Trustworthiness of Evidence: Role and Responsibilities of Biomedical Journals (Editors)

Howard Bauchner, MD
Editor-in-Chief, JAMA and The JAMA Network
Professor of Pediatrics and Public Health
Boston University School of Medicine (on leave)

Why is this important

- Journals have become communication networks
- Conduit between the scientific community and investigators, clinicians, public, and media
- Far greater interest in medicine/science than in the past
- Patient participation in care is increasing
- Time of near facts, partial facts, half-facts
- Health care increasingly expensive

Reach of JAMA

- **Readers**
  - 310,000 subscribers
  - 150,000 MDs read weekly content in CMJ
  - 600,000 weekly eTOC alerts
  - 1.2 million weekly on-line alerts
  - 120,000 users TJN reader
  - 20,000 MDs view content on Univadis
- **Social Network**
  - Twitter 220,000+
  - Facebook 440,000+
- **Listeners**
  - 10,000 listen to EICs weekly podcast
  - 100,000+ listen to other podcasts monthly
- **Viewers**
  - 8,000,000 see/hear monthly JAMA report video
- **Learners**
  - ~3000 participate in weekly CME quizzes

We touch ~ 1.5M physicians each week with our content
2017 ~ 32 Million PDF/HTML downloads!!!

Responsibility of Editors

- Understand conflict of interest
- Conduct adequate peer-review
- “Frame” important articles, minimize “hype”
- Understand the power of opinion
- Use language carefully
- Ensure accuracy of scientific literature (correct errors)
- Continually review policies

Conflict of Interest

EDITORIAL

Conflict of Interest and Medical Journals

Phil Fontanarosa, MD, MBA; Howard Bauchner, MD

Conflict of interest (COI) affects every aspect of medicine, including clinical care, teaching, and research. According to one definition, "A conflict of interest exists when professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain). Perceptions of conflict of interest are as important as actual conflicts of interest."[1] Over the past decade, there has been increasing attention to virtually every aspect of COI in medicine, including reports from authoritative national committees,[2] federally mandated reporting of industry payments to physicians,[3] enhanced policies and procedures governing COI at academic medical centers and research institutions, and efforts to harmonize reporting of COI overall[4] and in scientific publications.[5]

Viewpoints pages 1717-1761

This theme issue of *JAMA* is devoted to presenting new information on the evolving nature of COI. The issue includes 23 scholarly Viewpoints that represent the multifaceted aspects and complexity of COI from numerous perspectives, ranging from academic medical centers and industry to patients and the public. Harvey Fineberg, MD, frames the theme issue by emphasizing that understanding, dealing with, and continually improving what is known about COI is critical if physicians are to retain the trust that patients have placed in the profession.[6] William Stead, MD, provides an overarching editorial on the various multidisciplinary aspects of COI covered in the Viewpoints and suggests that a systematic approach is needed in which all stakeholders in the health professions and biomedical sciences work together to protect professional judgment and integrity while ensuring medical progress.[7]

In addition, 2 research reports in this issue of *JAMA* present findings on COI involving physicians. In one study, Tringale and colleagues[8] analyzed data from the Open Payments reports of industry payments to physicians in 2015 and found that 449 864 (approximately 48%) US physicians were reported to have received a total of $2.4 billion in industry-related payments, with a higher likelihood and higher value of payments to physicians in surgical specialties than those in primary care specialties and to male physicians than female physicians. In another study, Larkin and colleagues[9] used information from a data set that included more than 16 million prescriptions and compared prescribing by 2126 physicians at 19 academic medical centers that implemented policies between January 2006 and June 2012 that restricting pharmaceutical representative sales visits to physicians ("detailing") with prescribing by a control group of 24 593 matched physicians who were not subject to such policies. Introduction of academic medical centers' detailing policies was associated with a 1.67-percentage point decrease in the market share of detailed drugs (representing an 8.7% relative reduction in market share following the intervention) and a 0.84-percentage point increase in the market share of nondetailed drugs (representing a 5.6% relative increase in market share).

