of the publications were available for free via open access networks. The remaining 131 publications (44.2%) were located behind a paywall — making the publications inaccessible to the public — available only through paid reader access. Approximately 109 publications (36.8%) made no mention of funding source. Public funding

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(95/296, 32.1%), such as state or government institutions, comprised the next most prevalent source of study funding. Publication authors disclosed no conflict of interest more frequently than conflicts of interest (174/296, 58.8 vs. 57/296, 19.2%); however, 65 publications (22.0%) had no author conflict of interest statement. Human participants were the most common study population in sample (154/269, 52.0%). Citation rates of these 296 publications by systematic reviews and meta-analyses can be found in Table 2.

Reproducibility Characteristics

Only 21 publications (21/194, 10.8%) made their raw data available. Nine of these publications with available raw data were downloadable by readers, while the rest was available upon request from the corresponding author of the publication. Of these 9 publications, only 3 provided complete raw datasets (Supplementary Table 2). An expanded description of study materials required to reproduce the study — laboratory instruments, stimuli, computer software — was provided as a supplement in 6/194 publications (3.1%). Of those publications with available materials, most (4/6) were only accessible to readers upon request to the corresponding author, rather than being listed in a protocol or methods section. Two publications provided their materials accessible as a supplement, but neither publication provided all of the materials necessary to replicate the study. None of the included publications made their analysis scripts accessible, which details the steps the authors used to prepare the data for interpretation. Only 5 (5/194, 2.6%) publications provided a protocol detailing the *a priori* study design, methods, and analysis plan. One publication (1/194, 0.05%) claimed to be a replication study; all remaining publications studies (193/194, 99.5%) claimed to be novel or did not provide a clear statement about being a replication study. Twenty-two publications (22/194, 11.3%) were cited within future systematic reviews/meta-analyses. Excluding preclinical publications (n=79), chart reviews (n=7), systematic reviews or meta-analyses (n=7), or publications with multiple study designs (n=13) in which pre-registration with trial databases, such as ClinicalTrials.gov, would not be relevant, we found 7 publications (7/88, 8.0%) with pre-registration statements. Of these 88 publications, 15 were clinical trials; however, only 6 (6/88, 6.8%) were pre-registered with ClinicalTrials.gov prior to commencement of the study. None of the systematic reviews and meta-analyses (n=7) were pre-registered with PROSPERO. A subgroup analysis of the 8 key reproducibility and transparency indicators demonstrated that 29 publications had 0 indicators, 62 publications had 1 indicator, 209 publications had 2 to 5 indicators, and 0 publications had 6 or more.

Discussion

Our cross-sectional investigation of a sample of the published oncology literature found that key reproducibility and transparency practices were lacking or entirely absent. Namely, we found that publications rarely pre-registered their methods, published their full protocol, or deposited raw data and analysis scripts into a publicly-accessible repository. Moreover, conflicts of interest were not discussed approximately 20% of the time and just over half of the included publications were not accessible due to journal paywalls. Given the challenges in understanding the molecular mechanisms that drive cancer, the continuum of research in the field of oncology is slow, laborious and inefficient[33]. To combat these inherent obstacles, transferring outcomes and information from preclinical to clinical research demands consistency and precision across the

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continuum. Otherwise, publications downstream in the cancer research continuum may be based on spurious results incapable of independent confirmation due to a lack of access to study data, protocols, or analysis scripts. Science advances more rapidly when people spend less time pursuing false leads[34], thus, for patients with cancer and for whom rapid scientific advancement is most significant, it is paramount that scientists, researchers and physicians advocate for an efficient research system that is transparent, reproducible, and free from bias.

Pre-registration of research study methods is a mechanism to improve the reproducibility of published results and prevent bias — either from selective reporting of outcomes or selective publication of a study[35]. Previously, it has been shown that the selective reporting of study endpoints affects the research portfolio of drugs or diseases[15,36,37]. For example, Wayant et. al found that 109 RCTs of malignant hematology interventions selectively reported their trial endpoints 118 times, with a significant portion doing so in a manner that highlighted statistically significant findings[36]. Were trial registries not available, these trials may have never been found to exhibit selective outcome reporting. Now, through trial registries, hematologists and other interested researchers are able to independently assess the robustness of not only study rationale and results, but also study rigor and reporting. The present study indicates that pre-registration of study methods was rare, even among trials and systematic reviews that have available registries. The importance of preregistration across the continuum of cancer research cannot be understated. For example, preclinical animal models serve as the foundation for clinical trials, but have exhibited suboptimal methods[38], which may explain why animal study results fail to successfully translate to clinical benefit. In fact, it was recently shown that many phase 3 trials in Oncology are conducted despite no significant phase 2 results[39]. One possible explanation for why phase 3 trials proceed despite nonsignificant phase 2 results is the strong bioplausibility demonstrated in preclinical studies. If it is true that preclinical studies exhibit poor research methods, it is not unlikely that they are affected by selective outcome reporting bias, just like clinical research studies. Thus, to strengthen oncology research evidence — from foundational, preclinical research to practice-changing trials — we recommend either the creation of relevant study registers or the adherence to existing registration policies. In so doing, one key aspect of research — the accurate reporting of planned study endpoints — could be monitored, detected, and mitigated.

Equally important to self-correcting, rigorous cancer research is the publication of protocols, raw data, and analysis scripts. Protocols include much more information than study outcomes — they may elaborate on statistical analysis plans or decisions fundamental to the critical appraisal of study results[40]. It is unlikely that anyone would be able to fully appraise a published study without access to a protocol, and far less likely that anyone would be capable of replicating the results independently. In fact, two recent efforts to reproduce preclinical studies revealed extant barriers to independent verification of published findings[20,41], including the absence of protocols, data, and analysis scripts. Our present investigation found that only 5 (2.6%) studies published a protocol, 9 (4.6%) fully published their data, and none published their analysis scripts. In the context of the recent failures to reproduce cancer research publications, one may reasonably conclude that our study corroborates the belief that oncology research is not immune to the same shortcomings that contribute to an ever-expanding cohort of irreproducible research findings[42]. Oncology research, like all biomedical research, is at an inflection point, wherein it may progress

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toward more transparent, reproducible, efficient research findings. However, in order to do so, the availability of protocols, data, and analysis scripts should be considered fundamental.

In summary, we found that key reproducibility and transparency characteristics were absent from a random sample of published oncology studies. The implication of this finding is a research system that is incapable of rapid self-correction, or a research system that places a stronger emphasis on what is reported rather than what is correct. We recommend three key action items which we believe benefit oncology research and all its stakeholders. First, require pre-registration for eligible trials and systematic reviews, since these study designs have existing registries available, and support the development of registries for preclinical studies. Second, understand that published reports are snapshots of a research study, and require protocols be published. Last, encourage a scientific culture that relies on data that is true and robust, rather than author reports of their data, by requiring the deposition of raw data, meta data, and analysis scripts in public repositories.

