COMMENTARY

P-values – a chronic conundrum

Jian Gao

Abstract

Background: In medical research and practice, the p-value is arguably the most often used statistic and yet it is widely misconstrued as the probability of the type I error, which comes with serious consequences. This misunderstanding can greatly affect the reproducibility in research, treatment selection in medical practice, and model specification in empirical analyses. By using plain language and concrete examples, this paper is intended to elucidate the p-value confusion from its root, to explicate the difference between significance and hypothesis testing, to illuminate the consequences of the confusion, and to present a viable alternative to the conventional p-value.

Main text: The confusion with p-values has plagued the research community and medical practitioners for decades. However, efforts to clarify it have been largely futile, in part, because intuitive yet mathematically rigorous educational materials are scarce. Additionally, the lack of a practical alternative to the p-value for guarding against randomness also plays a role. The p-value confusion is rooted in the misconception of significance and hypothesis testing. Most, including many statisticians, are unaware that p-values and significance testing formed by Fisher are incomparable to the hypothesis testing paradigm created by Neyman and Pearson. And most otherwise great statistics textbooks tend to cobble the two paradigms together and make no effort to elucidate the subtle but fundamental differences between them. The p-value is a practical tool gauging the “strength of evidence” against the null hypothesis. It informs investigators that a p-value of 0.001, for example, is stronger than 0.05. However, p-values produced in significance testing are not the probabilities of type I errors as commonly misconceived. For a p-value of 0.05, the chance a treatment does not work is not 5%; rather, it is at least 28.9%.

Conclusions: A long-overdue effort to understand p-values correctly is much needed. However, in medical research and practice, just banning significance testing and accepting uncertainty are not enough. Researchers, clinicians, and patients alike need to know the probability a treatment will or will not work. Thus, the calibrated p-values (the probability that a treatment does not work) should be reported in research papers.

Keywords: P-values, Type I error, Significance testing, Hypothesis testing, Research reproducibility, Calibrated P-values

Background

Without any exaggeration, humankind’s wellbeing is profoundly affected by p-values: Health depends on prevention and intervention, ascertaining their efficacies relies on research, and research findings hinge on p-values. The p-value is a sine qua non for deciding if a research finding is real or by chance, a treatment is effective or even harmful, a paper will be accepted or rejected, a grant will be funded or declined, or if a drug will be approved or denied by U.S. Food & Drug Administration (FDA).

Yet, the misconception of p-values is pervasive and virtually universal. “The P value is probably the most ubiquitous and at the same time, misunderstood, misinterpreted, and occasionally miscalculated index in all of
biomedical research [1].” Even “among statisticians there is a near ubiquitous misinterpretation of p values as frequentist error probabilities [2].”

The extent of the p-value confusion is well illustrated by a survey of medical residents published in the Journal of the American Medical Association (JAMA). In the article, 88% of the residents expressed fair to complete confidence in understanding p-values, but 100% of them had the p-value interpretation wrong [1, 3]. Make no mistake, they are the future experts and leaders in clinical research that will affect public health policies, treatment options, and ultimately people’s health.

The survey published in JAMA used multiple-choice format with four potential answers for a correct interpretation of p > 0.05 [3]:

a. The chances are greater than 1 in 20 that a difference would be found again if the study were repeated.

b. The probability is less than 1 in 20 that a difference this large could occur by chance alone.

c. The probability is greater than 1 in 20 that a difference this large could occur by chance alone.

d. The chance is 95% that the study is correct.

How could it be possible that 100% of the residents selected incorrect answers when one of the possible choices was supposed to be correct? As reported in the paper [3], 58.8% of the residents selected choice c which was designated by the authors as the correct answer. The irony is that choice c is not correct either. In fact, none of the four choices are correct. So, not only were the residents who picked choice c wrong but also the authors as well. Keep in mind, the paper was peer-reviewed and published by one of the most prestigious medical journals in the world.

This is no coincidence – most other great statistics textbooks make no effort or fail to clarify the massive confusion about p-values, and even provide outright wrong interpretations. The confusion is near-universal among medical researchers and clinicians [4–6].

Unfortunately, the misunderstanding of p-values is not inconsequential. For a p-value of 0.05, the chance a treatment doesn’t work is not 5%; rather, it is at least 28.9% [7].

After decades of misunderstanding and inaction, the pendulum of p-values finally started to swing in 2014 when the American Statistical Association (ASA) was taunted by two pairs of questions and answers on its discussion forum:

Q: Why do so many colleges and grad schools teach p = 0.05?

