Chapter 2
Funding and Bias

Information Dissemination

The patient-centered movement in the medical profession reinforces patient autonomy while patients make their health care decisions. Truly autonomous decision-making relies crucially on informed consent, and in turn, informed consent requires information [1]. All this begs the question: where does this information come from? Put another way, how do the results of researchers' studies reach patients? The information chain from researcher to patient is comprised of multiple players, including: the researcher, the funder of the research, the medical journal editor, the journalist whose interpretation of the study appears in popular media, the doctor reading the study, and the patient reading the journalist's article. Together, these players serve to fund, research, disseminate, and implement new medical advances. How effective is this process in transporting a clear message from start (researcher) to finish (patient)? Consider the playground game of "Telephone," in which children sit in a row and whisper a message from one end of the line to the other. As in the game, even when no one intentionally distorts the message, the end result the patient hears is often radically different than the one the researcher meant to deliver. Distortion can occur without necessarily malicious intent because each player in the process brings his or her own biases into the process.

Bias

Now is the time to define the word bias, for both physician and patient. Bias carries a negative connotation in the popular lexicon. In everyday language, only judgmental, close-minded people are biased. This chapter will heavily review how

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explicit kinds of biases affect research studies. However, from a psychological standpoint, the construct of a bias can also refer to a neutral process. **Biases** are our brains' automatic and unconscious processes that occur without our intent [2]. In the field of psychology, everyone is biased. Biases operate to affect our thinking and subsequent behavior without conscious awareness. This category of biases is said to be "implicit" [2]. Cognitive psychologists refer to a bias when they describe any particular systematic "lean" of our brains. Psychologists consider these biases systematic because they function in a relatively predictable fashion; that is, they are not random.

To Explain to a Patient

Biases can be thought of as sunglasses for our brains. Sunglasses are not inherently bad. They might even serve some goals well: to look attractive, to filter out harmful UV rays, or to reduce the discomfort of bright light. Sunglasses accomplish all these goals by way of distortion. Biases in our brains are the same. They create slight distortions to serve a goal (e.g., to react quickly, to reduce cognitive burden, to simplify disparate details into a cohesive story). When people wear sunglasses for a long time, they eventually "forget" they are wearing them. Their brains stop consciously noting that the environment looks darker, and they begin to operate as if this is the way the world always looks. Anyone who has ever forgotten to remove their sunglasses even once they have entered a building has experienced how easy it is to lose track of a distortion. This is what biases do. They provide distortions for such a prolonged time that your brain does not notice them. Biases are systematic, in that they are not random; they work in one way. Similarly, one pair of sunglasses can also only make things look darker. They do not sometimes make things darker, other times lighter, and other times tinted green or yellow. However your sunglasses distort, they distort this way every time. Each bias is like that, too. Even though we often do not notice them, they behave in a predictable fashion.

Biases exist in everyone's brains and affect our behavior. Because the chain of information from researcher to patient involves a myriad of people, all of those biases gradually distort the message as it winds its way through the chain. We will examine different biases that occur among the parties to affect their behaviors within the research process.

A bias affecting people who are involved in research projects spanning years is called the **sunk cost fallacy**. This bias exists because people do not make each decision in their lives independently of others they have already made. Instead, people perform something called "mental accounting," in which they take their previous decisions into account when making a new one. This bias is designed to keep people on track with their goals. For example, when someone is deciding

whether or not to eat a piece of cake, that individual will factor into their decision that they already indulged in ice cream and cookies earlier in the day. The true decision is not whether to eat cake or not eat cake, the decision is whether to eat cake in addition to the other sweets consumed that day. In this fashion, mental accounting can be helpful.

However helpful mental accounting may be, the sunk cost fallacy bias that distorts thinking and prompts people to put more energy into an endeavor if they have already put some energy into it previously [2]. It takes a great deal of effort for people to realize their project is not reaping benefits, and that subsequently, stopping is the most cost-effective choice. In deciding whether or not to stop, people utilize mental accounting and factor in everything they have already poured into the project. They want the work to pay off to justify all of their previous efforts. As much as this makes sense on the surface, the logic is only a result of our faulty mental accounting. In truth, once something is done, it becomes a "sunk cost." It cannot be recouped at any point regardless of the next move. Take, as an example of a sunk cost, startup costs for a company. The money spent to start the company is spent before the company can generate a return. It is gone, regardless of whether the company makes money or does not.

To Explain to a Patient

Ask your patient if they have ever spent more time on something than they originally intended to because by the time they realized it was not going well, it felt too late to stop. If they found themselves putting in more time and energy into something that was not going well than they normally would, ask them if it was because they had already spent time on it. This is the sunk cost fallacy.

Researchers are not immune to the sunk cost fallacy. Initial interest prompts researchers into their fields of study. This interest represents an emotional investment in their work. They complete many years of advanced schooling to enter positions for conducting their research. These years—of at least forgoing income while studying, if not also paying outright for tuition—represent time and financial costs. Once finally able to begin conducting their own studies, researchers have already invested considerable cost into their work. The sunk cost fallacy is ripe to unconsciously distort their behaviors at this stage. No matter how objective researchers consciously strive to remain, the sunk cost fallacy urges them to unconsciously hope for one outcome over another.

