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Mapping conflict of interests: scoping review

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ABSTRACT

OBJECTIVE

To identify all known ties between the medical product industry and the healthcare ecosystem.

DESIGN

Scoping review.

METHODS

From initial literature searches and expert input, a map was created to show the network of medical product industry ties across parties and activities in the healthcare ecosystem. Through a scoping review, the ties were then verified, cataloged, and characterized, with data abstracted on types of industry ties (financial, non-financial), applicable policies for conflict of interests, and publicly available data sources.

MAIN OUTCOME MEASURES

Presence and types of medical product industry ties to activities and parties, presence of policies for conflict of interests, and publicly available data.

RESULTS

A map derived through synthesis of 538 articles from 37 countries shows an extensive network of medical product industry ties to activities and parties in the healthcare ecosystem. Key activities include research, healthcare education, guideline development, formulary selection, and clinical care. Parties include non-profit entities, the healthcare profession, the market supply chain, and government. The medical product industry has direct ties to all parties and some activities through multiple pathways; direct ties extend through interrelationships among parties and activities. The most frequently identified parties were within the healthcare profession, with individual professionals described in 422 (78%) of the included studies. More than half (303, 56%) of the publications documented medical product industry ties to research, with clinical care (156, 29%),

health professional education (145, 27%), guideline development (33, 6%), and formulary selection (8, 1%) appearing less often. Policies for conflict of interests exist for some financial and a few non-financial ties; publicly available data sources seldom describe or quantify these ties.

CONCLUSIONS

An extensive network of medical product industry ties to activities and parties exists in the healthcare ecosystem. Policies for conflict of interests and publicly available data are lacking, suggesting that enhanced oversight and transparency are needed to protect patient care from commercial influence and to ensure public trust.

Introduction

In an influential 2009 report, the Institute of Medicine described a multifaceted healthcare ecosystem rife with industry influence.¹ Central to the ecosystem are healthcare providers, researchers, clinical care facilities, journals, professional societies, and other healthcare institutions and supporting organizations engaged in medicine's core professional activities: providing beneficial care to patients, conducting valid research, and providing evidence based clinical education and guidance. In so doing, these individuals and institutions frequently collaborate with pharmaceutical, medical device, and biotechnology product manufacturers.¹⁻⁵ Although these for profit entities play a crucial role in the ecosystem, particularly in developing new tests and treatments, their primary objective is to ensure financial returns to shareholders. Thus, industry collaborations inevitably introduce potential commercial bias into the healthcare ecosystem. With absent rigorous conflict of interest oversight across the entire system, the Institute of Medicine warned that medicine's extensive ties to the medical product industry "threaten the integrity of scientific investigations, the objectivity of medical education, the quality of patient care, and the public's trust in medicine."¹

Controlling conflict of interest across the ecosystem, however, requires a system level understanding of how influence can enter and circulate through it. Research on the influence of the medical product industry is voluminous and expanding, aided in no small part by new data sources such as Open Payments,⁶⁻⁹ a US federal database that makes public nearly all payments to physicians and teaching hospitals by pharmaceutical, medical device, and other healthcare product manufacturers. Other lines of inquiry have begun to explore the ties between medical product companies and regulators, patient advocacy groups, and other influential parties in the healthcare ecosystem.^{3 4 10-12} And the analytic lens has broadened to include not

WHAT IS ALREADY KNOWN ON THIS TOPIC

Most studies of conflict of interests related to pharmaceutical, medical device, and biotechnology companies have focused on one party (eg, prescribers, organizations) or activity (eg, research, education, clinical care) in the healthcare ecosystem

The range and interrelationships of company ties across the healthcare ecosystem are incompletely described

WHAT THIS STUDY ADDS

The medical product industry maintains numerous ties with all major healthcare parties and activities

This extensive network of ties is often unregulated and non-transparent

Enhanced oversight and transparency are needed to shield patient care from commercial influence and to preserve public trust in healthcare

only financial ties but also non-financial ones, such as medical product manufacturers offering healthcare professionals research data, authorship, and other opportunities for professional advancement.¹³⁻¹⁵

Yet, with few exceptions,^{1 2 16 17} most analyses focus on one or two narrow types of ties between the medical product industry and a single party, such as healthcare professionals, hospitals, or journals, or a single activity, such as research, education, or clinical care. The reality is that companies take a multipronged approach to developing and marketing products, enlisting the assistance of multiple influential parties throughout the healthcare ecosystem. The US opioid epidemic, for example, provides numerous instances of pharmaceutical manufacturers strategically developing financial ties with multiple entities in the healthcare ecosystem and leveraging those to create secondary influences, resulting in profound patient harm.^{16 17} The complex interactions evident in the case of opioids, however, are seldom documented or explored in the literature on conflict of interests. We are unaware of any study that has endeavored to identify and characterize the full extent of medical product industry ties across the healthcare ecosystem, which involves individuals who and organizations that deliver healthcare, as well as politicians, regulators, supply chain entities, and others who shape the practice of medicine indirectly. The entire spectrum of direct ties, and subsequent indirect pathways for potential influence, could result in cumulative effects on patient care and public trust and are thus important to systematically document and assess.

We therefore developed an evidence based map to encompass the complex network of ties between the pharmaceutical, medical device, and biotechnology industries and healthcare ecosystem. To identify all known pathways that could enable companies to ultimately influence patient care, we systematically explored the full range of direct industry ties, both financial and non-financial, across the ecosystem, as well as indirect ties to and from other parties and activities within the healthcare ecosystem. We also cataloged the presence of conflict of interests oversight along these routes, as well as the extent to which industry ties are transparent to regulators, the public, and other key audiences. Our results provide a system level view of the medical product industry's potential for influence across the healthcare ecosystem, ultimately culminating at patient care.

Methods

Our methods were twofold. First, we used targeted literature searches and expert input to draft a map depicting the ties between the pharmaceutical, medical device, and biotechnology industries and the key healthcare related activities and parties that shape utilization (ie, prescribing and use of medical devices and biotechnology products). Then we conducted a systematic scoping review to verify and refine the map and to catalog and characterize all documented industry ties across the healthcare ecosystem.

Mapping

We began by reviewing publications known to the research team (in particular, the Institute of Medicine's extensive 2009 report¹) and cataloged all identified parties (individuals and organizations involved in healthcare, such as hospitals, prescribers, public health agencies), activities (domains of clinical inquiry, judgment, and decision making, such as research, clinical care, guideline development), and linkages among them. Using terms such as "pharmaceutical industry", "device industry", and "conflict of interest", and the "similar articles" function, we then conducted a targeted search of the medical and scientific literatures (through PubMed) to document industry ties to these parties and activities, as well as any additional parties, activities, and linkages in the healthcare ecosystem. To further explore additional, poorly documented ties, we used Google to search the gray literature, business publications, and lay literature, such as newspaper and magazine articles. All investigators independently performed searches in Google until saturation was achieved—that is, no new activities, parties, or linkages being identified. We used these findings to draft a preliminary map of the healthcare ecosystem, showing the network of ties between industry and each party and activity, as well as ties among parties and activities.

Next we obtained input from an international panel of experts with broad expertise in industry ties and deep knowledge of specific parties and activities (supplementary appendix A). We selected prominent experts on industry ties to healthcare parties or domains, or both. Experts were also selected who could reflect on these problems internationally, not just in the US context. Additionally, we included experts with deep knowledge of pricing and distribution systems, as these topics seldom appear in the literature on conflict of interest. Through WebEx we conducted semistructured interviews (supplementary appendix B) with experts individually to review the map, using their feedback on an ongoing basis to further search the literature, evaluate depicted ties, identify missing ties, and refine the map accordingly. We worked iteratively, making alterations to the general approach, categorizations, and visual presentation until reaching agreement within the research team. Experts were recruited until saturation was achieved (with no further changes suggested), which occurred after eight experts had been interviewed. We also solicited additional comments and final approval from the experts by email. Finally, we worked with design experts to optimize the visual clarity of the map.

Scoping review

We conducted a systematic scoping review of medical product industry ties to verify and refine the map, cataloging and characterizing documented financial and non-financial ties across the broad healthcare ecosystem. Our methods are reported according to the preferred reporting items for systematic reviews and

meta-analyses extension for scoping reviews (PRISMA-ScR) (supplementary appendix C).¹⁸

Protocol

Scoping reviews are not eligible for registration in Prospero; nonetheless, we used Prospero's systematic review protocol for planning and reporting purposes (supplementary appendix D).

Eligibility criteria

The scoping review included qualitative and quantitative experimental and observational studies with English language full text available. Included studies documented ties between industry and a party or activity in the healthcare ecosystem. The scoping review excluded commentaries, conference presentations, abstracts, literature reviews, letters, and editorials.