A: Because that’s still what the scientific community and journal editors use.

Q: Why do so many people still use p = 0.05?

A: Because that’s what they were taught in college or grad school.

The questions and answers, posted by George Cobb, Professor Emeritus of Mathematics & Statistics from Mount Holyoke College, spurred the ASA Board into action. In 2015, for the first time, the ASA board decided to take on the challenge of developing a policy statement on p-values, much like the American Heart Association (AHA) policy statement on dietary fat and heart disease. After months of preparation, in October 2015, a group of 20 experts gathered at the ASA Office in Alexandria, Virginia and laid out the roadmap during a two-day meeting. Over the next three months, multiple drafts of the p-value statement were produced. On January 29, 2016, the ASA Executive Committee approved the p-value statement with six principles listed on what p-values are or are not [8].

Although the statement hardly made any ripples in medical journals, it grabbed many statisticians’ attention and ignited a rebellion against p-values among some scientists. In March 2019, Nature published a comment with over 800 signatories calling for an end of significance testing with p < 0.05 [9]. At the same time, the American Statistician that carried the ASA’s p-value statement published a special issue with 43 articles exploring ways to report results without statistical significance testing. Unfortunately, no consensus was reached for a better alternative in gauging the reliability of studies, and the authors even disagreed on whether the p-value should continue to be used or abandoned. The only agreement reached was the abolishment of significance testing as summarized in the special issue’s editorial: “statistically significant” – don’t say it and don’t use it [10].

So, for researchers, practitioners, and journals in the medical field, what will replace significance testing? And what is significance testing anyway? Is it different from hypothesis testing? Should p-values be banned too? If not, how should p-values be used and interpreted? In healthcare or medicine, we must accept uncertainty as the editorial of the special issue urged, but do we need to know how likely a given treatment will work or not?

To answer these questions, we must get to the bottom of the misconception and confusion, and we must identify a practical alternative(s). However, despite numerous publications on this topic, few studies aimed for these goals are understandable to non-statisticians and retain mathematical rigor at the same time. This paper is intended to fill this gap by using plain language and concrete examples to elucidate the p-value confusion.
from its root, to intuitively describe the true meaning of p-values, to illuminate the consequences of the confusion, and to present a viable alternative to the conventional p-value.

**Main text**

**The root of confusion**

The p-value confusion began 100 years ago when the father of modern statistics, Ronald Aylmer Fisher, formed the paradigm of significance testing. But it should be noted Fisher bears no blame for the misconception; it is the users who tend to muddle Fisher’s significance testing with hypothesis testing developed by Jerzy Neyman and Egon Pearson. To clarify the confusion, this section uses concrete examples and plain language to illustrate the essence of significance and hypothesis testing and to explicate the difference between the p-value and the type I error.

**Significance testing**

Suppose a painkiller has a proven track record of lasting for 24 h and now another drug manufacturer claims its new over-the-counter painkiller lasts longer. An investigator wants to test if the claim is true. Instead of collecting data from all the patients who took the new medication, which is often infeasible, the investigator decided to randomly survey 50 patients to gather data on how long (hours) the new painkiller lasts. Thus, the investigator now has a random variable $X$, the average hours from a sample of 50 patients. This is a random variable because the 50 patients are randomly selected, and nobody knows what value this variable will take before conducting the survey and calculating the average. Nevertheless, each survey does produce a fixed number, $\bar{x}$, which itself is not a random variable, rather it is a realization or observation of the random variable $X$ (hereafter, let $X$ denote a random variable and $\bar{x}$ denote a fixed value, an observation of $X$).

Intuitively, if the survey yielded a value (average hours the painkiller lasts) very close to 24, say, 23 or 25, the investigator would not believe the new painkiller is worse or better. If the survey came to an average of 32 h the investigator would believe it indeed lasts longer. However, it would be hard to form an opinion if the survey showed an average of 22 or 26 h. Does the new painkiller really last shorter, longer, or is it due to random chance (after all, only 50 patients were surveyed)?

This is where the significance test formulated by Fisher in the 1920s comes in. Note that although modern significance testing began with the Student’s $t$-test in 1908, it was Fisher who extended the test to the testing of two samples, regression coefficients, as well as analysis of variance, and created the paradigm of significance testing.