Funders with a vested interest (i.e., financial incentive) in one outcome over another are also prone to sunk cost fallacy. Pharmaceutical companies consider the money they stand to make should a study go well, and the money they will lose if study results are delayed or disappointing. In some cases, the desire for a return

on investment is more than simply an implicit bias—it is a conscious anxiety that affects pharmaceutical companies' choices, which we will see later in detail.

Another bias in research affecting people who have an idea that one outcome is more likely than another is the **confirmation bias** [2]. All people with ideas experience confirmation bias. Whenever people have a preconceived opinion about something, the confirmation bias leads them to selectively look for evidence in favor of their opinion and discount information that does not fit their opinion. Just as with other implicit biases, confirmation bias is not intentional.

To Explain to a Patient

Ask your patient how they perform searches on the Internet. For example, imagine they have been worried about how much juice is safe to give their child. Do they enter, "Recommended daily juice intake for children" or do they enter, "How much juice is too much for children?" Many patients will enter the latter. That is because we search for information based on what we already expect to find. But confirmation bias is not finished yet. After performing the search, most people would skim over results that indicate any possible health benefits of some juice intake and click on the links that highlight overconsumption and the effects thereof. This selective searching and acquisition of new information is confirmation bias.

Researchers, certain funders, academic journal editors, pediatricians, and patients alike experience confirmation bias. Researchers want to find a positive outcome, whether that outcome is a cure for a disease or a new neuronal explanation for a disorder. The modern scientific process depends on researchers first theorizing and choosing a hypothesis before starting their study. Requiring researchers to first form a hypothesis is a direct path to confirmation bias. Pharmaceutical companies have a somewhat more explicit confirmation bias at play, and we will review the behavioral outcomes of the bias in this group. Academic journal editors decide what papers to accept based on how the study will be received by the medical community. Making this determination can only be done if those editors have their own ideas about hypotheses and trends in science. They then accept papers that reinforce their ideas. When physicians and patients read about new studies (whether in the medical literature or in the media), confirmation bias prompts them to spend more time reading studies that reinforce what they already believe or hope to be true. When individuals read studies refuting their hypotheses, skepticism increases. Skepticism prompts them to initiate searches for flaws in the design or other information that will help them discount the study findings.

The last bias affecting essentially everyone in the research chain is the **novelty preference**. This bias operates in humans because we are primed to attend to stimuli that are new and different for the purposes of learning [3]. (Of course at other times people evince a familiarity bias; the two seem to serve different

purposes.) New events or knowledge represent a possible source of benefit or harm beyond people's typical experiences. The novelty preference helps individuals pay attention to learn whether this new stimulus is helpful or harmful. Psychologists describe things that command an outsize place of precedence in our minds as being **salient**. Newness is highly salient.

To Explain to a Patient

Ask your patients to imagine their houses in their minds. Most pieces of furniture and decorations are in the same place every day. Has the patient ever, one day, moved something? What happened when they came back home later that day or woke up the next day? Did they suddenly "notice" that piece of furniture or decoration in a way they hadn't before they moved it? That is novelty preference. There is no reason for their notice of this item beyond the novelty of the location. The novelty preference means we pay more attention to something just because it is novel and not because that novelty is necessarily good or bad.

The field of research seeks to uncover new information. Even historians, who research past events, search for new developments in their field. Other than replication studies—a necessary part of the scientific process—all studies conducted are rooted in the idea that the results will uncover some new, as of yet unknown information. The novelty preference leads researchers to believe their findings are inherently important and worthy of attention because they are new. Pharmaceutical companies use patients' novelty preference to sell "me too" drugs: medications essentially the same as the preexisting medications. Marketers easily sell these kinds of medications to consumers based solely on their newness [4]. Medical journal editors are tasked with publishing innovative findings. The general public reads newspapers or online media to find out what has recently happened. Readers are not interested in yesterday's news. Journalists prefer writing about new treatments, aware that these articles will garner more reader interest than if they were to write about established treatments.

The implicit biases discussed here are, with a few exceptions, largely blameless. Implicit cognitive biases influence how all people operate their lives. These barely perceptible distortions naturally influence the chain of communication from researcher to patient. Because implicit biases operate below our consciousness, patients are likely unaware how such biases influence what they seek out and read about research. Discussing these implicit biases can help patients remove their metaphorical sunglasses, if only temporarily.

In addition to implicit biases, explicit biases influence the research process and are not morally neutral. Explicit biases function in conscious awareness and can result in everything from neglect and carelessness to outright fraud. The remainder of this chapter focuses on one of the greatest sources of conscious bias in research:

funding bias. While the medical profession is designed to help people, the pharmaceutical industry is designed to earn a profit for shareholders and CEOs. This divergence of goals has not escaped many patients' notice. Yet self-interest is not the all-powerful motivator some believe it to be [5]. Patients can benefit from an increased understanding as to how funding is more or less likely to affect study outcomes. Armed with this knowledge, they can more accurately calibrate their opinions on the research results they encounter.