Information sources and search strategy

Using search terms derived from our initial literature review, including “drug”, “device”, “industry influence”, “commercial support”, and “conflict of interest”, we conducted a scoping review (through PubMed, Scopus, and Embase) of the medical, scientific, and gray literatures to 31 December 2019, to systematically identify all published investigations documenting these and other emergent activities, relevant parties in the healthcare ecosystem, and linkages. We also included records from our previous manual searches that focused on poorly documented potential ties.

Relevant policies for conflict of interests and publicly available data sources that appeared in our searches were collated for separate analysis. To supplement our search for the policies and transparency sources, we also gathered information from MediSpend Legislative Watch, an industry facing website that compiles summaries and links for policies for conflict of interests and transparency requirements in countries across North America, Europe, the Middle East, and Asia.¹⁹

Study selection process

All search results were imported into Covidence, an online systematic review software program. The eligibility criteria were imported as a set of codes that were used for screening. To ensure reliability, multiple reviewers (SC, MM, SZ, DK) screened all items, with differences resolved through discussion.

Data items and data collection process

For all included articles, we abstracted data on activities, parties, types of ties (financial, non-financial), year and location of study, type of publication (gray, peer reviewed), and funding source. The data abstraction form (supplementary appendix E) was piloted on random samples of 10 included studies and modified as needed using feedback from the team. Full data abstraction began after four rounds of pilot testing, once sufficient intercoder agreement had been obtained (93.48-100%); calculable κ statistics ranged

from 0.63-0.95, indicating substantial to near perfect agreement. Subsequently, one of two team members (MM, SZ) abstracted each included study, with additional feedback from others (SC, DK) as needed.

Methodological quality appraisal

We did not appraise methodological quality or risk of bias of the included articles, which is consistent with guidance on the conduct of scoping reviews.

Synthesis

Microsoft Excel was used to create descriptive statistics to characterize the publications identified in our scoping review along the extracted domains. Data from our scoping results was used to refine and verify our map, identifying, characterizing, and organizing all known pathways by which companies might potentially influence patient care. We created additional maps to separately show industry's financial and non-financial entry points to the system.

Patient and public involvement

We did not include patients or members of the public in the research, as this was beyond the study's scope. A patient representative reviewed the manuscript after submission.

Results

Mapping: Industry and the healthcare ecosystem

Figure 1 depicts the healthcare ecosystem, mapping the complex network of ties associated with the pharmaceutical, medical device, and biotechnology industries across the key activities and parties in the healthcare ecosystem. Beyond its direct ties to all parties and some activities, the medical product industry has numerous indirect ties across the healthcare ecosystem. Similarly, non-financial ties might reinforce or extend companies' financial ones (fig 2 and fig 3).

Relevant parties in the system operate in diverse sectors of public and private life and include non-profit entities (eg, foundations, advocacy groups), the healthcare profession (eg, journals, medical schools, individual professionals), the market supply chain (eg, payers, purchasing and distribution agents), and government (eg, public officials, regulators). The medical product industry also has direct ties to patients and prescribers (box 1 and supplementary appendix F). Notably, the prescriber category is distinct from the individual professionals category, although some clinicians might belong to both categories: Prescriber denotes clinicians in a patient care role (eg, physicians, nurses, physician assistants, advanced nursing professionals) who directly determine utilization of pharmaceuticals, medical devices, and biotechnology products, whereas individual professionals more broadly includes clinicians, researchers, and other healthcare professionals and experts engaged in research, guideline development, formulary selection, health professional education, and other extraclinical activities.

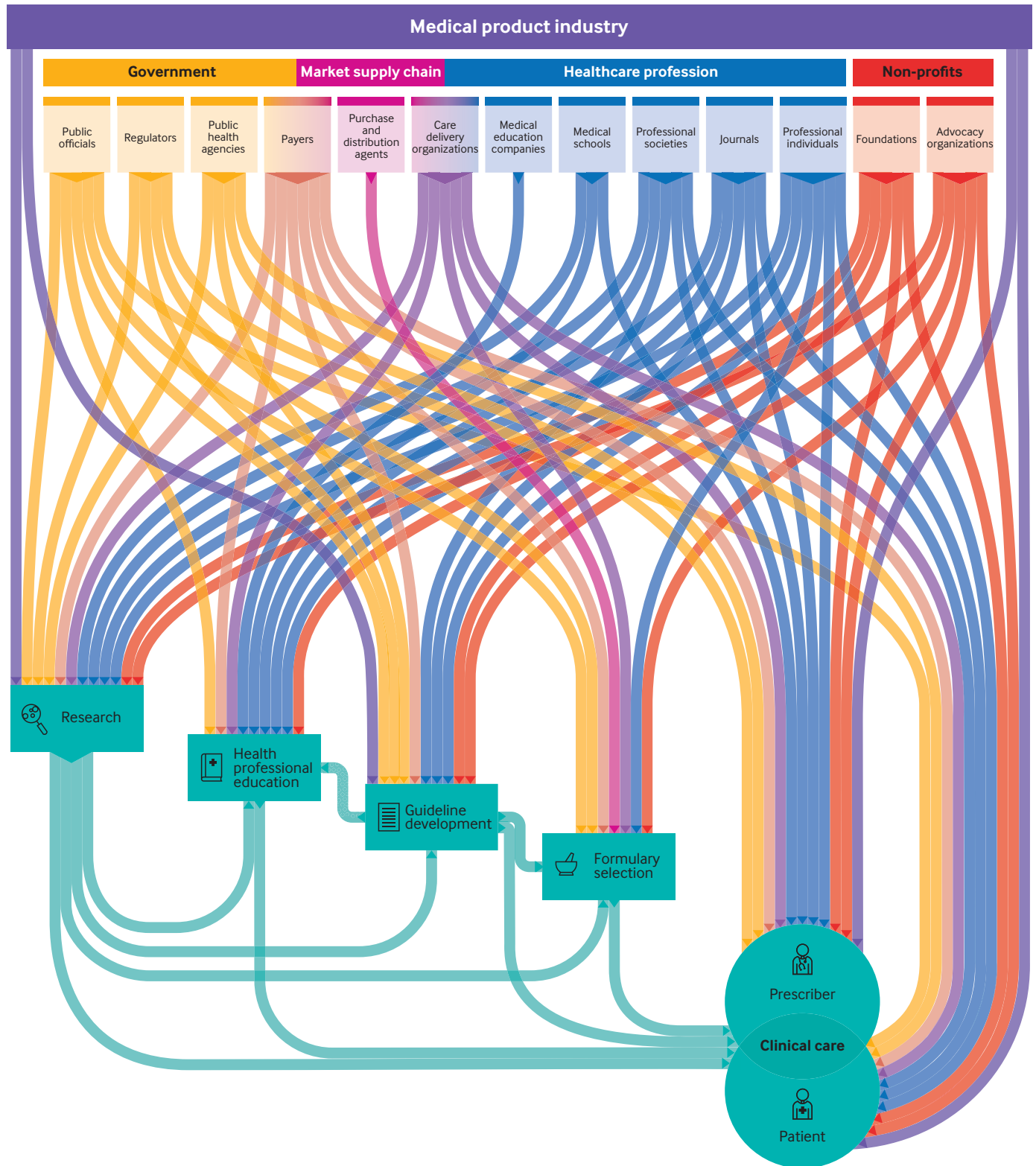


Fig 1 | Ties between the medical product industry and healthcare ecosystem

Many medical product industry ties to these parties are financial, involving money or items of financial value, as when companies negotiate prices with supply chain agents; purchase reprints from journals; make contributions to public officials for campaigns; provide consultancy, speaking, or key opinion leader payments

to healthcare professionals; or financially support government agencies, healthcare organizations, and non-profit entities through donations, grants, or fees. Other ties are non-financial, as in companies' direct-to-consumer advertising to patients, advertising and detailing of prescribers, unpaid professional