This study has several strengths and limitations. First, for strengths, we sampled 300 published oncology articles indexed in PubMed. In doing so we captured a diverse array of research designs in an even more diverse range of journals. As such, all oncology researchers can read our paper and glean useful information and enact changes to improve the reproducibility of new evidence. With respect to our limitations, our study is too broad to make absolute judgments about specific study designs. All signals that suggest irreproducible research practices from our study fall in line with prior data in other areas of medicine[25–27], but are nonetheless signals rather than answers. For example, an examination of biomedical literature by Wallach et. al found that less than 30% provided study materials as a supplement; however, none of the available materials allowed for replication of the protocol or contained analysis scripts and exactly 1 study (1/104) had a linkable protocol. Furthermore, about 18% provided data availability statements, yet none of these publications shared the complete raw data for the study[27]. Similarly, an examination of the social sciences by Hardwicke et. al found that no publications made their protocol publicly available, less than 2% provided the raw data, and exactly 1 publication had an accessible link to the study's analysis scripts[25]. Therefore, we suggest more narrow investigations of the reproducibility of specific study designs and suggest trials and animal studies be prioritized due to their potential influence (present or future) on patient care. Moreover, we do not suggest that irreproducible research findings are false; however, the trust in the results may be blunted. Further, replicating (ie, reconducting) a study is not necessary in all cases to assess the rigor of the results. If a protocol, statistical analysis plan, and raw data (including metadata) are available, one fundamental pillar of science would be reinforced: self-correction.

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Author Contributions: DT and MV developed the protocol and conceptualized the study. CGW, ZH, CW, NV, MW, JC, DT, and MV will conduct all literature searches. CGW, ZJH, CW, and NV will conduct all statistical analyses. CGW and DT will manage all data, including the management of the OSF repository. CGW, ZH, CW, NV, CW, MW, JC, DT, and MV will participate in all writing. CGW, ZH, CW, NV, MW, JC, DT, and MV are equally the guarantors of the study and the integrity of the data.

Material and Data Availability: All datasets, materials, and the protocol are available online at https://doi.org/10.1101/19001917.

Patient and Public Involvement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research

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Legends:

Figure 1: PRISMA Diagram of Included Studies

Table 1: Reproducibility Characteristics of Oncology Studies

Table 2: Characteristics of Oncology Studies

Supplementary Table 1: Additional Reproducibility Characteristics

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Supplemental Table 2: Characteristics of Publications with Data Availability statements

Table 1: Reproducibility Characteristics of Oncology Studies			
Characteristics		**Variables**	
		N (%)	**95% CI**
Data Availability (N=194 studies)	Statement, some data are available	21 (10.8)	7.2-16.0
	Statement, data are not available	0	0
	No data availability statement	173 (89.2)	84.0-92.8
Material Availability (N=194 studies)	Statement, some materials are available	6 (3.1)	1.5-6.8
	Statement, materials are not available	0	0
	No materials availability statement	188 (96.8)	93.2-98.5
Protocol Available (N=194 studies)	Full Protocol	5 (2.6)	1.1-5.90
	No Protocol	189 (97.4)	94.1-98.9
Analysis Scripts (N=194 studies)	Statement, some analysis scripts are available	0	0
	Statement, analysis scripts are not available	0	0
	No analysis script availability statement	194	1

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Replication Studies (N=194 studies)	Novel study	193 (99.5)	97.1-99.9
	Replication	1 (0.05)	0.0-2.9
Pre-registration (N=88 studies)	Statement, says was pre--registration	7 (8.0)	3.9-15.4
	Statement, was not pre--registration	0	0
	No - there is no pre--registration statement	81 (92.0)	83.3-95.4

Table 2: Characteristics of Oncology Studies

Characteristics (N=296 studies)		**Variables**	
		N (%)	**95% CI**
Test Subjects	Animals	25 (8.5)	-
	Humans	154 (52.0)	-
	Both	0	-
	Neither	117 (39.5)	-
Country of journal publication	US	156 (52.7)	-
	UK	71 (24.0)	-
	Greece	18 (6.1)	-
	Netherlands	11 (3.7)	-
	Ireland	11 (3.7)	-
	South Korea	6 (2.0)	-
	India	4 (1.4)	-

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	Italy	2 (0.7)	-
	Japan	2 (0.7)	-
	Germany	1 (0.3)	-
	Unclear	9 (3.0)	-
	Other	5 (1.7)	-
Country of corresponding author	US	87 (29.4)	-
	China	52 (17.6)	-
	Japan	19 (6.4)	-
	Germany	16 (5.4)	-
	South Korea	13 (4.4)	-
	UK	12 (4.0)	-
	Italy	10 (3.4)	-
	Canada	7 (2.4)	-
	France	6 (2.0)	-
	India	6 (2.0)	-
	Unclear	8 (2.7)	-
	Other	60 (20.3)	-
Funding	University	32 (10.8)	7.8-14.9
	Hospital	8 (2.7)	1.4-5.2
	Public	95 (32.1)	27.0-37.6
	Private/Industry	6 (2.0)	0.9-4.4
	Non-profit	7 (2.4)	1.2-4.8
	No statement listed	109 (36.8)	31.5-42.5

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	No funding received	18 (6.1)	3.9-9.4
	Mixed	21 (7.1)	4.7-10.6
Conflict of Interest statement	Statement, one or more conflicts of interest	57 (19.2)	15.2-24.1
	Statement. no conflict of interest	174 (58.8)	53.1-64.2
	No conflict of interest statement	65 (22.0)	17.6-27.0
Publication Year	2014	63 (21.3%)	17.0-26.3
	2015	54 (18.2%)	14.3-23.0
	2016	49 (16.5%)	12.8-21.2
	2017	57 (19.3%)	15.2-24.1
	2018	73 (24.7%)	20.1-29.9
Open Access	Yes - found via Open Access Button	139 (47.0)	41.4-52.7
	Yes - found article via other means	26 (8.8)	6.1-12.6
	No Could only access through paywall	131 (44.2)	38.7-50.0
5 Year Impact Factor	Median	3.445	-
	1st quartile	2.2705	-
	3rd quartile	5.95	-

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	Interquartile range	2.2705-5.95	-
Most Recent Impact Factor Year	2014	4 (1.4)	-
	2015	0	-
	2016	4 (1.4)	-
	2017	271 (91.5)	-
	2018	1 (0.3)	-
	Not Found	16 (5.4)	-
Most Recent Impact Factor	Median	3.346	-
	1st quartile	2.37375	-
	3rd quartile	6.471	-
	Interquartile range	2.37375-6.471	-
Cited within a Systematic Review/Meta-Analysis N=296 (a)	No Citations	257 (86.8%)	83.5-90.2
	A Single Citation	22 (7.4%)	5.0-11.0
	One to Five Citations	17 (5.8%)	3.6-9.0
	Greater than Five Citations	0	-
Abbreviations: CI, Confidence Interval. a - Five studies were explicitly excluded from the systematic reviews/meta-analyses that cited the original article.			