Before discussing how funding can influence outcomes, we will preview how outcomes are typically reached in research studies. The next chapter provides a complete review of how studies are run and conclusions drawn. Many studies seek to determine if a new treatment provides better health outcomes than the preexisting treatment (if one exists). As such, researchers directing these studies look for evidence of a difference between the treatments. Differences are observed through the use of inferential statistics. These statistics are based on a concept of disputing the null hypothesis, which is a concept that presupposes there will be no difference between the groups. Studies showing evidence in favor of a difference between the groups are said to be "significant." Notably, statistical significance and clinical significance are separate issues, which we will discuss in depth later in this book. Much as how the American legal system is based on a presumption of innocence (placing the burden on the plaintiff or prosecution to supply enough evidence of wrongdoing), research studies presume no difference between two groups, and the results of the research study shoulder the responsibility of rejecting the null hypothesis. The null hypothesis is rejected on the basis that it is statistically extremely unlikely that the difference observed between the two groups is by chance. The null hypothesis itself can never be proven, because in this case, it is not possible to prove a negative (this is relevant when discussing the limitations of research studies with parents).

Funding Sources

Funding in medical research can be divided into two large categories: publicly funded and privately funded. Public funds come from sources such as the government or charities, where money (typically from taxes or donations) is disbursed with the aim of funding the activities that constitute a civil society. Public funds are designed to promote the public good and are not intended to have a specific agenda. People who give their dollars to charities do not do so with the aim of getting more money in return (although some may hope their charitable donations curry favor or win them influence).

Private funds come from privately held companies, in which individuals invest their money with the stated aim of seeing a return on their investment. The goal for dollars from private funding is to earn more dollars. For example, a company that invests its own money in research and development is anticipating eventually selling the resulting product at a profit.

The main source of public funding in medical research is the National Institute of Health (NIH) [6]. The United States founded the NIH the late nineteenth century. It now disburses approximately 30.1 billion dollars annually [6]. Funded with taxpayer dollars, the NIH is government-run and nonprofit. The NIH does not take in money based on its research efforts, although a small percentage of its research dollars fund grants and contracts through Small Business Innovation Research and Small Business Technology Transfer initiatives [7]. Therefore, NIH-funded research trials are fairly unlikely to be influenced by financial motives. The dedicated cynic will point out that it is impossible to be truly disinterested in money. Nevertheless, influence due to money is observed to occur less in publicly funded trials than in privately funded ones, as discussed below.

Private funding for medical research overwhelmingly comes from pharmaceutical companies [8]. While the NIH continues to be the primary funder for basic research science, in the mid-1980s pharmaceutical companies surpassed the NIH as the primary funder of biomedical research [8, 9]. In 2013, the top pharmaceutical company spent over 8 billion dollars in research and development [10]. Even as far back as a decade ago, estimates found that for-profit entities sponsored 75% of clinical research [8].

As corporate entities, the goal of a pharmaceutical manufacturer is to make money, ideally as quickly as possible. If shares of the company are traded on the stock market, their earnings are reported quarterly. This produces a near-constant pressure to perform well (i.e., make money). This pressure causes myopia of goals, prioritizing short-term monetary outcomes over long-term health gains.

Conducting research is a costly and time-consuming effort. Given their profit motives, it seems paradoxical that pharmaceutical companies would fund research at all. Yet they do not have a choice. By law, prior to selling a new medicine or treatment, companies must prove to the Food and Drug Administration (FDA) that the product passed efficacy and safety standards [11]. This proof is available only through research. Hence, pharmaceutical companies find themselves involved simultaneously in two activities—marketing and research—with divergent goals. The goal of marketing is to make money, and making money requires that the information be in the product's favor. The goal of research is to expand knowledge in the field (whatever that knowledge may show), and in doing so, it expends vast sums of money. These goals are not quite diametrically opposed, but there is significant tension between them. This tension creates an inherent conflict of interest that serves as a common thread running through all pharmaceutical research.

For a multitude of practical reasons, pharmaceutical companies typically do not conduct research in-house [11]. Instead, these companies previously relied heavily on academic researchers to assist in conducting their trials [11]. Including academic researchers was thought to mitigate the pharmaceutical company's desire for money by offsetting it with the researcher's desire to be perceived well in the field by striving to conduct objective, bias-free, pure research. Academic researchers viewing their careers through a long-term lens are incentivized to keep their priorities from shifting to the short-term focus of the pharmaceutical companies. By assigning each entity in the process its own goal, this arrangement was

established as a kind of checks and balances system. High-profile academic names tied to pharmaceutical studies benefitted the companies because of the implicit assumption that academic researchers' quest for knowledge placed them above the desire for money, however unrealistic this perception may be [11, 12]. Of course researchers are not immune to the influence of money. Pharmaceutical companies provide equity ownership of their companies, consultancy positions, and funding to researchers. All of these activities cost money to pharmaceutical companies. As they are not charities, companies continually spending money in this fashion can be assumed to lead to a direct benefit for the companies [12].

While there is great prestige for companies when they involve academic researchers, this partnership comes at a cost. As stated, academic research is costly and takes notoriously long to conduct. Various approvals processes in academic centers, such as the Institutional Review Board (established to protect the rights of human participants) and Sponsored Programs Administrations (which oversee the distribution and use of funds awarded for research purposes), are required before study activities can begin. In some cases, companies found that it took too long to recruit enough patients to reach the numbers needed for the study [11]. These delays directly impact the pharmaceutical companies' bottom line. Delays in research mean delays in obtaining FDA approval. Each day a drug cannot be sold costs the company approximately 1.3 million dollars [11].