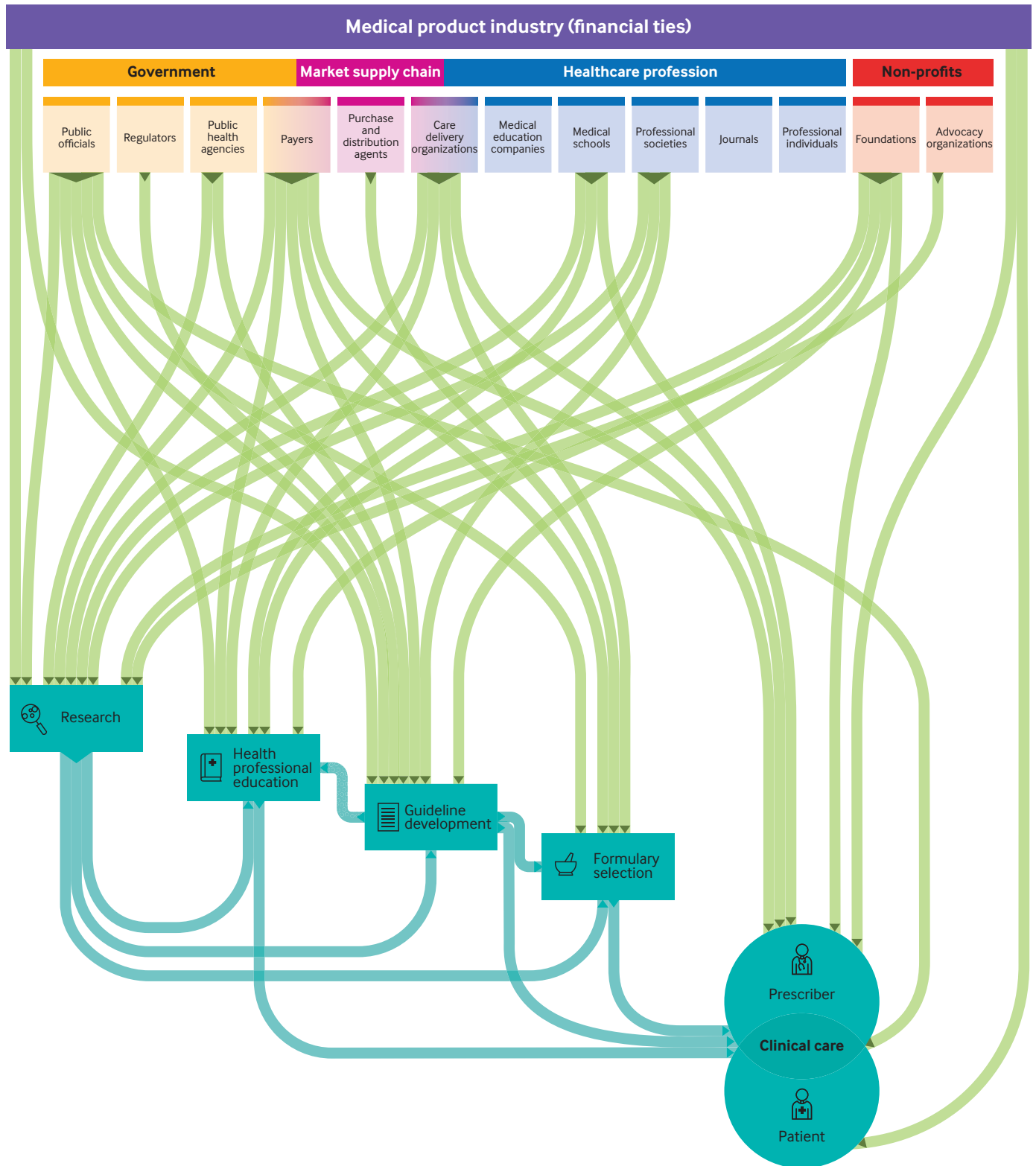


Fig 2 | Pathways of financial ties between the medical product industry and healthcare ecosystem

consultancy work, or the offer of data, authorship, and other professional opportunities to clinicians and researchers. All party types have financial ties to medical product companies. Only payers and distribution agents lack additional, non-financial ties (table 1, supplementary appendix E).

The healthcare ecosystem also includes five activities of clinical inquiry, judgment, and decision making at risk of commercial bias (box 1 and table 1). The medical product industry directly participates in two such activities—research and guideline development. Again, ties might be financial or non-financial, or both.

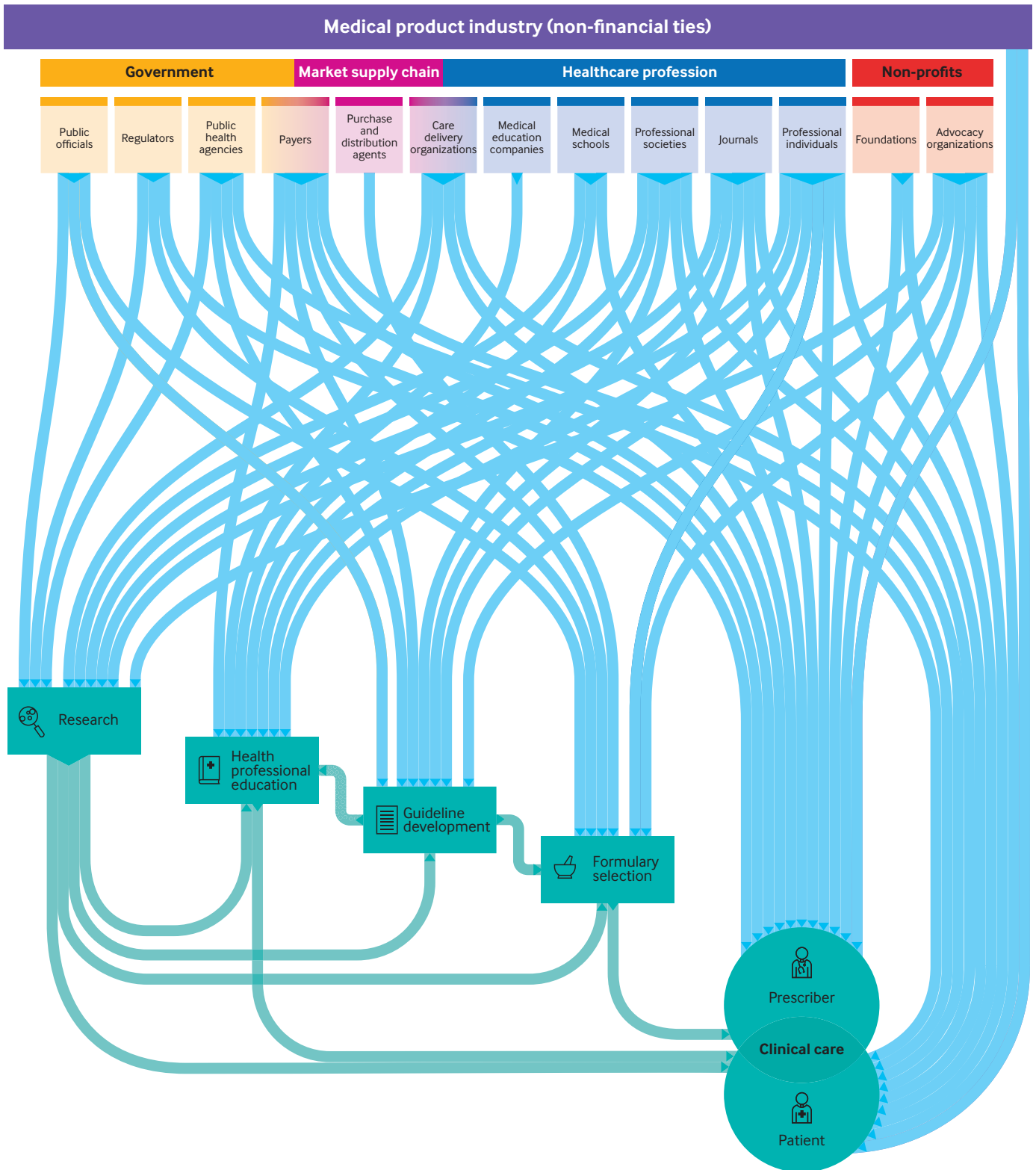


Fig 3 | Pathways of non-financial ties between the medical product industry and healthcare ecosystem

For example, companies might directly fund research or guideline development and might directly provide data, content, or other non-financial assets in support of these activities.

The medical product industry also has numerous, indirect connections to three additional activities—

formulary selection, medical education, and clinical care. We found no documentation to support that companies directly participate in these activities. However, they maintain extensive ties with parties who participate in these activities. For example, individuals and organizations with medical product industry

Box 1: Definitions of terms used in the healthcare ecosystem**Medical product industry**

- Pharmaceutical, medical device, and biotechnology companies that develop and manufacture medical products used in patient care¹

Parties

- *Public officials*—elected or appointed individuals in government positions²⁰
- *Regulators*—government bodies that regulate healthcare delivery or payments²¹
- *Public health agencies*—government agencies that are involved in healthcare but do not directly deliver or regulate healthcare²²
- *Payers*—private and public health insurers²³
- *Purchasing and distribution agents*—organizations that mediate pharmaceutical pricing, payment, and distribution (eg, pharmacy benefit managers, group purchasing organizations, wholesalers)²³
- *Care delivery organizations*—facilities in which clinical care occurs, including hospitals, medical centers, clinics, private practices
- *Medical education companies*—independent privately held businesses, usually for profit entities, that provide education to healthcare professionals²⁴
- *Medical schools*—institutions that award degrees for doctor of medicine or doctor of osteopathic medicine and support academic activities²⁵
- *Professional societies*—membership organizations consisting, and serving the interests, of healthcare professionals of the same type (eg, nurse practitioners) or from the same specialty (eg, family practitioners); activities might include education, development of guidelines and ethical codes, lobbying and advocacy, and publishing²⁶
- *Journals*—publications that report clinical and scientific information to physicians and other healthcare professionals²⁷
- *Individual professionals*—clinicians, researchers, journal editors, healthcare executives, and other experts engaged in research, guideline development, formulary selection, clinical education, or other professional activities outside of clinical care
- *Foundations*—entities that support charitable activities by making grants to unrelated organizations or institutions or to individuals for scientific, educational, cultural, religious, or other charitable purposes²⁸
- *Advocacy organizations*—entities that provide patient focused or caregiver focused support, advocacy, and education, often focused on a disease or set of diseases¹¹
- *Prescribers*—clinicians engaged in patient care activities, including prescribing and use of medical devices and biotech products (eg, physicians, nurse practitioners, physician assistants)