In Fisher’s significance testing, the Central Limit Theorem (CLT) plays a vital role, which states that given a population with a mean of $\mu$ and a variance of $\sigma^2$, regardless of the shape of its distribution, the sample mean statistic $\bar{X}$ has a normal distribution with the same mean $\mu$ and variance $\frac{\sigma^2}{n}$, or $\frac{(\bar{X}-\mu)}{\sigma/\sqrt{n}}$ has a standard normal distribution with a mean of 0 and a variance of 1, as long as the sample size $n$ is large enough. In practice, the distribution of the study population is often unknown and $n \geq 30$ is considered sufficient for the sample mean statistic to have an approximately normal distribution.

In conducting the significance test, a null hypothesis is first formed, i.e., there is no difference between the new and old painkillers, or the new painkiller also lasts for 24 h (the mean of $X = \mu = 24$). Under this assumption and based on CLT, $X$ is normally distributed with a mean of 24 and a variance of $\sigma^2/50$. Assume $\sigma^2 = 200$ (typically $\sigma^2$ is unknown but can be estimated), then $\bar{X}$ has a normal distribution $N (24, 2)$, or $Z = (\bar{X} - 24)/2$ has a standard normal distribution with a mean of 0 and standard deviation of 1 ($Z$ is a standardized random variable). The next step is to calculate $z = |\bar{x} - 24|/2$ based on the survey data and then find the p-value or the probability of $|Z| > z$ from a normal distribution table ($z$ is a fixed value or an observation of $Z$). Fisher suggested if the $p$-value is smaller than 0.05 then the hypothesis is rejected. He argued that the farther the sample mean $\bar{x}$ from the population mean $\mu$, the smaller the $p$-value, the less likely the null hypothesis is true. Just as Fisher stated, “Either an exceptionally rare chance has occurred or the theory [H0] is not true [11].”

Based on this paradigm, if the survey came back with an average of 26 h, i.e., $\bar{x} = 26$, then $z = 1$ and $p = 0.3173$, as a result, the investigator accepts the null hypothesis (orthodoxically, fails to reject the null hypothesis), i.e., the new painkiller does not last longer and the difference between 24 and 26 h is due to chance or random factors. On the other hand, if the survey revealed an average of 28 h, i.e., $\bar{x} = 28$, then $z = 2$, and $p = 0.0455$, thus the null hypothesis is rejected. In other words, the new painkiller is deemed lasting longer.

Now, can the p-value, 0.0455, be interpreted as the probability of the type I error, or only 4.55% chance the new painkiller does not last longer (no difference), or the probability that the difference between 24 and 28 h is due to chance, or the investigator could make a mistake by rejecting the null hypothesis but only wrong about 4.55% of the time? The answer is No.

So, what is a p-value? Precisely, a p-value tells us how often we would see a difference as extreme as or more
extreme than what is observed if there really were no difference. Drawing a bell curve with the p-value on it will readily delineate this definition or concept.

In the example above, if the new painkiller also lasts for 24 h, the p-value of 0.0455 means there is a 4.55% chance that the investigator would observe \( \bar{x} \geq 20 \) or \( \bar{x} \geq 28 \); it is not 4.55% chance the new painkiller also lasts for 24 h. It is categorically wrong to believe the p-value is the probability of the null hypothesis being true (there is no difference), or 1 − p is the probability of the null hypothesis being false (there is a difference) because the p-value is deduced based on the premise that the null hypothesis is true. The p-value, a conditional probability given \( H_0 \) is true, is totally invalidated if the null hypothesis is deemed not true.

In addition, p-values are data-dependent: each test (survey) produces a different p-value; for the same analysis, it is illogical to say the error rate or the type I error is 31.73% based on one sample (survey) and 4.55% based on another. There is no theoretical or empirical basis for such frequency interpretations. In fact, Fisher himself was fully aware that his p-value, a relative measure of evidence against the null hypothesis, does not bear any interpretation of the long-term error rate. When the p-value was misinterpreted, he protested the p-value was not the type I error rate, had no long-run frequentist characteristics, and should not be explained as a frequency of error if the test was repeated [12].

Interestingly, Fisher was an abstract thinker at the highest level, but often developed solutions and tests without solid theoretical foundation. He was an obstinate proponent of inductive inference, i.e., reasoning from specific to general, or from sample to population, which is reflected by his significance testing.