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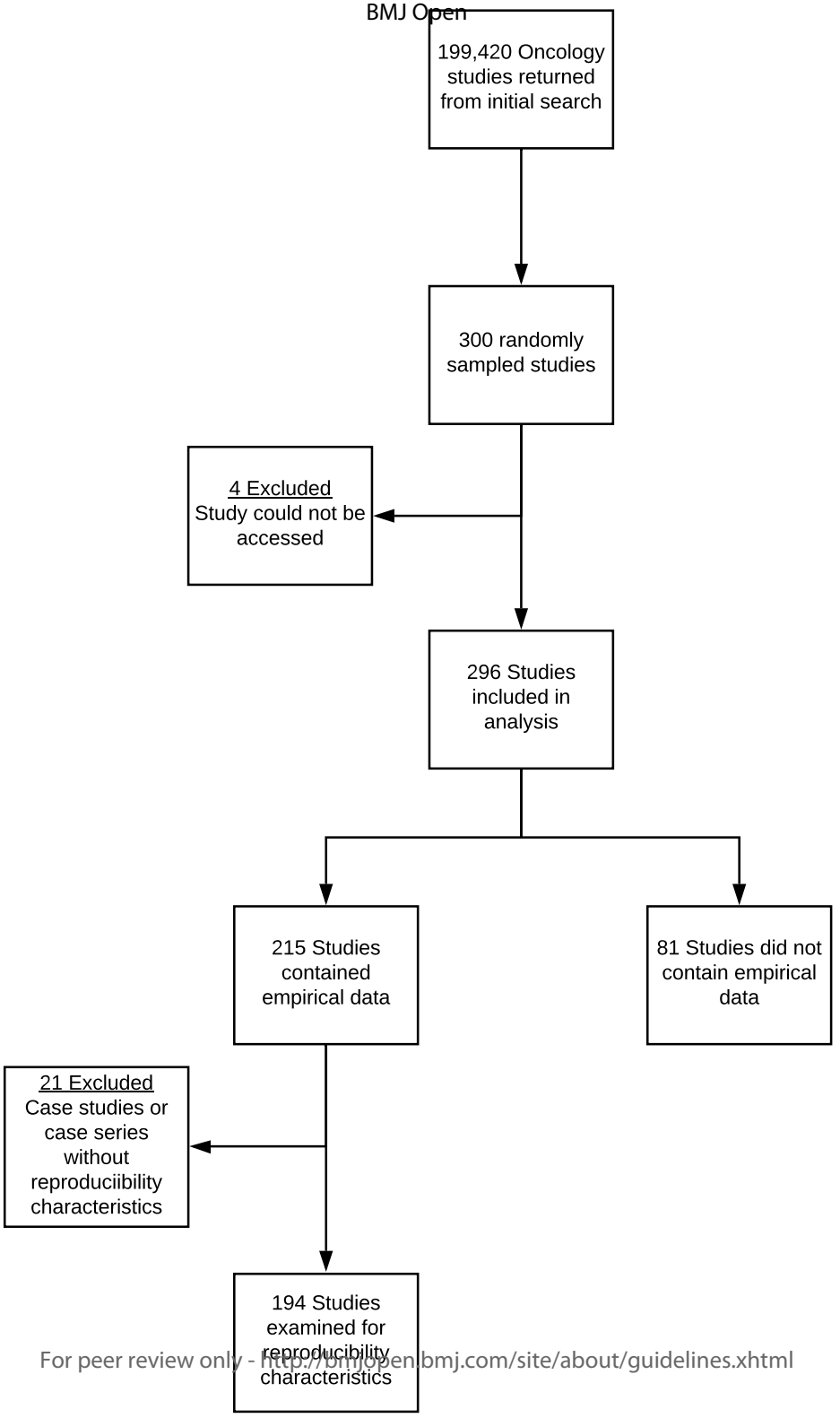

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Supplemental Table 1: Additional Reproducibility Characteristics[a]		
Characteristics		**Variables**
		No.
Type of Study N=296	Non empirical	81
	Meta-analysis	7
	Observation	10
	Cross-Sectional	5
	Clinical Trial	15
	Case Study	14
	Case Series	7
	Cohort	44
	Chart Review	7
	Case Control	8
	Survey	6
	Laboratory	79
	Multiple	9
	Other	4
Material availability	Personal or institutional	1
	Supplementary information hosted by the journal	1
	Online third party	0
	Upon Request	4

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	Yes, material was accessible	2
	No, material was not accessible	4
Data availability	Personal or institutional	1
	Supplementary information hosted by the journal	8
	Online third party	1
	Upon Request	10
	Yes, data could be accessed and downloaded	9
	No, data count not be accessed and downloaded	12
	Yes, data files were clearly documented	8
	No, data files were not clearly documented	1
	Yes, data files contain all raw data	3
	No, data files do not contain all raw data	4
	Unclear if all raw data was available	2

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Pre-registration	Pre-registered on ClinicalTrials.gov	6
	Yes, pre-registration was accessible	6
	No, pre-registration was not accessible	1
	Hypothesis was pre-registered	3
	Methods were pre-registered	6
	Analysis plan was pre-registered	1
Protocol	Hypotheses was included in the protocol	1
	Methods were included in the protocol	4
	Analysis plan was included in the protocol	2
a - additional analysis script characteristics were excluded because none were found in the analyzed journals		

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Supplemental Table 2: Characteristics of Publications with Data Availability statements

Publication	Year	Journal	Accessible	Type of Data	Data Location
Assessment of dual-probe Her-2 fluorescent in situ hybridization in breast cancer by the 2013 ASCO/CAP guidelines produces more equivocal results than that by the 2007 ASCO/CAP guidelines	2016	Breast Cancer Research and Treatment	Yes	Complete dataset	Supplementary information hosted by the journal
BIX02189 inhibits TGF-β1-induced lung cancer cell metastasis by directly targeting TGF-β type I receptor	2016	Cancer Letters	No	-	Supplementary information hosted by the journal
Carvedilol suppresses malignant proliferation of mammary epithelial cells through inhibition of the ROS-mediated PI3K/AKT signaling pathway	2018	Oncology Reports	No	-	Upon request from the authors
Characteristics and outcome in patients with non-specific symptoms and signs of cancer referred to a fast track cancer patient pathway; a retrospective cohort study	2017	BMC Cancer	No	-	Upon request from the authors
Clonal History and Genetic Predictors of Transformation Into Small-Cell Carcinomas From Lung Adenocarcinomas	2017	Journal of Clinical Oncology	Yes	Incomplete dataset	Supplementary information hosted by the journal
CT imaging features associated with recurrence in non-small cell lung cancer patients after stereotactic body radiotherapy	2017	Radiation Oncology	No	-	Upon request from the authors

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Etiologic Heterogeneity Among Non-Hodgkin Lymphoma Subtypes: The InterLymph Non-Hodgkin Lymphoma Subtypes Project	2014	Journal of the National Cancer Institute	Yes	Incomplete dataset	Supplementary information hosted by the journal
Expression of Idh1(R132H) in the Murine Subventricular Zone Stem Cell Niche Recapitulates Features of Early Gliomagenesis.	2016	Cancer Cell	Yes	Complete dataset	Gene Expression Omnibus
Identification of a novel microRNA signature associated with intrahepatic cholangiocarcinoma (ICC) patient prognosis	2015	BMC Cancer	Yes	Incomplete dataset	Gene Expression Omnibus
Knockdown of NUPR1 inhibits the proliferation of glioblastoma cells via ERK1/2, p38 MAPK and caspase-3	2017	Journal of Neurooncology	Yes	Incomplete dataset	Supplementary information hosted by the journal
MiR-216b inhibits cell proliferation by targeting FOXM1 in cervical cancer cells and is associated with better prognosis	2017	BMC Cancer	Yes	Incomplete dataset	Supplementary information hosted by the journal
NADH dehydrogenase complex I is overexpressed in incipient metastatic murine colon cancer cells	2018	Oncology Reports	No	-	Upon request from the authors
O-GlcNAcylation modulates Bmi-1 protein stability and potential oncogenic function in prostate cancer	2017	Oncogene	Yes	Incomplete dataset	Supplementary information hosted by the journal
Radiotherapy of MRI-detected involved internal mammary lymph nodes in breast cancer	2017	Radiation Oncology	No	-	Upon request from the authors