Activities

- *Research*—rigorous investigation into biology, human disease, or healthcare delivery, the results of which guide best healthcare practices²⁹
- *Health professional education*—Knowledge or skill acquisition related to healthcare that occurs away from patients as a free standing activity, with undergraduate, graduate, and continuing (postgraduate) components
- *Guideline development*—systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances³⁰
- *Formulary selection*—the development of ranked or tiered lists of prescription drugs that are covered by a health plan or stocked by a healthcare facility; tiers typically carry different levels of cost sharing (eg, copayments or coinsurance levels)^{23 31}
- *Clinical care*—Clinical interaction between patient and healthcare professional

Ties

- *Financial*—economic assets or monetary payments, including but not limited to consulting fees, research funds, salary, stocks, patents, licenses, gifts, meals, travel funds, educational funds, and materials and equipment for research, education, and clinical care
- *Non-financial*—other assets, including but not limited to information (eg, advertising, literature, reprints, and textbooks, and educational and training sessions), authorship, and data

Table 1 | Examples of parties' and activities' direct financial and non-financial ties to the medical product industry

	Financial ties	Non-financial ties
Activities		
Research ³²	Funding	
Guideline development ³³	Funding	
Parties		
Public officials ³⁴⁻³⁶	Campaign contributions, gifts	Lobbying, professional relationships, information
Regulators ^{37 38}	Funding	Professional relationships
Public health agencies ^{10 39 40}	Funding	Professional relationships
Payers ⁴¹	Rebates	
Purchasing and distribution agents ⁴²	For example, rebates, discounts	
Care delivery organizations ^{1 2}	Funding, gifts, food, patents, royalties	Detailing, information and content, samples, board memberships
Medical education companies ²⁴	Funding	Content
Medical schools ⁴³	Research grants, funding of fellowships, funding of sponsored meetings	Board memberships
Professional societies ^{44 45}	Funding, grants, purchasing membership lists	Content at meetings
Journals ^{46 47}	Ads, supplements, reprints	Content
Individual professionals ^{3 4 32 48}	Gifts, samples, meals, grants, consulting and speaking fees, key opinion leader payments	Professional opportunities, data for research, content, guest authorship
Foundations ⁴⁹	Funding	Professional relationships
Advocacy organizations ⁵⁰⁻⁵⁵	Funding	Content, board memberships
Prescribers ⁵⁶	Reprints, patient materials	Adverts, detailing, throw away journals and other marketing products
Patients ⁵⁷	Copay coupons	Direct-to-consumer adverts, other messages and content

ties often participate in formulary decision making, educational activities, or patient care. Similarly, linkages among activities offer companies indirect ties across the healthcare ecosystem—for example, research informs guideline development, formulary selection, and health professional education.^{1 2} The clinical care activity is unique; representing the intersection between patients and prescribers, it is shaped by all other activities and is the ultimate target of industry interest.^{1 58 59}

Scoping review

The literature search resulted in 2457 citations (fig 4), after elimination of duplicates. On screening of the titles or abstracts and assessing full text for eligibility, we included 538 articles for data abstraction and synthesis (table 2). The articles were published between 1980 and 2019, with half appearing after 2012. The publications spanned 37 countries, with 348 (65%) based in the United States and 190 (35%) in other geographical regions. Most of the articles (451, 84%) were peer reviewed research studies. Overall, 498 (93%) examined pharmaceutical companies, 162

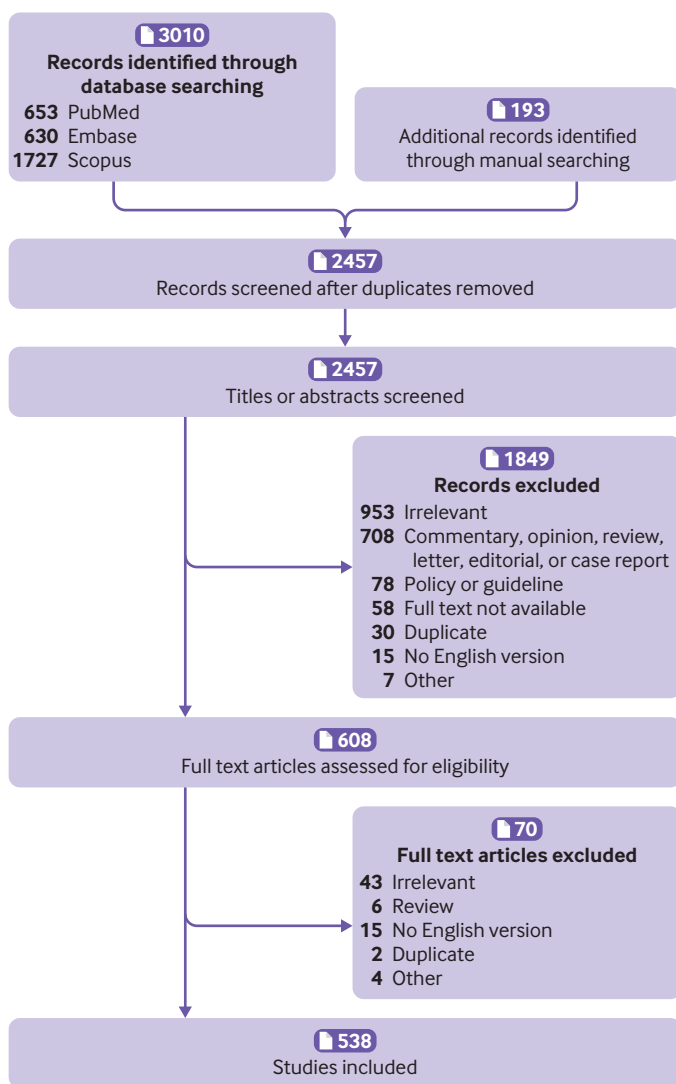


Fig 4 | Flow of articles through scoping review

Table 2 | Characteristics of 538 studies included in scoping review

Characteristics	No (%)
Study type:	
Peer reviewed research	451 (84)
Gray literature	87 (16)
Study location:	
Multiple continents	50 (9)
North America	380 (71)
US	348 (65)
Canada	28 (5)
Mexico	4 (1)
Europe	69 (13)
UK	19 (4)
Denmark	13 (2)
Germany	8 (1)
Other	29 (5)
Asia	24 (4)
East Asia	12 (2)
West Asia and Middle East	8 (1)
South Asia	3 (1)
South East Asia	1 (1)
Australia	18 (3)
South America	6 (1)
Africa	3 (1)
Funding source:	
Medical product industry	13 (2)
Government	81 (15)
Other	98 (18)
None	113 (21)
Not mentioned	171 (32)
Not applicable	62 (12)
Industry type:	
Pharmaceutical	498 (93)
Medical device and biotechnology	162 (30)
Activities:	
Research	303 (56)
Health professional education	145 (27)
Guideline development	33 (6)
Formulary selection	8 (1)
Clinical care	156 (29)
Parties with identified medical product industry ties:	
Public officials	6 (1)
Regulators	19 (4)
Public health agencies	7 (1)
Payers	1 (1)
Purchasing and distribution agents	5 (1)
Care delivery organizations	27 (5)
Medical education companies	6 (1)
Medical schools	34 (6)
Professional societies	31 (6)
Journals	17 (3)
Individual professionals	422 (78)
Foundations	4 (1)
Advocacy groups	22 (4)
Prescribers	65 (12)
Patients	16 (3)
Types of ties:	
Financial	501 (93)
Non-financial	158 (29)

(30%) studied the medical device and biotechnology industries, and 22 (4%) included all three. Notably, nearly all articles in our analysis documented financial transactions (501 (93%)), with non-financial ties appearing less often (158 (29%)).

The most frequently identified parties were within the healthcare profession. Individual professionals

were described in 422 (78%) of the studies, prescribers in 65 (12%), medical schools in 34 (6%), and professional societies in 31 (6%). All other parties appeared in fewer than 5% of the included studies (table 2). The medical product industry's party ties first appeared in the literature in 1980; however, our scoping review found recent citations (2018 or later) for ties to all parties except payers and medical education companies (the most recent documentation dated from 2010 and 2008, respectively).

