Articles combining the results from multiple studies have been published for over a century. However, the term meta-analysis and many of the fundamental principles of standardizing and synthesizing effect estimates were first introduced in the late 1970s. Over the next 2 decades, as the methodology was further formalized and adopted, there was a linear increase in the number of published health-related meta-analyses. However, since 2000, exponential growth rates have been observed, raising concerns about the number of overlapping, conflicting, and misleading meta-analyses. These findings led Ioannidis to hypothesize that it is likely that “more systematic reviews of trials than new randomized trials are published annually.”

In this issue of *JAMA Internal Medicine*, Niforatos and colleagues evaluated a similar hypothesis by comparing the ratio of published systematic reviews and meta-analyses to randomized clinical trials (RCTs) available on PubMed from 1995 to 2017. The authors reported that the ratio of systematic reviews and meta-analyses to RCTs increased from 0.045 in 1995 to 0.871 in 2017, suggesting that nearly 1 review is now published for every RCT. Although the results differed across clinical topic areas, they support previous concerns about the mass production of systematic reviews and meta-analyses.

There are a number of factors that can explain these trends. Recent technological advances, including easily searchable databases and digital software for screening and synthesizing evidence, have enabled the rapid production of reviews that can be conducted with or without meta-analytical expertise. Furthermore, reviews involve fewer barriers (ie, institutional review board requirements) and are less expensive to conduct than trials. On average, reviews receive more citations than all other study designs, and given the academic incentive structure, which is often focused on citations and H-indices, researchers, editors, and journals may be preferentially pursuing and publishing review articles. It is also possible that there is a perceived demand for review articles that provide up-to-date summaries of rapidly evolving fields. For example, Niforatos et al found that in hematology/oncology, one specialty with an overwhelming number of new studies published each year, the ratio of published reviews to trials was 1.443.

Although these and other research practices can explain the growth in the number of published reviews, it is also worth noting that the true ratio of systematic reviews and meta-analyses to RCTs is difficult to measure. As the authors outline, they relied on PubMed classifications, and previous studies have suggested that fewer than one-third of studies tagged in PubMed as a “systematic review” actually meet the stringent criteria of this study design. Furthermore, the number of articles indexed as RCTs in PubMed has been increasing over time. Little is known about their purpose, size, quality, and how many of these are actually secondary analyses of existing trials. Although Niforatos et al provided an estimate of the number of studies classified as systematic reviews/meta-analyses and RCTs, the ratio of reviews containing only RCTs to new RCTs is unknown and is more difficult to establish without manual screening of articles.

Although these trends indicate an alarming growth in the popularity of reviews across different specialties, rigorous systematic reviews and meta-analyses are still among the most informative research studies. The findings reported by Niforatos et al do not suggest that reviews should be abandoned or that more trials are necessary. Instead, they support efforts to prioritize more robust trials and reviews, including living reviews in which meta-analyses are available online and continuously updated as additional studies are identified, as well as prospective and individual patient-level meta-analyses. Priority should be given to reviews that are conducted by nonconflicted investigators, including meta-analytical experts and research librarians, who help formulate search terms, identify relevant databases, and minimize any search inadequacies. To help curtail the production (and publication) of redundant, biased, and conflicted reviews, peer reviewers and editors may need additional training to assess the quality of submitted manuscripts. Together, these efforts can help slow the meta-analysis metastasis.

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1. Ioannidis JP. The mass production of redundant, misleading, and conflicted systematic reviews and meta-analyses. Milbank Q. 2016;94(3):485-514. doi:10.1111/milb.12210


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**Letters**

**Industry Payments to Physician Directors of National Cancer Institute–Designated Cancer Centers, 2015–2017**

National Cancer Institute (NCI)-designated cancer centers shape cancer care in the United States and are supported by substantial public funds (in fiscal year 2018, $330 million in core funding for 70 cancer centers). Cancer care is also shaped by industry, because developing new cancer therapeutics represents a major market opportunity. Industry payments to aca-
Academic physicians risk blurring the line between innovation and evaluation of new therapies. We used Open Payments data from the Centers for Medicare & Medicaid Services (CMS) to examine industry payments made to physician directors of NCI-designated cancer centers.

**Methods** | We obtained data on industry payments for calendar years 2015 through 2017 from the Open Payments database. Pharmaceutical and medical device companies are required to provide this information for all US physicians; nonphysician directors of NCI-designated cancer centers (16 in 2017) are not in the database. We identified physician directors using cached versions of the NCI website (https://www.cancer.gov/research/nci-role/cancer-centers) obtained from archive.org. As of July 2017, there were 53 physician directors. We then looked back to determine whether the director held the position in prior years (using cached data from July 2016 and July 2015). We sought data on all industry payments (total payments) and for their component research payments and payments unrelated to research, which includes consulting fees, travel and lodging, and honoraria. Although physicians may dispute the accuracy of their data, no payments were disputed in the data we examined.