**Hypothesis testing**

On the contrary, mathematicians Jerzy Neyman and Egon Pearson dismissed the idea of inductive inference all together and insisted reasoning should be deductive, i.e., from general to specific. In 1928, they published the landmark paper on the theoretical foundation for a statistical inference method that they called "hypothesis test [12]." In the paper, they introduced the concepts of alternative hypothesis \( H_1 \), type I and type II errors, which were groundbreaking. The Neyman and Pearson’s hypothesis test is deductive in nature, i.e., reasoning from general to particular. The type I and type II errors, which must be set ahead, formulate a “rule of behavior” such that “in the long run of experience, we shall not be too often wrong,” as stated by Neyman and Pearson [13].

The hypothesis test can be illustrated by a four-step process with the painkiller example.

The first step is to lay out what the investigator seeks to test, i.e. to establish a null hypothesis, \( H_0 \) and an alternative hypothesis, \( H_1 \):

\[
H_0 : \text{mean of } \bar{X} = \mu = 24 \\
H_1 : \text{mean of } \bar{X} = \mu = 28
\]

The second step is to set the criteria for the decision, or to specify an acceptable rate of mistake if the test is conducted many times. Specifically, that is to set the probability of the type I error, \( \alpha \), and the probability of the type II error, \( \beta \).

A type I error refers to the mistake of rejecting the null hypothesis when it is true (claiming the treatment works or the new drug lasts longer but actually it does not). Conventionally and almost universally, the probability of the type I error or \( \alpha \) is set to 0.05, which means 5% of the time one will be wrong if carrying out the test many times. A type II error is the failure to reject the null hypothesis that is not true; the probability of the type II error, \( \beta \), is conventionally set as 0.2, which is equivalent to a power of 0.8, the probability of detecting the difference if it exists.

Table 1 summarizes the type I and type II errors.

The third step is to select a statistic and the associated distribution for the test. For the painkiller example, the statistic is \( Z = (\bar{X} - 24)/2 \), and the distribution is the standard normal. Because the type I error has been set to 0.05 and \( Z \) has a standard normal distribution under the null hypothesis, as shown in Fig. 1, 1.96 becomes the critical value, \(-1.96 \leq z \leq 1.96 \) becomes the acceptance region, and \( z \leq -1.96 \) or \( z \geq 1.96 \) becomes the rejection regions.

The final step is to calculate the \( z \) value and make a decision. Similar to significance testing, if the survey resulted in \( \bar{x} = 26 \), then \( z = 1 < 1.96 \) and the investigator accepts the null hypothesis; if the survey revealed \( \bar{x} = 28 \), then \( z = 2 > 1.96 \) and the investigator rejects the null hypothesis and accepts the alternative hypothesis. It is interesting to note, in significance testing, “one can never accept the null hypothesis, only failed to reject it,” while that is not the case in hypothesis testing.

Unlike Fisher’s significance test, the hypothesis test possesses a nice frequency explanation: one can be wrong by rejecting the null hypothesis but cannot be wrong more than 5% of the time in the long run if the test is performed many times. Quite intuitively, every time the null hypothesis is rejected (when \( z < -1.96 \) or \( z > 1.96 \)) there is a chance that the null hypothesis is true, and a mistake is made. When the null hypothesis is true, \( Z = (\bar{X} - 24)/2 \) is a random variable with a standard normal distribution as shown in Fig. 1, thus 5% of the time \( z = (\bar{X} - 24)/2 \) would fall outside \((-1.96, 1.96)\) and the decision will be wrong 5% of the time. Of course, when the null hypothesis is not true, rejecting it is not a mistake.
Noticeably, the \( p \)-value plays no role in hypothesis testing under the framework of the Neyman-Pearson paradigm [12, 14]. However, most, including many statisticians, are unaware that \( p \)-values and significance testing created by Fisher are incomparable to the hypothesis testing paradigm created by Neyman and Pearson [14, 15], and many statistics textbooks tend to cobble them together [2, 14]. The near-universal confusion is, at least in part, caused by the subtle similarities and differences between the two tests:

1. Both the significance and hypothesis tests use the same statistic and distribution, for example, \( Z = (X - 24)/2 \) and \( N(0, 1) \).
2. The hypothesis test compares the observed \( z \) with the critical value 1.96, while the significance test compares the \( p \)-value (based on \( z \)) to 0.05, which are linked by \( P(|Z| > 1.96) = 0.05 \).
3. The hypothesis test sets the type I error \( \alpha \) at 0.05, while the significance test also uses 0.05 as the significance level.