These costly delays prompted pharmaceutical companies to partner elsewhere for their research needs [11]. Contract-research organizations (CROs) and site-management organizations (SMOs) cropped up to meet this need of the pharmaceutical companies [11]. CROs are centers specifically designed to conduct research studies [11]. When a commercial advertises a product as "clinically proven," they are likely referring to a clinic such as can be found in a CRO. The purpose of a CRO is to make money, and they do so by obtaining contracts from pharmaceutical companies who need their products tested. SMOs are similar in that they are involved in testing, but they are often contracted with CROs, so that they become subcontracted with pharmaceutical companies. As the pharmaceutical company pays the CRO, it becomes the customer in the arrangement. The phrase "the customer is always right," is often bandied about in modern customer service. The sentiment in this phrase is remarkably apt when the customer (the pharmaceutical company) has orders of magnitude more money and influence than the entity they are choosing to send their business to. CROs competing with one another for pharmaceutical companies' business have every financial incentive to keep the pharmaceutical companies satisfied with their tests' findings.

One can see how this arrangement between the large pharmaceutical companies and the relatively weaker CROs could lead to subpar research quality. From the start, the pharmaceutical company typically creates a study design and gives it to the CRO to follow, like a chef handing a recipe off to a line cook. There is no independent oversight of these study designs to ensure that they are properly powered, ethical, and valid [11].

Just as in academic research studies, pharmaceutical companies typically establish protocols whereby two groups of people are compared—those who get the

new treatment, and those get something else (either nothing, a placebo, or a pre-existing treatment for the same ailment). Despite this key similarity, many meaningful differences have been consistently observed between privately funded and publicly funded studies. Privately funded studies often use surrogate outcome measures rather than actual clinical outcomes [4]. For example, a study of executive functioning in children might examine whether children become better at a study measure such as playing computer games (theorized by the treatment developer to represent underlying executive functioning abilities) rather than whether or not the child is actually turning in more of their homework on time (the functional outcome most parents and teachers care about). Such a study would conclude that the client's program helps children's executive functioning, when in reality is only helps them get better at playing a game.

Many privately funded studies exist for the purposes of FDA approval, a one-time goal. Therefore, they do not spend the copious amounts needed to fund long-term trials, examining what happens to the people in their trials after years have passed. By not conducting such longitudinal studies, long-term health effects of the treatment or medication, including adverse events, are not included in test results [4]. Subsequently, some extreme adverse events, such as toxicity, have occurred in the general population taking a drug because it had never been tested for long-term safety before the drug came to market [4]. For this reason alone, statistically speaking, an old drug that is still used by the medical profession is more likely to be safe than a newer one [13]. If a drug has been used clinically for a generation, the range of likely adverse events is already known.

Privately funded studies are also more likely to compare new drugs to a placebo than are NIH-funded trials, which are more likely to compare to another active treatment [14]. It is obviously easier to find a difference between two treatments when one of the treatments is a sugar pill. By using placebos more often than other active treatments, privately funded studies are designed to more easily find the difference they need for FDA approval. Even when privately funded studies use an active treatment as a comparator, investigations have found they often underdose the comparator when compared to the new treatment [15]. Similar to the placebo issue, it is easier to conclude a drug is successful when comparing it to a drug that is less effective due to underdosing [15].

Privately funded studies are also more likely to use participants who are not true users of the drug [4]. For example, a blood pressure medicine, which would give the most relief to the elderly, was tested in healthy young participants [4]. A study using people who are already healthy can skew results of the drug, making it appear the healthy outcomes are more due to the drug than they really are. Another effect of recruiting young people for studies is that they are known to experience fewer adverse side effects to drugs in general [11]. The researchers can then honestly state they found few adverse events among participants in their study. When actually ill patients take the drug after approval, they will experience more adverse events than were reported in a set of healthy participants [11].

In addition to these design flaws that are clearly employed to yield more favorable outcomes, privately funded studies also occasionally violate the principles of

ethical research involving human participants. Specifically, it has been shown that privately funded studies have stopped prematurely due solely to cost concerns [8]. This violates the risk/benefit ratio agreements made with participants when they consented to participate [8]. Publicly funded studies can be stopped prematurely as well, but the reasons must be limited to emerging data that changes the risk/benefit ratio for participants. For example, if another researcher acting independently concludes that the treatment being studied is not as effective as current treatment, or is harmful, this represents a change in the risk/benefit ratio originally presented to possible participants when they were deciding whether or not to participate. The new ratio might change their willingness to continue to participate, so they must be informed. In some cases, the study is halted altogether in light of the new information. In these cases, a clinical population of participants would naturally want to know that so they could discontinue the study and resume the current treatment. Notice that the early termination of the study is done to benefit the participants, not the researcher. Stopping a study due to cost concerns benefits solely the researcher and could be at the expense of the participants.

Once a privately funded study is complete and the data have been collected, pharmaceutical companies often invite academic researchers to put their name on the study, despite the fact that the researcher was not involved in the study design or execution [11]. These requests for academic researcher names are motivated by the same reasons that pharmaceutical companies used to work with academic centers in the first place. Private studies aim for prestige and an appearance of being more scholarly and objective than commercially minded. When academic researchers choose to lend their names to studies like this, they are required to follow the International Committee of Medical Journal Editors' (ICMJE) standards for making sure they met authorship criteria [11, 16]. Academic researchers do not always follow these standards [11]. One study revealed that of the manuscripts reviewed, 19% had authors who did not meet the criteria [17]. The practice of ghostwriting, in which the pharmaceutical company contracts someone to write the article, provides another violation of the ICMJE guidelines [11]. The same study found that 11% of articles employed a ghostwriter [17]. These misrepresentations of authorship further complicate the task of determining the validity of the study.