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Rapid evaporative ionisation mass spectrometry of electrosurgical vapours for the identification of breast pathology: towards an intelligent knife for breast cancer surgery	2017	Breast Cancer Research and Treatment	No	-	Upon request from the authors
Risk of second primary cancers in cancer patients treated with cisplatin: a systematic review and meta-analysis of randomized studies	2017	BMC Cancer	No	-	Upon request from the authors
Targeted knockdown of polo-like kinase 1 alters metabolic regulation in melanoma	2017	Cancer Letters	No	-	Upon request from the authors
Targeting MCL-1 sensitizes human esophageal squamous cell carcinoma cells to cisplatin-induced apoptosis	2017	BMC Cancer	No	-	Upon request from the authors
The feasibility analysis of omission of elective irradiation to level IB lymph nodes in low-risk nasopharyngeal carcinoma based on the 2013 updated consensus guideline for neck nodal levels	2017	Radiation Oncology	No	-	Upon request from the authors
Tumor-derived exosomes induce N2 polarization of neutrophils to promote gastric cancer cell migration	2018	Molecular Cancer	No	-	Upon request from the authors
Twist1 is essential in maintaining mesenchymal state and tumor-initiating properties in synovial sarcoma	2014	Cancer Letters	Yes	Complete dataset	Supplementary information hosted by the journal

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Do oncology researchers adhere to reproducible and transparent principles? : A cross-sectional survey of published oncology literature

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Title: Do oncology researchers adhere to reproducible and transparent principles? : A cross-sectional survey of published oncology literature

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Abstract

Objectives: As much as 50%-90% of research is estimated to be irreproducible, costing upwards of $28 billion in the United States alone. Reproducible research practices are essential to improving the reproducibility and transparency of biomedical research, such as including pre-registering studies, publishing a protocol, making research data and metadata publicly available, and publishing in open access journals. Here we report an investigation of key reproducible or transparent research practices in the published oncology literature.

Design: We performed a cross-sectional analysis of a random sample of 300 oncology publications published from 2014-2018. We extracted key reproducibility and transparency characteristics in a duplicative fashion by blinded investigators using a pilot tested Google Form.

Setting: N/A

Participants: N/A

Primary Outcome Measures: The primary outcome of this investigation is the frequency of key reproducible or transparent research practices followed in published biomedical and clinical oncology literature.

Results: Of the 300 publications randomly sampled, 296 were analyzed for reproducibility characteristics. Of these 296 publications, 194 were contained empirical data that could be analyzed for reproducible and transparent research practices. Raw data was available for 9 studies (4.6%). Five publications(2.6%) provided a protocol. Despite our sample including 15 clinical trials and 7 systematic reviews/meta-analyses, only 7 included a pre-registration statement. Less than 25% (65/194) of publications provided an author conflict of interest statement.

Conclusion: We found that key reproducibility and transparency characteristics were absent from a random sample of published oncology publications. We recommend required pre-registration for all eligible trials and systematic reviews, published protocols for all manuscripts, and deposition of raw data and metadata in public repositories.

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Strengths and Limitations:

- This investigation is an observational study using a cross sectional design based on a broad sample of the oncology literature, which increases the generalizability of our findings.
- We extracted 8 key reproducibility and transparency characteristics finding that 29 publications had 0 indicators, 62 publications had 1 indicator, 209 publications had 2 to 5 indicators, and 0 publications had 6 or more.
- We engaged in extensive training as a research team prior to analysis, and conducted all data extraction and data analysis in a double blind manner to avoid bias.
- Because of the breadth of this analysis, questions remain about the reproducibility and transparency in specific study designs (e.g., randomized trials).
- A lack of reporting reproducibility or transparency characteristics may not equate to failure to engage in reproducible and transparent research practices.

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Introduction

The ability to reproduce, or replicate, research results is a cornerstone of scientific advancement[1,2]. Absent efforts to advance the reproducibility of scientific research, advancements in patient care and outcomes may be delayed[3,4], in part due to a failure in the translation of evidence to practice[5]. Evidence may fail translation to practice owing to bias[6,7], lack of publication[4], or poor reporting[8]. Thus, it may not be surprising that recent estimates of irreproducible research span a range of 50%-90% of all articles, costing upwards of $28 billion in the United States alone[9]. Moreover, it may not be surprising that large-scale efforts to replicate (i.e., re-enact or reconduct previously published research studies) have failed[10], in part due to an inability to navigate published methods. What is lost when scientific research fails to be reproducible carries significant weight; namely, the ability of science to be self-correcting[11] and produce trustworthy results[12].

It is commonly accepted that certain items are essential to improving the reproducibility of biomedical research. Examples of such items include pre-registering studies, publishing a protocol, making research data and metadata publicly available, and publishing in such a way to allow free access to the final manuscript. Pre-registering a study and publishing a protocol are important to prevent selective publication of studies with "positive" results[13] and preventing the reordering of endpoints based on statistical significance[14,15]. Providing access to one's raw research data, metadata, and analysis script allows independent researchers to computationally reproduce results, tailor results to specific patient populations, and determine the rigor of statistical analysis[16,17]. Publishing in open access journals or using preprint servers allows readers across economically diverse countries to access research articles that have implications for clinical practice[18]. Altogether, reproducible research practices aim to increase the efficiency, usefulness, and rigor of published research[5].

Despite a high rate of author endorsement of reproducible practices[19,20], some evidence suggests that authors infrequently implement them[21]. Absent such reproducible research practices, attempts to validate study findings may be thwarted. For example, Bayer and Amgen both attempted to replicate oncology research studies, with each failing to do so[22,23]. Bayer's attempt to reproduce prior research studies is especially significant because they attempted to reproduce internal studies. Other non-pharmaceutical entities have attempted to replicate cancer research studies with similar results[24]. One may hypothesize that improved use and reporting of key reproducible or transparent research practices would improve future efforts to reproduce oncology research studies and build trust in existing evidence. Building on recent, similar analyses[25–27], here we report an investigation of key reproducible or transparent research practices in the published oncology literature as part of a larger initiative to examine reproducible and transparent research practices across medical specialties

Methods

We performed an observational study using a cross sectional design based on methods developed by Hardwicke et. al.[25] with modifications. Our study employed best-practice design in accordance with published guidance, where relevant[28,29]. Study protocol, raw data, and other pertinent materials are available on the Open Science Framework (https://osf.io/x24n3/). This

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study did not meet U.S. regulation requirements to be classified as human research, therefore it is exempt from Institutional Review Board approval[30].