One of the key differences is, for the \( p \)-value to be meaningful in significance testing, the null hypothesis must be true, while this is not the case for the critical value in hypothesis testing. Although the critical value is derived from \( \alpha \) based on the null hypothesis, rejecting the null hypothesis is not a mistake when it is not true; when it is true, there is a 5\% chance that \( z = (X - 24)/2 \) will fall outside \((-1.96, 1.96)\), and the investigator will be wrong 5\% of the time (bear in mind, the null hypothesis is either true or false when a decision is made). In addition, the type I error and the resultant critical value is set ahead and fixed, while the \( p \)-value is a moving “target” varying from sample to sample even for the same test.

As it was not confusing enough, the understanding and interpretation of \( p \)-values are also complicated by non-experimental studies where model misspecifications and even p-hacking are common, which often misleads the audience to believe the model and the findings are valid for its small \( p \)-values [16]. In fact, \( p \)-values have little value in assessing if the relationship between an outcome and exposure(s) is causal or just an artifact of confounding – one cannot claim the use of smartphones causes gun violence even if the \( p \)-value for their correlation is close to zero. To see the \( p \)-value problem at its core and to elucidate the confusion, the discussion of \( p \)-values should be in the context of experimental designs such as randomized controlled trials where the model or the outcome and exposure(s) are correctly specified.

## Table 1 Type I and Type II Errors

|                         | Null hypothesis (H0) is true | Null hypothesis (H0) is false |
|-------------------------|-----------------------------|-----------------------------|
| Reject the null hypothesis | Type I error                | Correct decision             |
|                         | False positive              | True positive               |
| Accept the null hypothesis | Correct decision            | Type II error                |
|                         | True negative               | False negative              |

### Fig. 1 Standard Normal Distribution with Critical Value 1.96

\[
\begin{align*}
\alpha/2 &= 0.025 \\
\sigma &= 1 \\
1 - \alpha &= 0.95 \\
-1.96 &< Z < 1.96
\end{align*}
\]
The Link between P-values and Type I Errors

The p-value fallacy can be readily quantified under a Bayesian framework [7, 17, 18]. However, “those ominous words [Bayes theorem], with their associations of hazy prior probabilities and abstruse mathematical formulas, strike fear into the hearts of most us, clinician, researcher, and editor alike [19],” as Frank Davidoff, former Editor of the Annals of Internal Medicine, wrote. It is understandable but still unfortunate that Bayesian methods such as Bayes factors, despite their merit, are still considered exotic by the medical research community.

Thanks to Sellke, Bayarri, and Berger, the difference between the p-value and the type I error is quantified [7]. Based on the conditional frequentist approach, which was formalized by Kiefer and further developed by others [20–23], Berger and colleagues established the lower bound of the error rate $P(H_0 \mid |Z| > z_0)$ or the type I error given the p-value [7]:

$$P(H_0 \mid |Z| > z_0) = \alpha(p) = \left\{1 + [-e \times p \times \ln(p)]^{-1}\right\}^{-1}.$$  

As shown, the lower bound equation is mathematically straightforward. Noteworthy is that the derivation of the lower bound is also ingeniously elegant (a simplified proof is provided in the Supplementary File for those who are interested in it). The relationship between p-values and type I errors (lower bound) can be readily seen from Table 2 showing some of the commonly reported results [7].

As seen in Table 2, the difference between p-values and the error probabilities (lower bound) is quite striking. A p-value of 0.05, commonly misinterpreted as only 5% chance the treatment does not work, seems to offer strong evidence against the null hypothesis; however, the true probability of the treatment not working is at least 0.289. Keep in mind, the relationship between the p-value and the type I error is the lower bound; in fact, many prefer to report the upper bound [6, 7].

The discrepancy between the p-value and the lower-bound error rate explains the big puzzle of why so many wonder drugs and treatments worldwide lose their amazing power outside clinical trials [24–26]. This discrepancy likely also contributes to the frequently reported contradictory findings on risk factors and health outcomes in observational studies. For example, an early study published in the New England Journal of Medicine found drinking coffee was associated with a high risk of pancreatic cancer [27]. The finding became a big headline in The New York Times [28] and the leading author and probably many frightened readers stopped drinking coffee. Later studies, however, concluded the finding was a fluke [29, 30]. Likewise, the p-value fallacy may also contribute to the ongoing confusion of dietary fat intake and heart disease. On the one hand, a meta-analysis published in Annals of Internal Medicine in 2014 concluded “Current evidence does not clearly support cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of total saturated fats [31].” On the other hand, in the 2017 recommendation, the American Heart Association (AHA) stated “Taking into consideration the totality of the scientific evidence, satisfying rigorous criteria for causality, we conclude strongly that lowering intake of saturated fat and replacing it with unsaturated fats, especially polyunsaturated fats, will lower the incidence of CVD [32].”