In some cases, pharmaceutical companies engaged in suppression of study results when they were either neutral (i.e., they were inconclusive and therefore could not be used to support the new drug) or actively detrimental (i.e., they showed the new drug was either ineffective or detrimental) [11]. In one instance, a drug company began arbitration in response to one of their academic collaborators who published undesirable findings from a research trial of their product [18]. Pharmaceutical companies have published other findings from the same contested study while the original draft is being held up in arbitration [11]. Most tragically, important safety information has been withheld for years [11].

Pharmaceutical-funded studies have produced more results favoring new therapies than publicly funded trials have [19]. Some argue that **publication bias**, wherein journals are more likely to publish significant results rather than

nonsignificant ones, drives this phenomenon. Because publication bias affects publicly funded trials as well as pharmaceutically funded ones, this bias cannot explain the difference between funding styles. A better explanation is that in most cases, pharmaceutical companies save money by only conducting research on drugs that have already shown some promise in-house [4].

While this practice makes sense in practical terms, it is not justified under the scientific method. A strict interpretation of the scientific method holds that two interventions can only be compared using statistics if the null hypothesis maintains there is no difference between the two interventions. The presumption of no difference must be made prior to testing, with the study then required to show if there is one. This uncertainty that a difference exists is what necessitates a research study in the first place, at least academically speaking. For pharmaceutical companies to study interventions they already have evidence in favor of against an older intervention violates this uncertainty principle [14]. While, it makes sense on a cost basis to only test what is likely to be effective, this is the scientific equivalent to "stacking the deck." It reveals that the companies are only using research for the purposes of gaining FDA approval, not for truly understanding more about the drug.

Pharmaceutical companies do produce advances in technology [12]. They have provided products, treatments, and drugs that have improved, lengthened, and saved the lives of countless people. The products they develop are often helpful, despite the fact that their studies are most certainly biased. An extensive meta-review of the literature shows that the issue is largely resolved when it comes to the question of bias in funding [20]. Rather than spend more time and money researching whether the bias exists, the time has come to begin to prevent it where possible and respond to it. Recommendations to improve the situation should be directed toward stakeholders and decision makers. Patients are certainly stakeholders, but unless they are interested in policy and advocacy work, they are not decision makers. Instead, physicians can help patients understand the biases that influence research into medical advances so that they can respond with appropriate skepticism.

Conflicts of Interest

By now, it should be clear that conflicts of interest exist in the running of research studies, particularly when great sums of money are on the line. Regulatory bodies have attempted to reduce the effects of these influences by requiring disclosures of interest [21]. The function of the disclosure is to satisfy "caveat emptor," or, "let the buyer beware." In order for people to avoid being deceived, they must have information about conflicts. Then, it is presumed they can decide if the conflict is one they will tolerate. The rationale is that once the discloser has revealed the extent of their conflict, consumers are then educated enough in the facts to make

an educated decision for themselves. Responsibility shifts from seller to buyer [21].

Disclosure is required in a number of settings, including in published papers and presentations [21]. However, disclosures can have a paradoxical effect on the people making them [21, 22]. Once a disclosure has been made, the discloser feels a reduced burden for any future possible negative outcomes [21]. Having warned the consumer, they feel relieved of further responsibility. The consumer is supposedly making an "informed" choice due to the disclosure. Disclosures can also have a paradoxical effect on the people reading them. Research shows that after hearing a disclosure, people trust the discloser even more [21].

This paradoxical effect does not operate to the same extent among educated consumers of the information. When people educated in a specific area read disclosures, doing so does not reassure them about the validity of the work, but rather increases their skepticism [21]. In one study, doctors reading disclosures of financial interest downgraded their assessment of the rigor of trials based on the disclosure of conflict alone [22]. These doctors were technically inaccurate in downgrading the rigor based on this information alone. A disclosure is not inherently tied to methodology, and rigor pertains to methodology alone. However, this bias among educated consumers of disclosures might, practically speaking, counteract the influence that conflicts have clearly been seen to have over research outcomes. In this case, the old adage about two wrongs not making a right might be incorrect. Experts unfairly downgrading the rigor of studies unfairly propped up due to financial interest may be an instance of the checks and balances system working.

Skepticism

Responding to the mounting skepticism of privately funded trial results, academic journal editors began setting more rigorous publication criteria for pharmaceutical companies' studies [23]. Some patients are aware of the specific biases pertaining to funding in the pharmaceutical industry. In general, people maintain skepticism of corporations and seek to determine motivations for corporate actions [24]. Consumers know that the primary goal of corporations is to make a profit. These consumers feel more comfortable when they can readily identify a profit motive for companies' activities, because these motives fit easily within their notions about companies. When corporations act in ways not directly tied to making a profit (or in actions that would seem to undercut their profit, as in the case of a cigarette company launching an anti-smoking campaign for teens), people's skepticism increases. They begin searching harder for a profit motive to explain the action, putting the company's actions under further scrutiny.