In total, 303 (56%) of the publications documented medical product industry ties to research, with clinical care and health professional education appearing somewhat less often: 156 (29%) and 145 (27%), respectively. Ties to guideline development and formulary selection appeared in 33 (6%) and eight (1%) publications, respectively (table 2). Although these activity ties appeared in the literature as early as 1980, our scoping review also identified citations dating from 2018 or later for all activities.

Oversight and transparency

For the medical product industry's direct ties to parties and activities, table 3 documents the presence or

absence of conflict of interests oversight and public data, as uncovered by our scoping review or documented on MediSpend Legislative Watch.¹⁹ Policies for medical product industry ties are widespread among healthcare professionals and organizations, with numerous national and international bodies promulgating standards for managing such exchanges. Few, however, substantively deal with non-financial ties. Government parties are subject to varying federal, state, and local policies. Medical product industry communications to patients are federally regulated in the US and New Zealand and more tightly restricted elsewhere, but no established guidelines or policies seem to deal with companies' financial incentives to patients (eg, copay coupons). Similarly, we found no conflict of interests oversight for medical product industry exchanges with non-profit organizations or supply chain agents.

Public databases are far from universal, and the ones we identified exclusively deal with financial transactions (table 3). For example, in the US, Open Payments makes transparent most but not all payments from the medical product industry to teaching hospitals and some prescribers (physicians and dentists, with data collection expanding in 2021

Table 3 | Medical product industry interactions: Sources of transparency and conflict of interests oversight, by activity and party

	Conflict of interests oversight	Public databases
Activities		
Research	None	National laws in Belgium, ^{5 19} Brazil, ^{19 60 61} Colombia, ^{19 62} Denmark, ^{19 63} Estonia, ^{19 64} France, ^{19 65} Indonesia, ^{19 66} Saudi Arabia, ^{19 67} Slovakia, ^{19 68} South Korea, ^{19 69 70} and US ⁶
Health professional education	State law in Vermont ⁷¹	National laws in Belgium, ^{5 19} Brazil, ^{19 60 61} Colombia, ^{19 62} Denmark, ^{19 63} France, ^{19 65} Indonesia, ^{19 66} Saudi Arabia, ^{19 67} Slovakia, ^{19 68} South Korea, ^{19 69 70} and US ⁶ ; state law in Vermont ⁷¹
Guideline development	IOM ¹ and GIN guidelines ⁷²	National law in Brazil ^{19 60 61}
Formulary selection	State law in Massachusetts ⁷³ ; varying institutional policies	National law in Colombia ^{19 62} ; state law in Massachusetts ⁷³
Clinical care	State laws in California, ⁷⁴ Maine, ⁷⁵ Massachusetts, ⁷³ Minnesota, ⁷⁶ New Jersey, ⁷⁷ and Vermont ⁷¹ ; varying institutional policies	National laws in Brazil, ^{19 60 61} Colombia, ^{19 62} Denmark, ^{19 63} Estonia, ^{19 64} France, ^{19 65} Hungary, ^{19 78} Indonesia, ^{19 66} ; Latvia, ^{19 79} Philippines, ^{19 80} Portugal, ^{19 81} Romania, ^{19 82} Slovakia, ^{19 68} South Korea, ^{19 69 70} and US ⁶ ; state laws in Maine ⁷⁵ and Vermont ⁷¹
Parties		
Public officials	None	OpenSecrets.org, ⁵⁷ FollowTheMoney.org ⁸³
Regulators	None	None
Public health agencies	None	None
Payers	None	None
Purchasing and distribution agents	None	None
Care delivery organizations	IOM ¹ and AAMC ² guidelines	National laws in Belgium, ^{5 19} Brazil, ^{19 60 61} Colombia, ^{19 62} Estonia, ^{19 64} France, ^{19 65} Hungary, ^{19 78} Indonesia, ^{19 66} Israel, ^{19 84} Latvia, ^{19 79} Philippines, ^{19 80} Portugal, ^{19 81} Romania, ^{19 82} Saudi Arabia, ^{19 67} and US ⁶
Medical education companies	ACCME policies, ⁸⁵ state law in Vermont ⁷¹	State law in Vermont ⁷¹
Medical schools	State law in Vermont, ⁷¹ AAMC, ² ACCME, ⁸⁵ ACGME ⁸⁶ ; varying Institutional Policies	National laws in Belgium, ^{5 19} Brazil, ^{19 60 61} Colombia, ^{19 62} Estonia, ^{19 64} France, ^{19 65} Hungary, ^{19 78} Indonesia, ^{19 66} Israel, ^{19 84} Latvia, ^{19 79} Philippines, ^{19 80} Portugal, ^{19 81} Romania, ^{19 82} Saudi Arabia, ^{19 67} and US ⁶ ; state law in Vermont ⁷¹
Professional societies	CMSS guidelines ⁸⁷	National laws in Brazil, ^{19 60 61} Colombia, ^{19 62} Estonia, ^{19 64} France, ^{19 65} Philippines, ^{19 80} Portugal, ^{19 81} Romania, ^{19 82} and Saudi Arabia ^{19 67}
Journals	ICMJE guidelines ⁸⁸	None
Individual professionals	State laws in California, ⁷⁴ Maine, ⁷⁵ Massachusetts, ⁷³ Minnesota, ⁷⁶ New Jersey, ⁷⁷ and Vermont ⁷¹ ; varying institutional policies	National laws in Belgium, ^{5 19} Brazil, ^{19 60 61} Colombia, ^{19 62} Denmark, ^{19 63} Estonia, ^{19 64} France, ^{19 65} Hungary, ^{19 78} Indonesia, ^{19 66} Israel, ^{19 84} Latvia, ^{19 79} Philippines, ^{19 80} Portugal, ^{19 81} Romania, ^{19 82} Saudi Arabia, ^{19 67} Slovakia, ^{19 68} South Korea, ^{19 69 70} and US ⁶ ; state laws in Massachusetts ⁷³ and Vermont ⁷¹
Foundations	State law in Vermont ⁷¹	National laws in Colombia ^{19 62} and France ^{19 65} ; state law in Vermont ⁷¹
Advocacy organizations	State law in Vermont ⁷¹	National laws in Belgium, ^{5 19} Brazil, ^{19 60 61} Colombia, ^{19 62} and France ^{19 65} ; state law in Vermont ⁷¹
Prescribers	Varying institutional policies	National laws in Colombia, ^{19 62} Denmark, ^{19 63} Estonia, ^{19 64} France, ^{19 65} Hungary, ^{19 78} Indonesia, ^{19 66} Israel, ^{19 84} Latvia, ^{19 79} Philippines, ^{19 80} Portugal, ^{19 81} Romania, ^{19 82} Saudi Arabia, ^{19 67} Slovakia, ^{19 68} South Korea, ^{19 69 70} and US ⁶

AAMC=Association of American Medical Colleges; ACCME=Accreditation Council for Continuing Medical Education; ACGME=Accreditation Council for Graduate Medical Education; CMSS=Council of Medical Specialty Societies; GIN=Guidelines International Network; ICMJE=International Committee of Medical Journal Editors; IOM=Institute of Medicine.

to include physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, and anesthesiological assistants), and Open Secrets and FollowTheMoney track companies' contributions to state and federal candidates and officials for political campaigns. In Europe, the United Kingdom, Australia, and elsewhere, public reporting systems provide varying degrees of transparency into medical product industry payments to diverse prescribers and individual professionals (in some cases, including physician assistants, nurse practitioners, and others), care delivery organizations, health professional schools, professional societies, foundations, and advocacy organizations. We found no transparency sources for medical product industry ties to regulators, public health agencies, payers, purchasing and distribution agents, or journals.

Discussion

We conducted an extensive scoping review and interviewed experts to document an extensive network of medical product industry ties to activities and parties in the healthcare ecosystem. The pharmaceutical and medical device and biotechnology industries have established numerous ties with non-profit entities, the healthcare profession, the market supply chain, and government. Beyond clinical care, critical activities in the network include research, health professional education, guideline development, and formulary selection.

We found that conflict of interests oversight exists for some financial and a few non-financial ties between the medical product industry and other parties in the healthcare ecosystem, potentially leaving many interactions unregulated. Moreover, public data sources seldom describe or quantify these ties. This observed lack of conflict of interests oversight and transparency offers ample opportunities for medical product industry ties to potentially influence diverse clinical activities, and ultimately patient care, without the public's knowledge. Efforts by all parties are urgently needed to deal with these gaps to protect patient care from commercial bias and to preserve public trust.

Implications

Our mapping illustrates the ways in which medical product industry influence could flow down through a complex network to reach clinical care and impact patients. Companies maintain direct ties to all parties and some activities; these direct ties then potentially extend through interrelationships among parties and activities. Industry influence might accumulate or amplify as it travels through multiple pathways to reach clinical care in ways that could be completely opaque to both clinicians and patients, yet indirect ties and the cumulative effects of those ties are seldom, if ever, examined in the literature. The medical product industry's direct financial ties to clinicians are known to influence prescribing and other activities in which the industry participates.^{1 2 7 9 89 90} Our mapping illustrates how evaluating individual industry ties

might underestimate the routes and magnitude of potential influence.