In short, the misunderstanding and misinterpretation of the relationship between the p-value and the type I error all too often exaggerate the true effects of treatments and risk factors, which in turn leads to conflicting findings with real public health consequences.

The future of P-values

It is readily apparent that the p-value conundrum poses a serious challenge to researchers and practitioners alike in healthcare with real-life consequences. To address the p-value complications, some believe the use of p-values should be banned or discouraged [33, 34]. In fact, since 2015, Basic and Applied Social Psychology has officially banned significance tests and p-values [35], and Epidemiology has a longstanding policy discouraging the use of significance testing and p-values [36, 37]. On the other hand, many are against a total ban [38, 39]. P-values do possess practical utility -- they offer insight into what is observed and are the first line of defense against being fooled by randomness. You would be more suspicious of a coin being fair if nine heads turned up after ten flips versus, for example, if seven heads did. Similarly, you would like to see how strong the evidence is against the null hypothesis: say, a p-value of 0.0499 or 0.0001.

“It is hopeless to expect users to change their reliance on p-values unless they are offered an alternative way of judging the reliability of their conclusions [40].” Rather than banning the use of p-values, many believe the conventional significance level of 0.05 should be lowered for better research reproducibility [41]. In 2018, 72 statisticians and scientists made the case for changing $p < 0.05$.

| Table 2 | P-values and Associated Type I Error Probabilities |
|---------|-------------------------------------------------|
| P-value | 0.20 | 0.15 | 0.10 | 0.05 | 0.02 | 0.01 | 0.005 | 0.001 |
| $\alpha(p)$ | 0.465 | 0.436 | 0.385 | 0.289 | 0.175 | 0.111 | 0.067 | 0.018 |
to $p < 0.005$ [42]. Inevitably, like most medical treatments, the proposed change is accompanied by some side effects. For instance, to achieve the same power of 80%, $\alpha = 0.005$ requires a 70% larger sample size compared to $\alpha = 0.05$, which could lead to fewer studies due to limited resources [43].

Other alternatives (e.g., second-generation $p$-values [44], and analysis of credibility [45]) have been proposed in the special issue of the *American Statistician*; however, no consensus was reached. As a result, instead of recommending a ban of $p$-values, the accompanying editorial of the special issue called for an end of statistical significance testing [46]: “statistically significant” – don’t say it and don’t use it [10].

Will researchers and medical journals heed the “mandate” banning significance testing? It does not seem to be likely, at least thus far. Even if they do, it is no more than just a quibble – a significance test is done as long as the $p$-value is produced or reported – anyone seeing the result would know the $p$-value is greater or less than 0.05; the only difference is “Don’t ask, don’t tell.”

In any event, it is the right call to end dichotomizing the $p$-value and using it as the sole criterion to judge the results [47]. There is no practical difference between $p = 0.049$ and $p = 0.051$, and “God loves the .06 nearly as much as the .05” [48].” Furthermore, not all the results with a $p$-value close to 0.05 are valueless. Doctors and patients need to put $p$-values into context when making treatment choices, which can be well illustrated by a hypothetical but not unrealistic example. Suppose a study finds a new procedure (a kind of spine surgery) is effective in relieving debilitating neck and back pain with a $p$-value of 0.05, but when the procedure fails, it cripples the patient. If the patient believes there is only a 5% chance the procedure does not work or fails, he or she would probably take the chance. However, after learning the actual chance of failure is nearly 30% or higher based on the calibrated $p$-value, one would probably think twice. On the other hand, even if the $p$-value is 0.1 and the real chance of failure is nearly 40% or higher, if it does not cause serious side effects when the procedure fails, one would probably like to give it a try.

Taken together, in medicine or healthcare, the use of $p$-values needs more context (the balance of harms and benefits) than thresholds. However, banning significance testing and accepting uncertainty as called for by the editorial of the special issue are not enough [10]. When making treatment decisions, what researchers, practitioners, and patients alike need to know is the probability that a treatment does or does not work (the type I error). In this regard, the calibrated $p$-value, compared to other proposals [44, 45], offers several advantages: (1) It provides a lower-bound, (2) it is fully frequentist although it can have a Bayesian interpretation, (3) it is easy to understand, and (4) it is easy to implement. Of course, other recommendations for improving the use of $p$-values may work well under different circumstances such as improving research reproducibility [49, 50].