We have been speaking of skepticism in a general sense. In the medical literature, skepticism is defined as the level of one's doubts that medical intervention can appreciably change one's health status [25]. Highly skeptical patients tend

to have certain characteristics compared to those with lower skepticism: they are younger, identify their race as white, earn lower incomes, attain less years of education, and perceive their own health status as better than their less skeptical peers, despite lower healthcare utilization and less healthy lifestyle [25]. While we cannot infer causation, skeptical patients are observed to lead less healthy lifestyles, experience poorer mental health, engage in fewer preventative medical activities, and utilize less medical care overall [25]. Additionally, skeptical patients were found to engage in other risky or health-reducing behaviors, such as smoking. The study authors surmised that these behaviors might have contributed to the skeptics' subsequent higher five-year mortality rates compared to non-skeptics [26], although again, a directly causal link was not tested. These authors propose a potential model to explain their findings: high levels of skepticism lead to less engagement with medical care and poorer health choices, which in turn, affected their mortality rates.

Clearly people's skepticism affects how they view the health care industry and their medical choices stemming from it. Pediatricians encounter parents who object to giving their children medications on the basis that the medications only exist to serve the pharmaceutical industry's profit motive. While, we have explored how this can be true in some cases (particularly with "me too" drugs), this blanket skepticism as to motives is not entirely fair. Health care providers have more effective and safe treatment options at their disposal, and they have them more rapidly than they would have without the pharmaceutical industry and privately funded trials.

Addressing skepticism is a matter of public health. If those who are skeptical of medical interventions engage in fewer health-promoting behaviors and have higher mortality rates, doctors will want to address those concerns. This daunting task must occur within a complicated context, given evidence that some medical interventions are, in fact, not necessary or less safe than established alternatives.

However, well-placed skepticism of medical research findings is in some cases, the skepticism often manifests in behaviors that can only be described as illogical. For example, it is established that privately funded trials do not test new drugs or methods over long periods of time to assess their longitudinal safety and efficacy, making them inherently riskier than preexisting models. Yet skeptical patients often evince wariness of well-established methods rather than new ones. For example, lately a vocal minority of patients became concerned that the amount of vaccines recommended for their child is influenced more by the pharmaceutical companies' profit motives than safety for their children. These patients subsequently decided to withhold vaccines (most commonly via spreading out doses over longer periods of time or outright refusal) from their children based on this presumption. Becoming concerned about profit motives but responding to that concern by avoiding well-established practices is an erroneous conflation of ideas. While it is true that pharmaceutical companies want to make a profit, vaccines delivered according to the well-researched guidelines for timing and dosage are inherently safer than individually experimenting with their own children's vaccination schedule. Exposing a child to risks by conducting individual "experiments"

negligibly affects the pharmaceutical companies' bottom lines and ignores the fact that the riskiest medicines are marketed as new and innovative. A patients' skepticism would be more logically applied if a parent were to refuse a newer version of a treatment for their child when an older one is available. This behavior corresponds to an actual, proven source of skepticism rather than a misplaced one.

Direct to Consumer Advertising

Other patients are not nearly as skeptical as they could be. Pharmaceutical companies frequently message individuals to acclimate them to new products with direct-to-consumer advertising (DTCA). DTCA began in 1708, when Nicholas Boone purchased an advertisement in a newspaper for a patent medicine [13]. The newspaper provided the information about the product directly to the people who might use it, rather to the doctors who would prescribe it. Since that early time, pharmaceutical companies have now come to spend twice as much on advertising as they do on research [10]. The top pharmaceutical company spent upwards of 17 billion dollars on marketing in 2013 [10]. Even though companies still spend comparatively more of their marketing budgets selling to physicians, the movement from paternalism to consumerism helped companies increasingly benefit from DTCA strategies [10, 13]. If these profit-driven companies spend so much of their operating budget on DTCA, it presumably works.

Disappointingly, surveys show that many people think that messages in DTCA have been pre-reviewed and approved by the FDA [13]. The same study revealed that this false assumption led them to believe that the promoted drugs were safer due to this supposed governmental intervention, that medications with serious side effects were banned from being marketed in this manner, and that only drugs that are "extremely effective" could be marketed in this fashion. None of these facts are true [13].

This perception of regulation where there is none is troubling. DTCA works: patients come to their doctors' offices requesting specific drugs. When doctors explain that the drug is not as well-established as older versions, they are confronted with first undoing patients' misconceptions [13]. It is inherently harder to undo a misconception than to educate someone from a neutral starting point. Clearing up these misconceptions also has an opportunity cost: it takes time away from discussing the patient's specific symptoms and other treatment options that might be more suitable for this individual [13]. Despite the challenges stemming from DTCA, patients still rate physicians as their most trusted interpersonal source of health information [27]. This trust should be carefully guarded, and doctors have an obligation to correct misconceptions their patients raise resulting from advertising.

Media

Advertising is not the only point of contact patients have with new treatment options. Patients read about research in the media they consume. Journalists working for publications with editorial oversight are expected to follow a journalistic code of ethics set forth by the Society of Professional Journalists. By agreeing to this code, journalists voluntarily assume some responsibility for their role in the accurate dissemination of information. Medical journalists reporting the results of research studies are no different in this regard, and their reporting has wide-ranging effects. When journalists present dramatic research findings, the public responds. As an illustration, news articles reporting long-term results of hormone replacement therapy sufficiently alarmed the public, promoting widespread abandonment of the treatment [28]. Regrettably, research shows that many articles presenting study results do not include adequate information to situate the findings within a meaningful context [29].