Journal Selection

We used the National Library of Medicine (NLM) catalog to search for all oncology journals using the subject terms tag Neoplasms[ST]. This search was performed on May, 29, 2019 which identified 344 journals. The inclusion criteria required that journals were both in "English" and "MEDLINE indexed". We extracted electronic ISSN (or linking if electronic was unavailable)for each journal to use in a PubMed search on May 31, 2019. We selected publications between January 1, 2014 to December 31, 2018. This date range is consistent with Hardwicke et. al. (2014-2017), but we chose to also include the most current year (2018) at the time of data extraction and was expanded to include 2018. Publications were evenly distributed across years. From search returns, we selected a random sample of 300 publications using Excel's random number function (https://osf.io/wpev7/).

Data Extraction

We used a pilot-tested Google Form based on the one provided by Hardwicke et. al. [25] with modifications (https://osf.io/3nfa5/). The first modifications were extracting the 5-year impact factor and the date of the most recent impact factor, neither of which were extracted by Hardwicke, et. al. Second, additional study designs were added to include cohort, case series, secondary analyses, chart reviews, and cross-sectional studies. Third, funding options were expanded that allowed for greater specification of university, hospital, public, private/industry, or non-profit sources. When screening studies, we relied on the authors' descriptions of their study designs.

The Google Form contained questions for investigators aimed at identifying whether a study demonstrated the information necessary to be reproducible (Table 1, Supplementary Table 1). Variations in study design changed the data that was extracted from each study. For example, publications with no empirical data (e.g. editorials, commentaries [without reanalysis], simulations, news, reviews, and poems) were unable to examined for reproducibility characteristics. However, for all publications, the following data were extracted: title of publication, 5 year impact factor, impact factor of the most recent year, country of corresponding author and publishing journal, type of study participants (e.g., human or animal), study design, author conflicts of interest, funding source, whether the publication claimed to be a replication study, and whether the article was open access (Table 2). Publications with empirical data were examined for the following characteristics in addition to those stated above: material and data availability, analysis scripts, and linkable protocol. Pre-registration statements were further assessed in publications for which pre-registration through trial databases, such as ClinicalTrials.gov, is the norm. Observational designs may also be registered on clinical trial registries. Systematic reviews and meta-analyses may be pre-registered through PROSPERO. Pre-registration for chart reviews and case studies and series is not typically performed. As, to our knowledge, there is not currently a registration site for preclinical studies[31], thus we have excluded these publications from examination of pre-registration statements. Together, the 8 key reproducibility and transparency indicators analyzed were as follows: material availability, raw data availability, analysis scripts, linkable protocol, trial pre-registration statements, author conflict of interest statement, and funding source. Open access was determined using

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www.openaccessbutton.org, an online service that searches for open access publications freely available to the public without a journal subscription. In the event a publication could not be found, investigators performed a Google search to see if the publication was freely available elsewhere. Novelty was assessed by searching each publication for whether the publication claimed to be novel, a replication study, or provided no statement related to study novelty. Web of Science was used to evaluate whether each examined publication 1) had been replicated in other works and 2) was included in future systematic reviews or meta-analyses.

Prior to data extraction, each investigator underwent a full day of training to increase the interrater reliability of the results between authors. This training consisted of an in-person session that reviewed study design, protocol, and Google Form. Investigators (C.G.W., N.V.) extracted data from 3 sample articles and differences were reconciled following extraction. A recording of this training session is available and listed online for reference (https://osf.io/tf7nw/). One investigator (C.G.W.) extracted data from all 300 publications. Z.J.H. extracted data for 200 publications and N.V. extracted data for 100 publications. C.G.W.'s data were compared to Z.J.H.'s and N.V.'s with discrepancies being resolved via group discussion. All authors were blinded to each other's results. A final consensus meeting was held by all authors to resolve disagreements. If no agreement could be made, final judgment was made by an additional author (D.T.). Our manuscript has been made available as a preprint, online at www.medRxiv.org (https://doi.org/10.1101/19001917).

Statistical Analysis

Descriptive statistics were calculated for each category with 95% confidence intervals using the Wilson formula for binomial proportions[32]. The total number of each data point present in the publications was presented in addition to the proportion of the whole sample.

Results

The NLM search identified 344 journals but only 204 fit our inclusion criteria. Our initial search string retrieved 199,420 oncology publications, from which, 300 were randomly sampled. Approximately 296 publications were analyzed for study reproducibility characteristics; 4 publications were not accessible, thus they were excluded from our analysis. Of these 296 publications, 215 contained empirical data and 81 did not. Publications without empirical data were unable to be analyzed for study reproducibility characteristics. Additionally, 21 publications with empirical data were case studies or case series. These case studies and series are unable to be replicated, thus are excluded from the analysis of reproducibility characteristics. In total, we were able to extract study reproducibility characteristics for 194 oncology publications (Figure 1).

Study Characteristics

In our sample of oncology publications, the publishing journals had a median 5 year impact factor of 3.445 (IQR 2.27-5.95). The majority (156/296, 52.7%) of journals were located in the United States. Over half (165/296, 55.8%) of the publications were available for free via open access networks. The remaining 131 publications (44.2%) were located behind a paywall — making the publications inaccessible to the public — available only through paid reader access. Approximately 109 publications (36.8%) made no mention of funding source. Public funding

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(95/296, 32.1%), such as state or government institutions, comprised the next most prevalent source of study funding. Publication authors disclosed no conflict of interest more frequently than conflicts of interest (174/296, 58.8 vs. 57/296, 19.2%); however, 65 publications (22.0%) had no author conflict of interest statement. Human participants were the most common study population in sample (154/269, 52.0%). Citation rates of these 296 publications by systematic reviews and meta-analyses can be found in Table 2.

Reproducibility Characteristics

Only 21 publications (21/194, 10.8%) made their raw data available. Nine of these publications with available raw data were downloadable by readers, while the rest was available upon request from the corresponding author of the publication. Of these 9 publications, only 3 provided complete raw datasets (Supplementary Table 2). An expanded description of study materials required to reproduce the study — laboratory instruments, stimuli, computer software — was provided as a supplement in 6/194 publications (3.1%). Of those publications with available materials, most (4/6) were only accessible to readers upon request to the corresponding author, rather than being listed in a protocol or methods section. Two publications provided their materials accessible as a supplement, but neither publication provided all of the materials necessary to replicate the study. None of the included publications made their analysis scripts accessible, which details the steps the authors used to prepare the data for interpretation. Only 5 (5/194, 2.6%) publications provided a protocol detailing the *a priori* study design, methods, and analysis plan. One publication (1/194, 0.05%) claimed to be a replication study; all remaining publications studies (193/194, 99.5%) claimed to be novel or did not provide a clear statement about being a replication study. Twenty-two publications (22/194, 11.3%) were cited within future systematic reviews/meta-analyses. Excluding preclinical publications (n=79), chart reviews (n=7), systematic reviews or meta-analyses (n=7), or publications with multiple study designs (n=13) in which pre-registration with trial databases, such as ClinicalTrials.gov, would not be relevant, we found 7 publications (7/88, 8.0%) with pre-registration statements. Of these 88 publications, 15 were clinical trials; however, only 6 (6/88, 6.8%) were pre-registered with ClinicalTrials.gov prior to commencement of the study. None of the systematic reviews and meta-analyses (n=7) were pre-registered with PROSPERO. A subgroup analysis of the 8 key reproducibility and transparency indicators demonstrated that 29 publications had 0 indicators, 62 publications had 1 indicator, 209 publications had 2 to 5 indicators, and 0 publications had 6 or more.