**Conclusions**

In medical research and practice, the $p$-value produced from significance testing has been widely misconstrued as the probability of the type I error, or the probability a treatment does not work. This misunderstanding comes with serious consequences: poor research reproducibility and inflated medical treatment effects. For a $p$-value of 0.05, the type I error or the chance a treatment does not work is not 5%; rather, it is at least 28.9%. Nevertheless, banning significance testing and accepting uncertainty, albeit well justified in many circumstances, offer little to apprise clinicians and patients of the probability a treatment will or will not work. In this respect, the calibrated $p$-value, a link between the $p$-value and the type I error, is practical and instructive.

In short, a long-overdue effort to understand $p$-values correctly is urgently needed and better education on statistical reasoning including Bayesian methods is desired [15]. Meanwhile, a rational action that medical journals can take is to require authors to report both conventional $p$-values and calibrated ones in research papers.

**Supplementary information**

Supplementary information accompanies this paper at https://doi.org/10.1186/s12874-020-01051-6.

**Additional file 1.**

**Abbreviations**

FDA: U.S. Food & Drug Administration; JAMA: Journal of the American Medical Association; ASA: American Statistical Association; CLT: Central Limit Theorem; AHA: American Heart Association

**Acknowledgements**

This material is based upon work supported (or supported in part) by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development. The author is indebted to Mr. Fred Malphurs, a retired senior healthcare executive, a visionary leader, who devoted his entire 38-year career to Veterans healthcare, for his unwavering support of research to improve healthcare efficiency and effectiveness. The author is also grateful to the Reviewers and Editorial Board members for their insightful and constructive comments and advice. The author would also like to thank Andrew Toporek and an anonymous reviewer for their helpful suggestions and assistance.

**Author’s contributions**

JG conceived/designed the study and wrote the manuscript. The author read and approved the final manuscript.

**Author’s information**

Director of Analytical Methodologies, Office of Productivity, Efficiency and Staffing, RAPID, U.S. Department of Veterans Affairs.

**Funding**

No.
Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
No.