Part of the responsibility can be placed with the researchers who interact with journalists about their published studies. Many researchers utilize press releases to spread the word about their work. Researchers use press releases because they work-statistics show journalists are more likely to cover a study if has a press release [30]. While journalists are tasked with reporting more than the content of the press release, as many as one-third of all medical articles published report no more than the information contained in the original press release [30]. Of course this lack of additional reporting is technically the responsibility of the journalist. But now that this neglect is common knowledge, researchers should assume the responsibility of providing more context themselves in the release.

Researchers can certainly improve in this area. One study examined press releases written by the original study author and found an overarching tendency to overstate the importance of a particular research finding and understate (or outright ignore) the limitations of the study's design and conclusions [30]. The bias of researchers distributing press releases overstating their work can be tied to the sunk cost fallacy and their emotional ties to their work. Researchers have often invested years of their careers into particular studies. They are also emotionally invested, influencing them to overstate their work's importance [31].

Like others in the chain of research, journalists are subject to funding bias. The media is comprised of companies with bottom lines, just like pharmaceutical companies. Media outlets make most of their profits from advertising [13]. Advertisers trying to get their message to as many people as possible pay more for outlets providing a large audience. Knowing this, the media is financially motivated to secure as many readers as possible to review their publications. While individuals within the media machine may be ethical, they experience a wide array of pressures to get the most "clicks," "likes," "shares," and "retweets." Knowing as we do that people prefer novelty, journalists write articles about research that they think readers will find new and exciting [32]. These funding biases would affect the chain of communication about research even if no specific individual in this chain were acting

reproachfully. It would be as fruitless to blame journalists for trying to make their work interesting as it would be to blame an individual person for choosing to read an article based on its "click-bait" headline.

While the responsibility rests with researchers and journalists to monitor the information they disseminate, neither a pediatrician nor a parent can compel them to do so. They can only be aware that practices of misrepresentation exist and respond by applying critical thinking skills when reading about studies. Pediatricians can review the study itself, if they have access to the medical journal in which it was originally published. Most pediatricians are unlikely to have investigated a specific study prior to their patient coming into inquire about it. As discussed in the introduction, doctors would ideally keep informed of new research advances, but time constraints make this extremely challenging. To supplement investigating studies themselves whenever possible, pediatricians can encourage their patients to examine the validity of the reporting themselves.

Almost any individual reading a news report of a study can conduct a cursory assessment to determine if it is worthwhile to look into it further. Woloshin and Schwartz recommend some basic rules of thumb for patients to gauge if studies have any applicability to their lives:

- **Animal studies**: Animal studies are, by their very nature, preliminary. They tend to be closer to "basic science" rather than having any clinical applicability.
- **Small studies**: Thirty or fewer participants represent a very small sample size, so any study with fewer than 30 should be judged to have limited inferential ability.
- **Studies that were controlled but not randomized**: If people were not assigned at random to one treatment/condition over another, the inferences from these studies are also limited due to confounding factors.
- **Studies that are described as "preliminary" or not published in a scientific journal**: Again, preliminary studies represent a step in the research process towards learning new information. This new information is not likely to have any direct bearing on a patient's life at this stage.
- **Studies that do not include mention of adverse events**: Without knowing the adverse outcomes, patients could not make an informed decision.

Provided a study passes these rules of thumb, patients (with the help of their doctors) can examine how well the reporting of the study has been placed in the overall context of medical research. Australian researchers developed a set of ten considerations to guide a critical reading of a popular media outlet's take on a research study [28]. Ask patients to print out a copy of the article or pull it up on their phone during an office visit to review the article with them using this checklist. The considerations are as follows, and each will be discussed specifically below:

1. genuine novelty of the treatment
2. availability of treatment
3. discussion (or at least mention) of alternative treatments

4. no evidence of "disease mongering"
5. objective evidence in favor of treatment
6. benefits framed in absolute terms rather than relative
7. mention of harms
8. mention of costs
9. mention of conflicts of interest
10. article includes reporting beyond the press release.

1. *Genuine novelty of the treatment*
   Help patient determines if this treatment is truly novel, or simply a re-hashing of a preexisting treatment. Some studies are replication studies, specifically tasked with investigating if they can find the same positive results as a previous study. Reporters, not realizing this, can publish replication studies as if they are new treatments. Other times, a treatment has been studied in one format, but researchers adapt it slightly for a new population or diagnostic subcategory. Although the study may be testing a new focus, the treatment itself is not actually novel.
2. *Availability of treatment*
   Some articles excitedly report findings of a groundbreaking new treatment, proclaiming its promise for saving lives. But if the treatment is so new as to be offered in only one location, the research results are, for intents and purposes, irrelevant.
3. *Discussion (or at least mention) of alternative treatments*
   Medical journalists should include a mention of what treatments are already available to treat the condition the new treatment addresses. If they have not, they leave this task to doctors.
4. *No evidence of "disease mongering"*
   Moynihan defines the methods of disease mongering: re-characterizing common ailments into medical problems, overstating mild symptoms as serious ones, interpreting personal problems as medical illnesses, conflating risk with disease, and stating the higher end of prevalence estimates to maximize potential markets. No matter which method is employed in disease mongering, the overall goal is to sell more products to people who otherwise would not have purchased them. Disease mongering essentially frightens people into purchasing treatments. Suggest that patients look for signs that the creators of the treatment or the journalists are using fear to prompt them to action.
5. *Objective evidence in favor of treatment*
   Help patients find studies reporting objective evidence, which are more convincing than those use subjective outcomes. Look for studies using objective outcomes whenever possible (e.g., a measure of blood pressure is more objective than asking how stressed someone is feeling). Also look for studies where the conclusions presented result from statistical analysis, rather than a qualitative review of the data. Objectivity of outcomes is not always possible (e.g., social science research, like psychology, often must employ subjective

measures—indeed, subjective experience is what people care about). But studies that use subjective measures where objective ones are available deserve careful scrutiny.