The findings from our scoping review illustrate the breadth of medical product industry ties to the healthcare ecosystem, with studies from 37 countries spanning six continents—documenting the great scope and diversity of industry targets across the globe. At the same time, our findings highlight the outsized focus in the literature on the healthcare profession, especially on individual professionals and prescribers. This emphasis could result from the relative availability of these data through Open Payments and other public sources. By compiling and mapping the full network of the medical product industry's reach across the healthcare ecosystem, we depict the ways in which potential influence moves well beyond the spheres of individual professionals and prescribers.

Recent examples illustrate the power and implications of the complex ties we expose. Appendix G details how opioid manufacturers provided funding and other assets to prescribers, patients, public officials, advocacy organizations, and other healthcare parties, who, in turn, pressured regulators and public health agencies to quash or undermine opioid related guidelines and regulations.^{47 49} Moreover, we found no evidence that the medical product industry's activities around opioids differed from routine company practices. Analyses of past cases of consumer harm related to medical product industry promotion, as with the drug Vioxx (rofecoxib; Merck)^{91 92} and the weight loss drug fenfluramine-phenteramine (American Home Products),⁹³ have shown a similar, multipronged strategy of outreach to numerous parties, culminating in severe patient harm. Many additional examples of harm from industry promoted products are likely to have been unrecognized or unattributed to medical product companies' activities. Such harms remain unexplored, but many might have led to physical harms as well as social, psychological, and other negative effects on patients.⁹⁴ Moreover, medical product industry influence could undermine healthcare equity and sustainability by driving up costs for individual patients and the healthcare system overall.⁹⁵⁻⁹⁹ In the context of eroding patient trust in the healthcare system, elucidating mechanisms of undue influence is critical.¹⁰⁰ Our analysis and resulting map will facilitate better understanding of these pathways of potential influence and might enable regulators and the healthcare community to better protect patients and ensure public trust.

Limitations of this study

This study has several limitations. First, our findings are limited to medical product industry ties known by our experts or documented in the academic, gray, and lay literatures. Additional ties might yet exist, although our strategy of systematic, duplicative searching and feedback from an international panel of experts is unlikely to have missed common or important ties. Second, we cannot quantify the magnitude of medical product industry influence along pathways in our map.

Third, our study documents not actual bias but the pathways for potential influence across the system. Fourth, our scoping review included older evidence that might not reflect current practices; however, half of included papers were published after 2012, and medical product industry ties to nearly all parties and activities have even more recent documentation, so the body of evidence likely remains relevant. Finally, our review might have missed some policies for conflict of interests and publicly available data sources because we focused on ties, although we did supplement our search by consulting MediSpend Legislative Watch.¹⁹ More research is needed to explore these issues.

Conclusions

The medical product industry maintains an extensive network of financial and non-financial ties with all major healthcare parties and activities. This network seems to be mostly unregulated and opaque. Although the medical product industry is a critical partner in advancing healthcare, companies must also work to maximize profits as part of fiduciary responsibility to shareholders or owners and thus use all available means to promote products. With absent effective conflict of interests oversight, such promotion might ultimately threaten the integrity, equity, and sustainability of healthcare systems and impact individual patients. It is therefore up to other key parties, including the healthcare profession and policy makers, to effectively manage commercial influence, protect patient safety, and ensure public trust.

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Contributors: DK, SC, BB, and PB interviewed experts. DK, SC, MM, and SZ did the scoping review. MM, SZ, SC, and DK analyzed the data. BB, SZ, SC, and DK produced the figures. SC and DK drafted the manuscript. SC, DK, MM, SZ, and PB revised the manuscript. SC and DK are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare support from Arnold Ventures and the Memorial Sloan Kettering Cancer Center. DK's spouse has equity interest and serves on the scientific advisory boards of Vedanta Biosciences and Opentrons and provides consulting for Fimbrion. PBB has received personal fees from Mercer, Foundation Medicine, Grail, Morgan Stanley, NYS Rheumatology Society, Cello Health, Anthem, Magellan Health, EQRx, Meyer Cancer Center of Weill Cornell Medicine, and National Pharmaceutical Council; personal fees and non-financial support from United Rheumatology, Oppenheimer, Oncology Analytics, Kaiser Permanente Institute for Health Policy, Congressional Budget Office, America's Health Insurance Plans, and Geisinger; and grants from Kaiser Permanente and Arnold Ventures outside the submitted work. We, the authors, would like to disclose a potential intellectual bias, in that our concern about undue medical product industry influence motivated us to conduct this study. In view of this, to ensure accurate, reproducible findings, we methodically solicited input on relevant parties, domains, and connections from an international panel of experts on conflict of interests. We then scoured the published literature for all available documentation of these parties, domains,

and connections, following rigorous standards for conducting scoping reviews.

Ethical approval: The institutional review board at Memorial Sloan Kettering Cancer Center determined the study as exempt, category 4 research.

Data sharing: Data are available upon reasonable request to the corresponding author.

The lead authors (SC and DK) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Dissemination to participants and related patient and public communities: We plan to disseminate our findings widely and have developed an interactive tool on our research group's website (www.drugpricinglab.org/tools/octopus/) to enable patients, the public, journalists, policy makers, researchers, and others to explore the flow of medical product industry assets through the healthcare ecosystem.

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- Lo B, Field MJ, eds. *Conflict of Interest in Medical Research. Education, and Practice*, 2009. www.ncbi.nlm.nih.gov/books/NBK22942/
- Association of American Medical Colleges. Industry Funding of Medical Education: Report of an AAMC Task Force. Association of American Medical Colleges, 2008.
- Campbell EG, Weissman JS, Ehringhaus S, et al. Institutional academic industry relationships. *JAMA* 2007;298:1779-86. doi:10.1001/jama.298.15.1779
- Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghostwriting in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. *JAMA* 2008;299:1800-12. doi:10.1001/jama.299.15.1800
- Mitchell AP, Basch EM, Dusetzina SB. Financial relationships with industry among national comprehensive cancer network guideline authors. *JAMA Oncol* 2016;2:1628-31. doi:10.1001/jamaoncol.2016.2710
- Centers for Medicare & Medicaid Services. Open Payments 2014. www.cms.gov/openpayments/ (accessed January 19 2016).
- DeJong C, Aguilar T, Tseng CW, Lin GA, Boscardin WJ, Dudley RA. Pharmaceutical Industry-Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries. *JAMA Intern Med* 2016;176:1114-22. doi:10.1001/jamainternmed.2016.2765
- Kesselheim AS, Robertson CT, Siri K, Batra P, Franklin JM. Distributions of industry payments to Massachusetts physicians. *N Engl J Med* 2013;368:2049-52. doi:10.1056/NEJMp1302723
- Mitchell AP, Trivedi NU, Gennarelli RL, et al. Are Financial Payments From the Pharmaceutical Industry Associated With Physician Prescribing?: A Systematic Review. *Ann Intern Med* 2021;174:353-61. doi:10.7326/M20-5665
- Lexchin J. Declarations of interest by members of Health Canada's special advisory committees and panels: a descriptive study. *CMAJ Open* 2019;7:E334-40. doi:10.9778/cmajo.20190010
- Rose SL, Highland J, Karafa MT, Joffe S. Patient Advocacy Organizations, Industry Funding, and Conflicts of Interest. *JAMA Intern Med* 2017;177:344-50. doi:10.1001/jamainternmed.2016.8443
- Anderson TS, Dave S, Good CB, Gellad WF. Academic medical center leadership on pharmaceutical company boards of directors. *JAMA* 2014;311:1353-5. doi:10.1001/jama.2013.284925
- Saitz R. 'We do not see the lens through which we look': screening mammography evidence and non-financial conflicts of interest. *Evid Based Med* 2013;18:81-2. doi:10.1136/eb-2013-101344
- Hakoum MB, Anouti S, Al-Gibbawi M, et al. Reporting of financial and non-financial conflicts of interest by authors of systematic reviews: a methodological survey. *BMJ Open* 2016;6:e011997. doi:10.1136/bmjopen-2016-011997
- Wiersma M, Kerridge I, Lipworth W. Dangers of neglecting non-financial conflicts of interest in health and medicine. *J Med Ethics* 2018;44:319-22. doi:10.1136/medethics-2017-104530
- Korenstein D, Chimonas S. Deadly Conflict: Physicians, the Medical Profession, and the Opioid Epidemic. *Am J Med Qual* 2021;36:197-9. doi:10.1097/O1.JMQ.0000735464.30763.fc
- Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A Brief History of the Opioid Epidemic and Strategies for Pain Medicine. *Pain Ther* 2018;7:13-21. doi:10.1007/s40122-018-0097-6.