**Results** | Of the 53 physician cancer center directors listed in 2017, 44 held the position in 2016 and 41 in 2015. Figure 1 shows the distribution of industry payments to these directors from 2015 to 2017. In 2017, total payments were $4.42 million, including $1.89 million in research payments to 12 directors and $2.53 million in nonresearch payments to 22 directors. Twenty-seven of the 53 directors (51%) received no payments, whereas 19 (36%) received more than $5000.

Physician directors were more likely to receive payments unrelated to research than research payments (Figure 2). In 2017, 12 of 53 (23%) had payments unrelated to research exceeding $5000, the threshold defined by the NCI for payments unrelated to research as a significant financial interest. Two directors received payments of more than $50,000. The larger of these payments was for $2.27 million, almost all of which was categorized in Open Payments as “compensation for services other than consulting, including serving as faculty or a speaker at a venue other than a continuing education program.”

The largest research payment in 2017 was $863,000; the median value of research payments was larger than the median value for payments unrelated to research ($37,036 [range, $136-$863,000] vs $58,288 [range, $15-$2,3 million]). Of the 12 directors receiving research payments, 10 received more than $5000 and 4 received more than $50,000.

**Discussion** | In 2017, about half of physician directors of NCI cancer centers received industry payments, and about half did not. Industry payments were thus less frequent than has been re-
reported for authors of National Comprehensive Cancer Network Guidelines in 2014 and leaders of academic oncology units in 2015 (ie, department chairs and section chiefs). Almost one-quarter of physician directors received more than $5000 in payments unrelated to research, constituting a significant financial interest as defined by the NCI (the NCI conflict of interest policy is silent on research payments).

Some argue that although physicians have few reasons to receive payments unrelated to research, payments for bona fide research are less problematic. Others have raised concerns about the far-reaching effects of industry funding of any type, because this funding can affect all stages of clinical research, from formulation of research questions and trial design to dissemination of research findings. Our findings raise the question of whether industry payments to the directors of publicly supported institutions, such as NCI-designated cancer centers, serve the public interest. Policy makers—and the public—should consider whether such payments should be allowed, limited (eg, to < $5000 a year), or eliminated.

Open payments data are limited because they lack detail about the specific service provided. Furthermore, they provide no information on whether the payments influenced the cancer center director.

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Concept and design: Both authors.

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COMMENT & RESPONSE

Reevaluating the Use of the Nationwide Inpatient Sample to Identify Incident Cases of Atrial Fibrillation After Aortic Valve Replacement

To the Editor Kalra et al1 used the Nationwide Inpatient Sample (NIS) to estimate the incidence of new-onset atrial fibrillation (AF) after transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (AVR) and reported that 50% of patients develop AF after TAVI or AVR. We are concerned about the accuracy of the study results based on the methods used.

The authors identified incident AF by excluding patients with a prior diagnosis of AF. No International Classification of Diseases, Ninth Revision, Clinical Modification code exists for prior AF, and the reported numbers from the NIS (an administrative database) include both incident and prevalent AF. This is supported by the significantly lower rates of AF incidence in the New York state inpatient database, which contains a present on arrival indicator (not available in the NIS) that helps to identify new diagnoses. The authors acknowledged that NIS data have less granularity and that their sample might have included some patients with chronic AF; however, this limitation cannot explain a 257% higher incidence of AF after TAVI and a 70% higher incidence of AF after AVR in the NIS compared with the validation cohort.

The authors discussed that the inflammatory threshold for postprocedural incident AF is low, which results in a high incidence of 50% after TAVI and AVR in the NIS. However, they then made an inconsistent observation that the incidence of AF in patients who have undergone AVR (30.6%) is more than twice that in patients who have undergone TAVI (14.1%) in the New York state inpatient database validation cohort. Higher incidence of new-onset AF after AVR (30% to 40%) compared with TAVI (5% to 10%) has been previously reported using randomized clinical trial data2 and registry data,3 which have more accurate patient-level clinical data points. In the current NIS study, the mean age of the TAVI sample (81 years) was much higher than the mean age of the AVR sample (68 years), but AF rates were similar. Prevalence of AF increases with age, which could explain the similar rates in both cohorts.

We strongly believe that the 50% AF rate reported in this study represents a combination of prevalent and incident AF. Several NIS-based studies and data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry have shown that the prevalence of AF in patients undergoing transcatheter or surgical AVR ranges from 40% to 46%, which is in line with previous findings. Therefore, this article should discuss periprocedural AF prevalence rather than incidence. Alternatively, the authors should conclude that the NIS cannot be used to estimate true incidence of new-onset AF after TAVI or AVR.

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