6. *Benefits framed in absolute terms rather than relative*
   The human brain is not well suited for probabilities. Articles reporting outcomes in relative terms require the reader to employ probabilistic thinking. Using relative terms makes differences sound larger or more meaningful than they really are. Describing the influence of a drug as helping to reduce symptoms by 50% sounds good. It becomes less interesting when realizing that if the overall prevalence of symptoms of the disease is extremely low, a 50% symptom reduction can, in some cases, be quite negligible. This is just an example, of course, but it shows how journalists describing benefits in relative terms make the story sound more interesting without giving the reader a clear picture of what's happening for the patient. Stating the benefits in absolute terms is much more clear for patients so they can decide if the benefit is worthwhile, e.g.: "participants taking the new drug had two outbreaks per month, whereas the control group had four."
7. *Mention of harms*
   Patients considering a new treatment should want to know what the potential harms are. If the article omits this information, patients cannot possibly make an informed decision about the treatment.
8. *Mention of costs*
   Similar to availability, patients should know what the costs of the treatment are—ongoing costs as well as initial. Prohibitively expensive treatments, or treatments so new that they cannot be covered by insurance, are once again, irrelevant to individual patients.
9. *Mention of conflicts of interest*
   While disclosures of financial interest are problematic, the scientific community is obligated to report them. Reporters familiar with writing medical research articles are aware of this obligation. Articles that omit disclosures indicate some oversight. Where disclosures of financial interest are reported, help patients decide if this conflict would bias anyone in the research chain (implicitly or explicitly) to present the findings as more important or relevant than they are to an individual patient.
10. *Article includes reporting beyond the press release*
    We saw that as many as one-third of articles include no additional reporting beyond the press release contents. When physicians have access to the press release, they can help patients compare the release to the article. Ask patients what they think it means if the two documents are identical. See if they can identify the problems discussed above that arise when journalists act as a medium for the researchers to spread their message at no cost, with no examination from the press. If the original press release is not available, examine the length of the article with patients. The shorter the article, the less information it includes. The more likely it is to be almost completely derived from the press release.

Investigate Source of Information

Pediatricians can encourage patients to apply various litmus tests to infer funding sources when they are unclear. Many people now get their information from the Internet. Website extensions provide a quick and easy way to begin to examine funding. Websites ending with ".com" are automatically disclosing their primary interest: commerce [33]. Any .com site faithfully represents itself as for-profit. Websites beginning with .gov are run by the government and are inherently designed to be free from as many conflicts as possible [33]. Of course conflicts can still exist, but at the very least, the government is nonprofit. Websites ending with .edu are primarily focused on education [33]. As with the government, education is not always free from conflict, by any means. Recent lawsuits against for-profit higher educational companies reveal institutions that placed profit motives above educational goals. Reputable educational organizations proceed at least somewhat cautiously with the information they present to the public. This caution protects their reputation and—in the cases of nonprofit institutions—their tax-exempt status. Websites with .org extensions are less clear at the outset as to their goals, given "org" stands simply for "organization" [33]. If patients find themselves on .org websites, they should proceed to the next litmus test.

Most websites of repute have some kind of "About Us" page outlining the entity's goals and missions. These pages list leaders among the organization, sometimes with short biographical details. A quick search on a search engine of these names will reveal important facts about the leaders that patients can consider. Is the leader of the organization a business leader or an academic leader? If the leader heads a charitable organization, how did they come to be dedicated to this cause? What experiences do they highlight as important or transformational moments in their lives? These experiences sometimes reveal an emotional investment that is subject to bias.

If patients cannot find an About Us section, they should look for any kind of oversight of the website at all. They might be on a personal blog, a questionably moderated forum, or a site created with the specific intention of spreading misinformation. Sites like these of course can create legitimate looking About Us sections, but the information therein would not hold up to further scrutiny with a subsequent online search.

To Explain to a Patient

Have you ever received an unanticipated phone call or email from your bank or credit card company, during which the message asks you to call them at a certain number? If you were to call that number, it would likely ask you for personal information, as these are commonly phishing attacks to obtain your personal data for identity theft. After getting a call or email like this, if you searched the phone number they wanted you to call or called your institution directly using the number posted on their official website, you would

quickly learn that the original call or email was a scam. Websites operate the same way. They can present themselves initially as legitimate, but they do not typically hold up when you try to confirm their authenticity from simply one or two other verifiable sources.

Finally, if patients want basic information about the study that was not included within the article, direct them to search for the study on ClinicalTrials.gov. This database was created in 1997. Over the years, it has increased the amount of information required of all researchers to post about their studies. As a result of International Committee of Medical Journal Editors policies, researchers must now report key elements of the data, basic results, and adverse events on ClinicalTrials.gov prior to publication. If patients cannot find the study on ClinicalTrials.gov, they should maintain skepticism until they obtain sufficient information as to its authenticity from a trusted source.

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