Discussion

Our cross-sectional investigation of a sample of the published oncology literature found that key reproducibility and transparency practices were lacking or entirely absent. Namely, we found that publications rarely pre-registered their methods, published their full protocol, or deposited raw data and analysis scripts into a publicly-accessible repository. Moreover, conflicts of interest were not discussed approximately 20% of the time and just over half of the included publications were not accessible due to journal paywalls. Given the challenges in understanding the molecular mechanisms that drive cancer, the continuum of research in the field of oncology is slow, laborious and inefficient[33]. To combat these inherent obstacles, transferring outcomes and information from preclinical to clinical research demands consistency and precision across the

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continuum. Otherwise, publications downstream in the cancer research continuum may be based on spurious results incapable of independent confirmation due to a lack of access to study data, protocols, or analysis scripts. Science advances more rapidly when people spend less time pursuing false leads[34], thus, for patients with cancer and for whom rapid scientific advancement is most significant, it is paramount that scientists, researchers and physicians advocate for an efficient research system that is transparent, reproducible, and free from bias.

Pre-registration of research study methods is a mechanism to improve the reproducibility of published results and prevent bias — either from selective reporting of outcomes or selective publication of a study[35]. Previously, it has been shown that the selective reporting of study endpoints affects the research portfolio of drugs or diseases[15,36,37]. For example, Wayant et. al found that 109 RCTs of malignant hematology interventions selectively reported their trial endpoints 118 times, with a significant portion doing so in a manner that highlighted statistically significant findings[36]. Were trial registries not available, these trials may have never been found to exhibit selective outcome reporting. Now, through trial registries, hematologists and other interested researchers are able to independently assess the robustness of not only study rationale and results, but also study rigor and reporting. The present study indicates that pre-registration of study methods was rare, even among trials and systematic reviews that have available registries. The importance of preregistration across the continuum of cancer research cannot be understated. For example, preclinical animal models serve as the foundation for clinical trials, but have exhibited suboptimal methods[38], which may explain why animal study results fail to successfully translate to clinical benefit. In fact, it was recently shown that many phase 3 trials in Oncology are conducted despite no significant phase 2 results[39]. One possible explanation for why phase 3 trials proceed despite nonsignificant phase 2 results is the strong bioplausibility demonstrated in preclinical studies. If it is true that preclinical studies exhibit poor research methods, it is not unlikely that they are affected by selective outcome reporting bias, just like clinical research studies. Thus, to strengthen oncology research evidence — from foundational, preclinical research to practice-changing trials — we recommend either the creation of relevant study registers or the adherence to existing registration policies. In so doing, one key aspect of research — the accurate reporting of planned study endpoints — could be monitored, detected, and mitigated.

Equally important to self-correcting, rigorous cancer research is the publication of protocols, raw data, and analysis scripts. Protocols include much more information than study outcomes — they may elaborate on statistical analysis plans or decisions fundamental to the critical appraisal of study results[40]. It is unlikely that anyone would be able to fully appraise a published study without access to a protocol, and far less likely that anyone would be capable of replicating the results independently. In fact, two recent efforts to reproduce preclinical studies revealed extant barriers to independent verification of published findings[20,41], including the absence of protocols, data, and analysis scripts. Our present investigation found that only 5 (2.6%) studies published a protocol, 9 (4.6%) fully published their data, and none published their analysis scripts. In the context of the recent failures to reproduce cancer research publications, one may reasonably conclude that our study corroborates the belief that oncology research is not immune to the same shortcomings that contribute to an ever-expanding cohort of irreproducible research findings[42]. Oncology research, like all biomedical research, is at an inflection point, wherein it may progress

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toward more transparent, reproducible, efficient research findings. However, in order to do so, the availability of protocols, data, and analysis scripts should be considered fundamental.

In summary, we found that key reproducibility and transparency characteristics were absent from a random sample of published oncology studies. The implication of this finding is a research system that is incapable of rapid self-correction, or a research system that places a stronger emphasis on what is reported rather than what is correct. We recommend three key action items which we believe benefit oncology research and all its stakeholders. First, require pre-registration for eligible trials and systematic reviews, since these study designs have existing registries available, and support the development of registries for preclinical studies. Second, understand that published reports are snapshots of a research study, and require protocols be published. Last, encourage a scientific culture that relies on data that is true and robust, rather than author reports of their data, by requiring the deposition of raw data, meta data, and analysis scripts in public repositories.

This study has several strengths and limitations. First, for strengths, we sampled 300 published oncology articles indexed in PubMed. In doing so we captured a diverse array of research designs in an even more diverse range of journals. As such, all oncology researchers can read our paper and glean useful information and enact changes to improve the reproducibility of new evidence. With respect to our limitations, our study is too broad to make absolute judgments about specific study designs. All signals that suggest irreproducible research practices from our study fall in line with prior data in other areas of medicine[25–27], but are nonetheless signals rather than answers. For example, an examination of biomedical literature by Wallach et. al found that less than 30% provided study materials as a supplement; however, none of the available materials allowed for replication of the protocol or contained analysis scripts and exactly 1 study (1/104) had a linkable protocol. Furthermore, about 18% provided data availability statements, yet none of these publications shared the complete raw data for the study[27]. Similarly, an examination of the social sciences by Hardwicke et. al found that no publications made their protocol publicly available, less than 2% provided the raw data, and exactly 1 publication had an accessible link to the study's analysis scripts[25]. Therefore, we suggest more narrow investigations of the reproducibility of specific study designs and suggest trials and animal studies be prioritized due to their potential influence (present or future) on patient care. Moreover, we do not suggest that irreproducible research findings are false; however, the trust in the results may be blunted. Further, replicating (i.e., reconducting) a study is not necessary in all cases to assess the rigor of the results. If a protocol, statistical analysis plan, and raw data (including metadata) are available, one fundamental pillar of science would be reinforced: self-correction.

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Author Contributions: DT and MV developed the protocol and conceptualized the study. CWalt, ZH, CW, NV, MW, JC, DT, and MV will conduct all literature searches. CWalt, ZH, CW, and NV will conduct all statistical analyses. CWalt and DT will manage all data, including the management of the OSF repository. CWalt, ZH, CW, NV, CW, MW, JC, DT, and MV will participate in all writing. CWalt, ZH, CW, NV, MW, JC, DT, and MV are equally the guarantors of the study and the integrity of the data.

Material and Data Availability: All datasets, materials, and the protocol are available online at https://doi.org/10.1101/19001917.