- 18 Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med* 2018;169:467-73. doi:10.7326/M18-0850
- 19 MediSpend. Legislative Watch. www.medispend.com/resources/legislativewatch/ (accessed May 14, 2021).
- 20 OECD. Annual Report on the OECD Guidelines for Multinational Enterprises: Conducting Business in Weak Governance Zones. Paris: OECD; 2006 (accessed May 13, 2021). <https://stats.oecd.org/glossary/detail.asp?ID=7252>.
- 21 Khemani R, Shapiro D. Glossary of Industrial Organization Economics and Competition Law: OECD; 1993 [Commissioned by the Directorate for Financial, Fiscal and Enterprise Affairs]. <https://stats.oecd.org/glossary/detail.asp?ID=3295> (accessed May 13, 2021).
- 22 Institute of Medicine (US) Committee on Educating Public Health Professionals for the 21st Century; Hernandez L, ed. Who Will Keep the Public Healthy? Educating Public Health Professionals for the 21st Century. Washington DC, 2003. www.ncbi.nlm.nih.gov/books/NBK221695/
- 23 Drug Pricing Lab. Glossary 2018. <https://drugpricinglab.org/learn/glossary/> (accessed December 3, 2019).
- 24 Golestaneh L, Cowan E. Hidden conflicts of interest in continuing medical education. *Lancet* 2017;390:2128-30. doi:10.1016/S0140-6736(17)32813-1
- 25 Gregg A, Turner EL, Scarborough H, et al. Medical Education: Encyclopaedia Britannica; 2014. www.britannica.com/science/medical-education (accessed December 3, 2019).
- 26 Rothman DJ, McDonald WJ, Berkowitz CD, et al. Professional medical associations and their relationships with industry: a proposal for controlling conflict of interest. *JAMA* 2009;301:1367-72. doi:10.1001/jama.2009.407
- 27 Stevens LM, Lynn C, Glass RM. JAMA patient page. Medical journals. *JAMA* 2006;295:1860-60. doi:10.1001/jama.295.15.1860
- 28 Grantspace. What is a Foundation?: Candid Learning; 2019. <https://grantspace.org/resources/knowledge-base/what-is-a-foundation/> (accessed December 3, 2019).
- 29 California Biomedical Research Association. What is Biomedical Research? 2018. <https://ca-biomed.org/wp-content/uploads/2020/08/FS-What-is-Biomedical.pdf> (accessed December 3, 2019)
- 30 Medicine 10. *Clinical Practice Guidelines: Directions for a New Program*. National Academies Press, 1990.
- 31 Werble C. Health Policy Brief: Formularies. *Health Affairs* 2017. doi:10.1377/hpb20171409.000177
- 32 Rasmussen K, Bero L, Redberg R, Gøtzsche PC, Lundh A. Collaboration between academics and industry in clinical trials: cross sectional study of publications and survey of lead academic authors. *BMJ* 2018;363:k3654. doi:10.1136/bmj.k3654
- 33 Mitchell AP, Basch EM, Dusetzina SB. Financial Relationships With Industry Among National Comprehensive Cancer Network Guideline Authors. *JAMA Oncol* 2016;2:1628-31. doi:10.1001/jamaoncol.2016.2710
- 34 Lucas ELS. Pharma Cash To Congress: Kaiser Health News; 2019. <https://khn.org/news/campaign/> (accessed December 5, 2019).
- 35 Rosenthal E. Drug Makers' Push Leads to Vaccines' Fast Rise. *New York Times* (1923-Current file) 2008:A1.
- 36 Facher L. Pharma funded more than 2,400 state lawmaker campaigns in 2020, new STAT analysis finds. *STAT News* June 9, 2021.
- 37 Chen C. FDA Repays Industry by Rushing Risky Drugs to Market: ProPublica. 2018. www.propublica.org/article/fda-repays-industry-by-rushing-risky-drugs-to-market
- 38 Loff B, Corder S. Australian government loosens its grip on the pharmaceutical industry. *Lancet* 2001;357:453. doi:10.1016/S0140-6736(05)71269-1
- 39 Lenzer J. Centers for Disease Control and Prevention: protecting the private good? *BMJ* 2015;350:h2362. doi:10.1136/bmj.h2362
- 40 Lupkin S. Big Pharma Greets Hundreds of Ex-Federal Workers At The 'Revolving Door': Kaiser Health News; 2018. <https://khn.org/news/big-pharma-greets-hundreds-of-ex-federal-workers-at-the-revolving-door/> (accessed December 5, 2019).
- 41 The Wave of PBM and Insurer Integration Continues as Cigna and Express Scripts Announce a Merger of Their Own: Hall Render, 2018. www.hallrender.com/2018/03/16/the-wave-of-pbm-and-insurer-integration-continues-as-cigna-and-express-scripts-announce-a-merger-of-their-own/
- 42 Shepherd J. Pharmacy Benefit Managers, Rebates, and Drug Prices: Conflicts of Interest in the Market for Prescription Drugs. *Yale Law Policy Rev* 2019;38. doi:10.2139/ssrn.3313828
- 43 Bhar RH, John D. Conflict of interest in systematic reviews and its implications for public health policy. *Indian J Med Ethics* 2019;4:288-93. doi:10.20529/IJME.2019.058
- 44 Dalsing MC. Industry working with physicians through professional medical associations. *J Vasc Surg* 2011;54(Suppl):41S-6S. doi:10.1016/j.jvs.2011.04.068
- 45 Antonelli M, Coopersmith CM. Professional medical societies: do we have any conflict of interest with industry? *Intensive Care Med* 2018;44:1762-4. doi:10.1007/s00134-018-5304-8
- 46 Liang F, Zhu J, Mo M, et al. Role of industry funders in oncology RCTs published in high-impact journals and its association with trial conclusions and time to publication. *Ann Oncol* 2018;29:2129-34. doi:10.1093/annonc/mdy305
- 47 Fugh-Berman A, Alladin K, Chow J. Advertising in medical journals: should current practices change? *PLoS Med* 2006;3:e130. doi:10.1371/journal.pmed.0030130
- 48 Kesselheim AS, Woloshin S, Lu Z, Tessema FA, Ross KM, Schwartz LM. Internal Medicine Physicians' Financial Relationships with Industry: An Updated National Estimate. *J Gen Intern Med* 2019;34:195-7. doi:10.1007/s11606-018-4688-z
- 49 Foundation P-CR. About PCRf. https://pcrfoundation.org/about_pcrf (accessed November 11, 2019).
- 50 Lexchin J. Association between commercial funding of Canadian patient groups and their views about funding of medicines: An observational study. *PLoS One* 2019;14:e0212399. doi:10.1371/journal.pone.0212399
- 51 Lavery H, Meulien P. The Innovative Medicines Initiative - 10 Years of Public-Private Collaboration. *Front Med (Lausanne)* 2019;6:275. doi:10.3389/fmed.2019.00275
- 52 Kopp E, Lupkin S, Lucas E. KHN launches "Pre\$cription for Power," a groundbreaking database to expose Big Pharma's ties to patient groups.: Kaiser Health News; 2018. <https://khn.org/news/patient-advocacy-groups-take-in-millions-from-drugmakers-is-there-a-payback/> (accessed December 5, 2019).
- 53 McCoy MS, Carniol M, Chockley K, Urwin JW, Emanuel EJ, Schmidt H. Conflicts of Interest for Patient-Advocacy Organizations. *N Engl J Med* 2017;376:880-5. doi:10.1056/NEJMs1610625
- 54 Lupkin S, Lucus E, Knight V. Big Pharma Gave Money To Patient Advocacy Groups Opposing Medicare Changes 2019. <https://khn.org/news/big-pharma-gave-money-to-patient-advocacy-groups-opposing-medicare-changes/> (accessed December 5, 2019).
- 55 Mandeville KL, Barker R, Packham A, Sowerby C, Yarrow K, Patrick H. Financial interests of patient organisations contributing to technology assessment at England's National Institute for Health and Care Excellence: policy review. *BMJ* 2019;364:k5300. doi:10.1136/bmj.k5300
- 56 Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on Physicians and Patients Pew Prescription Project: Pew Trusts; 2013. www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients (accessed December 5, 2019).
- 57 Center for Responsive Politics. Open Secrets. www.opensecrets.org/
- 58 Morgan DJ, Leppin AL, Smith CD, Korenstein D. A Practical Framework for Understanding and Reducing Medical Overuse: Conceptualizing Overuse Through the Patient-Clinician Interaction. *J Hosp Med* 2017;12:346-51. doi:10.12788/jhm.2738
- 59 Dana J, Loewenstein G. A social science perspective on gifts to physicians from industry. *JAMA* 2003;290:252-5. doi:10.1001/jama.290.2.252
- 60 Ross JS, Lackner JE, Lurie P, Gross CP, Wolfe S, Krumholz HM. Pharmaceutical company payments to physicians: early experiences with disclosure laws in Vermont and Minnesota. *JAMA* 2007;297:1216-23. doi:10.1001/jama.297.11.1216
- 61 Gibbons RV, Landry FJ, Blouch DL, et al. A comparison of physicians' and patients' attitudes toward pharmaceutical industry gifts. *J Gen Intern Med* 1998;13:151-4. doi:10.1046/j.1525-1497.1998.00048.x
- 62 Resolution 002881: Colombian Ministry of Health and Social Protection. 2018. www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/DIJ/resolucion-2881-de-2018.pdf [In Spanish.]
- 63 Lake L, Kroon M, Sanders D, et al. Child health, infant formula funding and South African health professionals: Eliminating conflict of interest. *South African Med J* 2019;109:902-06. doi:10.7196/SAMJ.2019.v109i12.14336
- 64 Medicinal Products Act. Estonia, 2004. www.riigiteataja.ee/en/eli/ee/525112013005/consolide/current
- 65 Sunshine Regulations: relating to the public declaration of interests provided for in Article L. 1451-1 of the Public Health Code and to the transparency of the advantages granted by companies producing or marketing products for health and cosmetic purposes intended for humans. 2016 Rule No. Decree No 2016-1939. www.legifrance.gouv.fr/jorf/id/JORFTEXT000033735450?r=7tmnlBwDxf
- 66 Oberlin DT, Gonzalez CM. Industry Ties in Medicine: Insight from the Open Payments Program. *Mayo Clin Proc* 2016;91:685-6. doi:10.1016/j.mayocp.2016.02.003
- 67 Transparency and Payment Disclosure Guidelines for Medical Companies. Saudi Food and Drug Authority, 2016.
- 68 Act on Medicinal Products and Medical Devices and on Amendments to Certain Acts. Act No 362. Slovakia, 2011.
- 69 Pharmaceutical Affairs Act. South Korea, 2016. https://elaw.klri.re.kr/eng_service/lawView.do?hseq=40196&lang=ENG