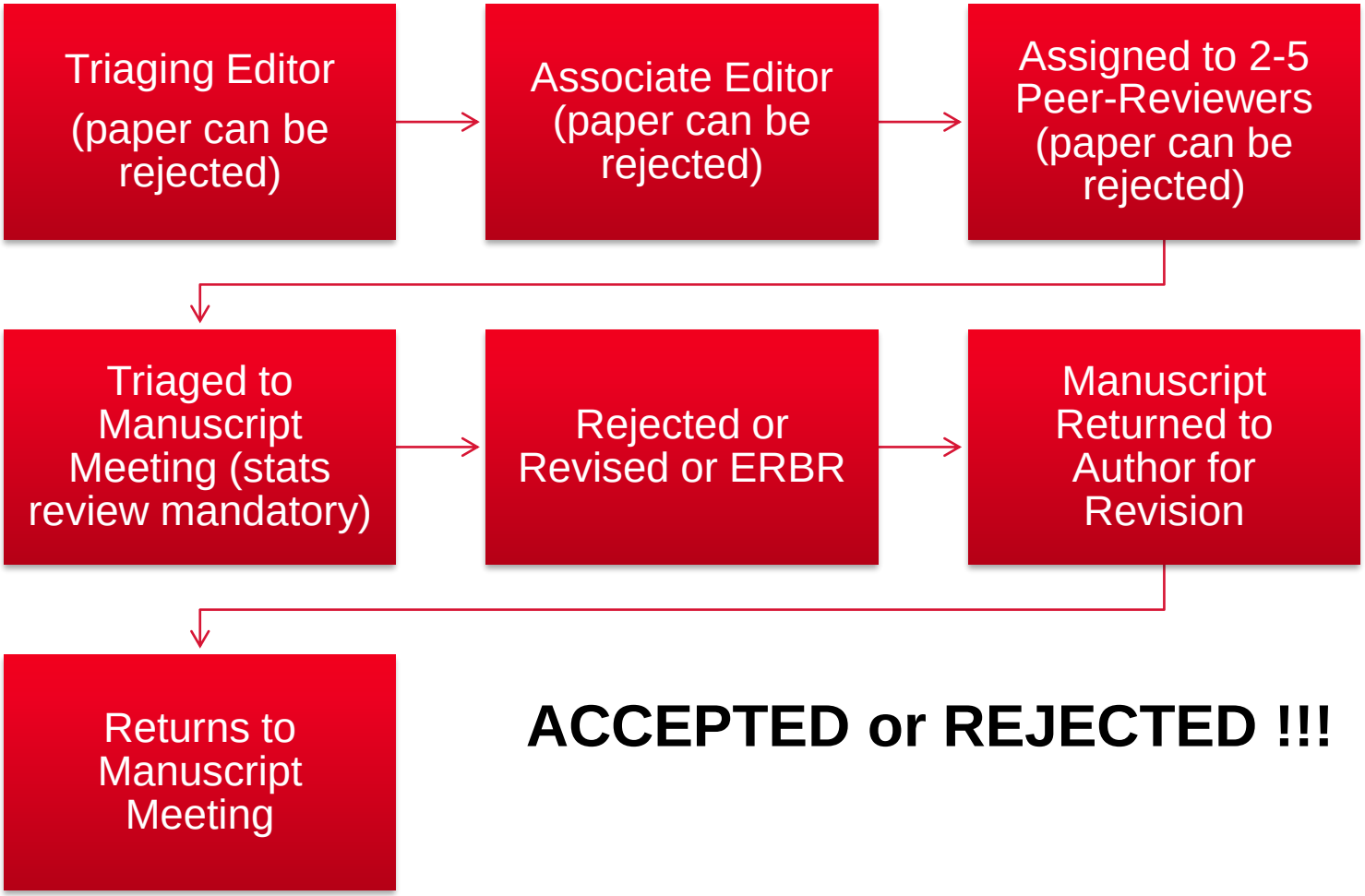
COI is a critically important issue for biomedical journals and editors. This editorial reviews journal policies governing COI and discusses important decisions and issues editors must address regarding COI related to research reports and opinion articles, resolving undisclosed COIs, and safeguarding against COI in the editorial decision process.