Patient and Public Involvement: It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research

Word Count: 3083 words

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Legends:

Figure 1: PRISMA Diagram of Included Studies

Table 1: Reproducibility Characteristics of Oncology Studies

Table 2: Characteristics of Oncology Studies

Supplementary Table 1: Additional Reproducibility Characteristics

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Supplemental Table 2: Characteristics of Publications with Data Availability statements

Table 1: Reproducibility Characteristics of Oncology Studies			
Characteristics		**Variables**	
		N (%)	**95% CI**
Data Availability (N=194 studies)	Statement, some data are available	21 (10.8)	7.2-16.0
	Statement, data are not available	0	0
	No data availability statement	173 (89.2)	84.0-92.8
Material Availability (N=194 studies)	Statement, some materials are available	6 (3.1)	1.5-6.8
	Statement, materials are not available	0	0
	No materials availability statement	188 (96.8)	93.2-98.5
Protocol Available (N=194 studies)	Full Protocol	5 (2.6)	1.1-5.90
	No Protocol	189 (97.4)	94.1-98.9
Analysis Scripts (N=194 studies)	Statement, some analysis scripts are available	0	0
	Statement, analysis scripts are not available	0	0
	No analysis script availability statement	194	1

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Replication Studies (N=194 studies)	Novel study	193 (99.5)	97.1-99.9
	Replication	1 (0.05)	0.0-2.9
Pre-registration (N=88 studies)	Statement, says was pre--registration	7 (8.0)	3.9-15.4
	Statement, was not pre--registration	0	0
	No - there is no pre--registration statement	81 (92.0)	83.3-95.4

Table 2: Characteristics of Oncology Studies

Characteristics (N=296 studies)		**Variables**	
		N (%)	**95% CI**
Test Subjects	Animals	25 (8.5)	-
	Humans	154 (52.0)	-
	Both	0	-
	Neither	117 (39.5)	-
Country of journal publication	US	156 (52.7)	-
	UK	71 (24.0)	-
	Greece	18 (6.1)	-
	Netherlands	11 (3.7)	-
	Ireland	11 (3.7)	-
	South Korea	6 (2.0)	-
	India	4 (1.4)	-

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	Italy	2 (0.7)	-
	Japan	2 (0.7)	-
	Germany	1 (0.3)	-
	Unclear	9 (3.0)	-
	Other	5 (1.7)	-
Country of corresponding author	US	87 (29.4)	-
	China	52 (17.6)	-
	Japan	19 (6.4)	-
	Germany	16 (5.4)	-
	South Korea	13 (4.4)	-
	UK	12 (4.0)	-
	Italy	10 (3.4)	-
	Canada	7 (2.4)	-
	France	6 (2.0)	-
	India	6 (2.0)	-
	Unclear	8 (2.7)	-
	Other	60 (20.3)	-
Funding	University	32 (10.8)	7.8-14.9
	Hospital	8 (2.7)	1.4-5.2
	Public	95 (32.1)	27.0-37.6
	Private/Industry	6 (2.0)	0.9-4.4
	Non-profit	7 (2.4)	1.2-4.8
	No statement listed	109 (36.8)	31.5-42.5

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	No funding received	18 (6.1)	3.9-9.4
	Mixed	21 (7.1)	4.7-10.6
Conflict of Interest statement	Statement, one or more conflicts of interest	57 (19.2)	15.2-24.1
	Statement. no conflict of interest	174 (58.8)	53.1-64.2
	No conflict of interest statement	65 (22.0)	17.6-27.0
Publication Year	2014	63 (21.3%)	17.0-26.3
	2015	54 (18.2%)	14.3-23.0
	2016	49 (16.5%)	12.8-21.2
	2017	57 (19.3%)	15.2-24.1
	2018	73 (24.7%)	20.1-29.9
Open Access	Yes - found via Open Access Button	139 (47.0)	41.4-52.7
	Yes - found article via other means	26 (8.8)	6.1-12.6
	No Could only access through paywall	131 (44.2)	38.7-50.0
5 Year Impact Factor	Median	3.445	-
	1st quartile	2.2705	-
	3rd quartile	5.95	-

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	Interquartile range	2.2705-5.95	-
Most Recent Impact Factor Year	2014	4 (1.4)	-
	2015	0	-
	2016	4 (1.4)	-
	2017	271 (91.5)	-
	2018	1 (0.3)	-
	Not Found	16 (5.4)	-
Most Recent Impact Factor	Median	3.346	-
	1st quartile	2.37375	-
	3rd quartile	6.471	-
	Interquartile range	2.37375-6.471	-
Cited within a Systematic Review/Meta-Analysis N=296 (a)	No Citations	257 (86.8%)	83.5-90.2
	A Single Citation	22 (7.4%)	5.0-11.0
	One to Five Citations	17 (5.8%)	3.6-9.0
	Greater than Five Citations	0	-

Abbreviations: CI, Confidence Interval. a - Five studies were explicitly excluded from the systematic reviews/meta-analyses that cited the original article.

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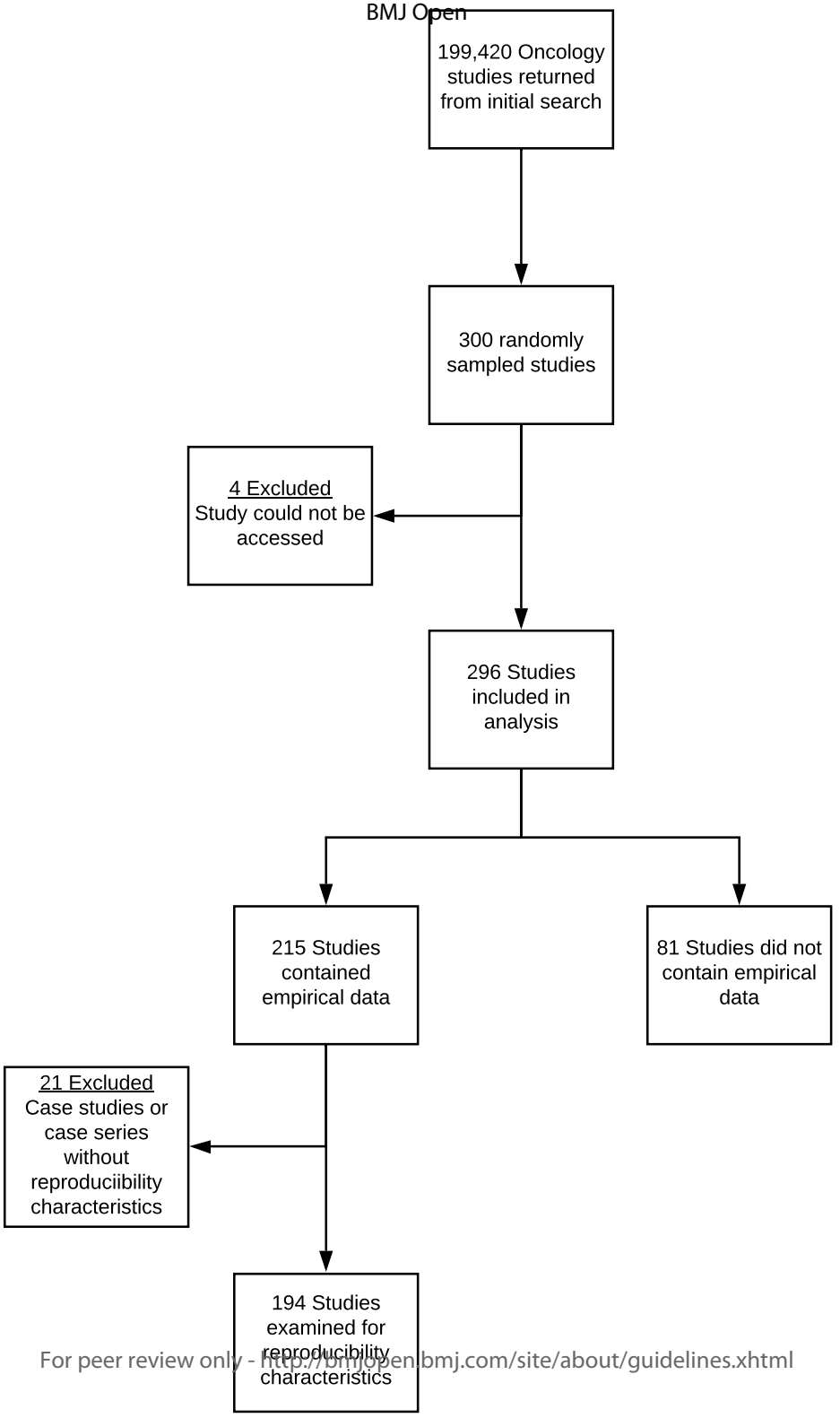