- 70 Medical Devices Act. South Korea, 2018. https://elaw.klri.re.kr/eng_service/lawView.do?hseq=48691&lang=ENG
- 71 Stack SJ. AMA Statement on Sunshine Act Data Release, 2015. www.ama-assn.org/press-center/press-releases/ama-statement-sunshine-act-data-release
- 72 Schünemann HJ, Al-Ansary LA, Forland F, et al, Board of Trustees of the Guidelines International Network. Guidelines International Network: Principles for Disclosure of Interests and Management of Conflicts in Guidelines. *Ann Intern Med* 2015;163:548-53. doi:10.7326/M14-1885
- 73 Pharmaceutical and medical device manufacturer conduct created as part of Chapter 305 of the Acts of 2008, An Act to Promote Cost Containment, Transparency and Efficiency in the Delivery of Quality Health Care. Code No 105 CMR 970.00. Massachusetts Department of Public Health, 2012. www.mass.gov/regulations/105-CMR-97000-pharmaceutical-and-medical-device-manufacturer-conduct
- 74 Chapter 8. *Drug Marketing Practices*. California Health and Safety Code, 2002.
- 75 An Act to Prohibit Certain Gifts to Health Care Practitioners, 2017. Public Law No: Title 32 Chapter 267.13759. www.mainelegislature.org/legis/bills/bills_124th/billpdfs/HP088101.pdf
- 76 Kessel M. Restoring the pharmaceutical industry's reputation. *Nat Biotechnol* 2014;32:983-90. doi:10.1038/nbt.3036
- 77 Limitations On and Obligations Associated with Prescriber Acceptance of Compensation From Pharmaceutical Manufacturers. Public Law No: Title 13 of Law and Public Safety Chapter 45J.1.3-45J.1.4. New Jersey Administrative Code, 2008. www.njconsumeraffairs.gov/regulations/Chapter-45J-Prescriber-Compensation.pdf
- 78 Act XCVIII of 2006 on safety and efficient supply of pharmaceuticals and medical devices as well as on the general rules of pharmaceuticals distribution. Ministry of Health, 2006.
- 79 Procedures for Advertising Medicinal Products and Procedures by Which a Medicinal Product Manufacturer is Entitled to Give Free Samples of Medicinal Products to Physicians. Latvia, 2011. [https://uk.practicallaw.thomsonreuters.com/w-030-0967?transitionType=Default&contextData=\(sc.Default\)&firstPage=true](https://uk.practicallaw.thomsonreuters.com/w-030-0967?transitionType=Default&contextData=(sc.Default)&firstPage=true)
- 80 Department of Health, Republic of the Philippines. Implementing Guidelines on the Promotion and Marketing of Prescription Pharmaceutical Products and Medical Devices. 2015. www.pcom.ph/sites/default/files/downloads/ao_on_marketing_of_drugs.pdf
- 81 Koch C, Stoll M, Klemperer D, Lieb K. Transparency of Conflicts of Interest: A Mixed Blessing? The Patients' Perspective. *Am J Bioeth* 2017;17:27-9. doi:10.1080/15265161.2017.1313338
- 82 Article 35 of "Annex 1 to Order of the Minister of Health no. 194/2015 Rules for Assessment and Approval of Advertising Medicinal Products for Human Use". Romania, 2015. <https://www.anm.ro/en/medicamente-de-uz-uman/legislatie/ordine-de-ministru/>
- 83 National Institute on Money in Politics. FollowTheMoney.org.
- 84 National Health Insurance Law. 1994.
- 85 Accreditation Council for Continuing Medical Education. Financial Relationships and Conflicts of Interest. 2019. www.icmje.org/recommendations/browse/roles-and-responsibilities/author-responsibilities--conflicts-of-interest.html (accessed 12/3/19).
- 86 Accreditation Council for Continuing Medical Education. Principles to Guide the Relationship between Graduate Medical Education, Industry, and Other Funding Sources for Programs and Sponsoring Institutions Accredited by the ACGME, 2011. www.acgme.org/globalassets/PFAssets/PublicationsPapers/GME-Funding-Industry-Other-Sources.pdf
- 87 Kahn NB Jr, Lichter AS, Council of Medical Specialty Societies. The new CMSS code for interactions with companies managing relationships to minimize conflicts. *J Vasc Surg* 2011;54(Suppl):34S-40S. doi:10.1016/j.jvs.2011.05.109
- 88 International Committee of Medical Journal Editors. Conflicts of Interest. 2019. www.icmje.org/recommendations/browse/roles-and-responsibilities/author-responsibilities--conflicts-of-interest.html (accessed 12/3/19).
- 89 Yeh JS, Franklin JM, Avorn J, Landon J, Kesselheim AS. Association of Industry Payments to Physicians With the Prescribing of Brand-name Statins in Massachusetts. *JAMA Intern Med* 2016;176:763-8. doi:10.1001/jamainternmed.2016.1709
- 90 Robertson C, Rose S, Kesselheim AS. Effect of financial relationships on the behaviors of health care professionals: a review of the evidence. *J Law Med Ethics* 2012;40:452-66. doi:10.1111/j.1748-720X.2012.00678.x
- 91 Krumholz HM, Ross JS, Presler AH, Egilman DS. What have we learnt from Vioxx? *BMJ* 2007;334:120-3. doi:10.1136/bmj.39024.487720.68
- 92 Waxman HA. The lessons of Vioxx—drug safety and sales. *N Engl J Med* 2005;352:2576-8. doi:10.1056/NEJMp058136
- 93 In D. *An Ethical Minefield*. 2001;20:302-3. doi:10.1377/hlthaff.20.6.302
- 94 Korenstein D, Chimonas S, Barrow B, Keyhani S, Troy A, Lipitz-Snyderman A. Development of a Conceptual Map of Negative Consequences for Patients of Overuse of Medical Tests and Treatments. *JAMA Intern Med* 2018;178:1401-7. doi:10.1001/jamainternmed.2018.3573
- 95 Dave DM. Effects of pharmaceutical promotion: A review and assessment. 2013; National Bureau of Economic Research, Cambridge, MA, USA. www.nber.org/system/files/working_papers/w18830/w18830.pdf
- 96 Lexchin JGG, Models for financing the regulation of pharmaceutical promotion. *Globalization Health* 2012;8:1-7.
- 97 Avorn J. Advertising And Prescription Drugs: Promotion, Education, And The Public's Health. *Health Affairs* 2003;22:W3-104.
- 98 Gagnon M-A. Corruption of pharmaceutical markets: addressing the misalignment of financial incentives and public health. *J Law Med Ethics* 2013;41:571-80.
- 99 Morgan SG, Bathula HS, Moon S. Pricing of pharmaceuticals is becoming a major challenge for health systems. *BMJ* 2020;368:l4627. doi:10.1136/bmj.l4627
- 100 Jain SH, Lucey C, Crosson FJ. The Enduring Importance of Trust in the Leadership of Health Care Organizations. *JAMA* 2020;324:2363-4. doi:10.1001/jama.2020.18555

Supplementary information: Appendices A-G