Received: 21 February 2020 Accepted: 12 June 2020
Published online: 24 June 2020

References
1. Goodman S. A dirty dozen: twelve p-value misconceptions. Semin Hematol. 2008;45(3):135–40.
2. Hubbard R, Bayarri MR. Confusion over measures of evidence (p’s) versus errors (α’s) in classical statistical testing. Am Stat. 2003;57(3):171–82.
3. Windish DM, Huot SJ, Green ML. Medicine residents’ understanding of the biostatistics and results in the medical literature. JAMA. 2007;298:1010–22.
4. Berger JO, Sellke T. Testing a point null hypothesis: the irreconcilability of p-values and evidence (with discussions). J Am Stat Assoc. 1987;82(397):112–39.
5. Schwertman M. P values: what they are and what they are not. Am Stat. 1996;50(3):203–6.
6. Berger JO. Could Fisher, Jeffreys and Neyman have agreed on testing? Stat Sci. 2003;18:1–32.
7. Sellke T, Bayarri MJ, Berger JO. Calibration of p for testing precise null hypotheses. Am Stat. 2001;55(1):162–71.
8. Wasserstein RL, Lazar NA. The ASA’s statement on p-values: context, process, and purpose. Am Stat. 2016;70(2):129–33.
9. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature. 2019;567(7748):305–7.
10. Wasserstein RL, Schirm AL, Lazar AN. Moving to a world beyond “p < 0.05”. Am Stat. 2019;73(S1):1–19.
11. Fisher RA. Statistical methods and scientific inference (2nd edition). Edinburgh: Oliver and Boyd; 1959.
12. Lehmann EL. Neyman’s statistical philosophy. Probab Math Stat. 1995;15:29–36.
13. Neyman J, Pearson E. On the use and interpretation of certain test criteria for purpose of statistical inference. Biometrika. 1928;20:175–240.
14. Lehmann EL. The Fisher, Neyman-Pearson theories of testing hypotheses: one theory or two? J Am Stat Assoc. 1993;88(424):1242–9.
15. Gigerenzer G. Mindless statistics. J Socio-Econ. 2004;33:587–606.
16. Greenland S, Senn SJ, Rothman KJ, et al. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol. 2016;31(4):337–50.
17. Goodman SN. Toward evidence-based medical statistics. 1: the P value fallacy. Ann Intern Med. 1999;130(12):995–1000.
18. Goodman SN. Toward evidence-based medical statistics. 2: the Bayes factor. Ann Intern Med. 1999;130(12):1005–13.
19. Davidoff F. Standing statistics right up. Ann Intern Med. 1999;130(12):1019–21.
20. Kierfer J. Admissibility of conditional confidence procedures. Ann Math Statist. 1976;48:636–65.
21. Kierfer J. Conditional confidence statements and confidence estimators (with discussion). J Am Stat Assoc. 1977;72:789–827.
22. Berger JO, Brown LD, Wolfer RL. A unified conditional frequentist and Bayesian test for fixed and sequential simple hypothesis testing. Ann Stat. 1994;22:1787–807.
23. Berger JO, Bouakiz B, Wang Y. Unified frequentist and Bayesian testing of a precise hypothesis (with discussion). Stat Sci. 1997;12:133–60.
24. Matthews R. The great health hoax. The Sunday Telegraph; 1998. Archived: http://junksciencearchive.com/sep98/matthews.html. Accessed 6 June 2020.
25. Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. JAMA. 2005;294(2):218–28.
26. Ioannidis JP. Why most discovered true associations are inflated. Epidemiology. 2008;19(5):640–8.
27. MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G. Coffee and cancer of the pancreas. N Engl J Med. 1981;304(11):630–3.
28. http://www.nytimes.com/1981/03/12/us/study-links-coffee-use-to-pancreas-cancer.html. Accessed 2 May 2020.
29. Hsieh CC, MacAnon B, Yen S, Trichopoulos D, Warren K, Nardi G. Coffee and pancreatic cancer (chapter 2). N Engl J Med. 1986;315(9):587–9.
30. Turati F, Galeone C, Edefonti V. A meta-analysis of coffee consumption and pancreatic cancer. Ann Oncol. 2012;23(2):311–8.
31. Chowdhury R, Wamakula S, Kunutsor S, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med. 2014;160:398–406.
32. Sacks FM, Lichtenstein AH, Wu JHY, et al. Dietary fats and cardiovascular disease: a presidential advisory from the American Heart Association. Circulation. 2017;136(3):e1–e23.
33. Goodman SN. Why is getting rid of p-values so hard? Musings on science and statistics. Am Stat. 2019;73(1):26–30.
34. Tong C. Statistical inference enables bad science; statistical thinking enables good science. Am Stat. 2019;73(1):246–26.
35. Trafimow D, Marks M. Editorial. Basic Appl Soc Psychol. 2015;37:1–2.
36. Lang JM, Rothman KJ, Cann C. That confounded P-value. Epidemiology. 1998;9(1):7–8.
37. http://journals.lww.com/epidem/Pages/informationforauthors.aspx. Accessed 2 May 2020.
38. Kuege JI, Heck PR. Putting the p-value in its place. Am Stat. 2019;73(1):122–8.
39. Greenland S. Valid p-values behave exactly as they should: some misleading criticisms of p-values and their resolution with s-values. Am Stat. 2019;73(1):106–14.
40. Colquhoun D. The false positive risk: a proposal concerning what to do about p-values. Am Stat. 2019;73(1):192–201.
41. Johnson VE. Revised standards for statistical evidence. Proc Natl Acad Sci U S A. 2013;110(48):19313–7.
42. Benjamin DJ, Berger JO, Johannesson M, et al. Redefine statistical significance. Nat Hum Behav. 2018;2:6–10.
43. Lakens D, Adolff FG, Albers CJ, et al. Justify your alpha. Nat Hum Behav. 2018;2:168–71.
44. Blume JD, Grewey RA, Welty VF, et al. An introduction to second-generation p-values. Am Stat. 2019;73(1):157–67.
45. Matthews RJ. Moving towards the post p < 0.05 era via the analysis of credibility. Am Stat. 2019;73(1):202–12.
46. McShane BB, Gal D, Gelman A, et al. Abandon statistical significance. Am Stat. 2019;73(S1):45–45.
47. Liao JM, Stack CB, Goodman S. Annals understanding clinical research: interpreting results with large p values. Ann Intern Med. 2018;169(7):485–6.
48. Rosnow RL, Rosenthal R. Statistical procedures and the justification of results. Contemp Clin Trials. 2008;29(3):248–56.
49. Rothman KJ, Greenland S. Modern epidemiology. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2013.
50. Greenland S. Valid p-values behave exactly as they should: some misleading criticisms of p-values and their resolution with s-values. Am Stat. 2019;73(1):106–14.
51.漏 diferent p-values and Bayes factors. Annual Review of Statistics and Its Application. 2018;5:393–419.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:
- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.
Learn more at biomedcentral.com/submissions