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Supplemental Table 1: Additional Reproducibility Characteristics[a]		
Characteristics		**Variables**
		No.
Type of Study N=296	Non empirical	81
	Meta-analysis	7
	Observation	10
	Cross-Sectional	5
	Clinical Trial	15
	Case Study	14
	Case Series	7
	Cohort	44
	Chart Review	7
	Case Control	8
	Survey	6
	Laboratory	79
	Multiple	9
	Other	4
Material availability	Personal or institutional	1
	Supplementary information hosted by the journal	1
	Online third party	0
	Upon Request	4

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	Yes, material was accessible	2
	No, material was not accessible	4
Data availability	Personal or institutional	1
	Supplementary information hosted by the journal	8
	Online third party	1
	Upon Request	10
	Yes, data could be accessed and downloaded	9
	No, data count not be accessed and downloaded	12
	Yes, data files were clearly documented	8
	No, data files were not clearly documented	1
	Yes, data files contain all raw data	3
	No, data files do not contain all raw data	4
	Unclear if all raw data was available	2

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Pre-registration	Pre-registered on ClinicalTrials.gov	6
	Yes, pre-registration was accessible	6
	No, pre-registration was not accessible	1
	Hypothesis was pre-registered	3
	Methods were pre-registered	6
	Analysis plan was pre-registered	1
Protocol	Hypotheses was included in the protocol	1
	Methods were included in the protocol	4
	Analysis plan was included in the protocol	2
a - additional analysis script characteristics were excluded because none were found in the analyzed journals		

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Supplemental Table 2: Characteristics of Publications with Data Availability statements

Publication	Year	Journal	Accessible	Type of Data	Data Location
Assessment of dual-probe Her-2 fluorescent in situ hybridization in breast cancer by the 2013 ASCO/CAP guidelines produces more equivocal results than that by the 2007 ASCO/CAP guidelines	2016	Breast Cancer Research and Treatment	Yes	Complete dataset	Supplementary information hosted by the journal
BIX02189 inhibits TGF-β1-induced lung cancer cell metastasis by directly targeting TGF-β type I receptor	2016	Cancer Letters	No	-	Supplementary information hosted by the journal
Carvedilol suppresses malignant proliferation of mammary epithelial cells through inhibition of the ROS-mediated PI3K/AKT signaling pathway	2018	Oncology Reports	No	-	Upon request from the authors
Characteristics and outcome in patients with non-specific symptoms and signs of cancer referred to a fast track cancer patient pathway; a retrospective cohort study	2017	BMC Cancer	No	-	Upon request from the authors
Clonal History and Genetic Predictors of Transformation Into Small-Cell Carcinomas From Lung Adenocarcinomas	2017	Journal of Clinical Oncology	Yes	Incomplete dataset	Supplementary information hosted by the journal
CT imaging features associated with recurrence in non-small cell lung cancer patients after stereotactic body radiotherapy	2017	Radiation Oncology	No	-	Upon request from the authors

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Etiologic Heterogeneity Among Non-Hodgkin Lymphoma Subtypes: The InterLymph Non-Hodgkin Lymphoma Subtypes Project	2014	Journal of the National Cancer Institute	Yes	Incomplete dataset	Supplementary information hosted by the journal
Expression of Idh1(R132H) in the Murine Subventricular Zone Stem Cell Niche Recapitulates Features of Early Gliomagenesis.	2016	Cancer Cell	Yes	Complete dataset	Gene Expression Omnibus
Identification of a novel microRNA signature associated with intrahepatic cholangiocarcinoma (ICC) patient prognosis	2015	BMC Cancer	Yes	Incomplete dataset	Gene Expression Omnibus
Knockdown of NUPR1 inhibits the proliferation of glioblastoma cells via ERK1/2, p38 MAPK and caspase-3	2017	Journal of Neurooncology	Yes	Incomplete dataset	Supplementary information hosted by the journal
MiR-216b inhibits cell proliferation by targeting FOXM1 in cervical cancer cells and is associated with better prognosis	2017	BMC Cancer	Yes	Incomplete dataset	Supplementary information hosted by the journal
NADH dehydrogenase complex I is overexpressed in incipient metastatic murine colon cancer cells	2018	Oncology Reports	No	-	Upon request from the authors
O-GlcNAcylation modulates Bmi-1 protein stability and potential oncogenic function in prostate cancer	2017	Oncogene	Yes	Incomplete dataset	Supplementary information hosted by the journal
Radiotherapy of MRI-detected involved internal mammary lymph nodes in breast cancer	2017	Radiation Oncology	No	-	Upon request from the authors

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Rapid evaporative ionisation mass spectrometry of electrosurgical vapours for the identification of breast pathology: towards an intelligent knife for breast cancer surgery	2017	Breast Cancer Research and Treatment	No	-	Upon request from the authors
Risk of second primary cancers in cancer patients treated with cisplatin: a systematic review and meta-analysis of randomized studies	2017	BMC Cancer	No	-	Upon request from the authors
Targeted knockdown of polo-like kinase 1 alters metabolic regulation in melanoma	2017	Cancer Letters	No	-	Upon request from the authors
Targeting MCL-1 sensitizes human esophageal squamous cell carcinoma cells to cisplatin-induced apoptosis	2017	BMC Cancer	No	-	Upon request from the authors
The feasibility analysis of omission of elective irradiation to level IB lymph nodes in low-risk nasopharyngeal carcinoma based on the 2013 updated consensus guideline for neck nodal levels	2017	Radiation Oncology	No	-	Upon request from the authors
Tumor-derived exosomes induce N2 polarization of neutrophils to promote gastric cancer cell migration	2018	Molecular Cancer	No	-	Upon request from the authors
Twist1 is essential in maintaining mesenchymal state and tumor-initiating properties in synovial sarcoma	2014	Cancer Letters	Yes	Complete dataset	Supplementary information hosted by the journal

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