Journal Policies on COI

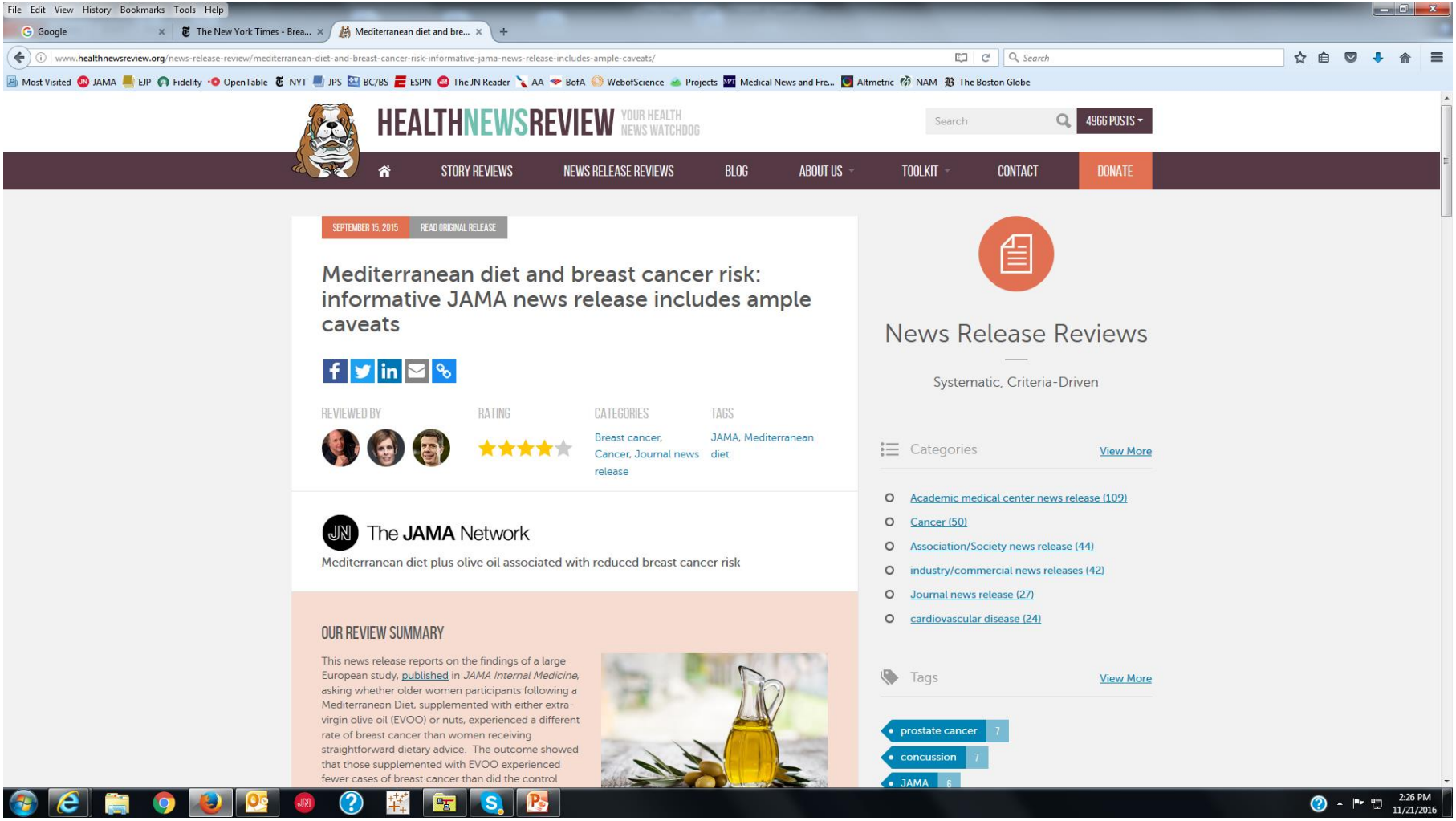
Effective evaluation and transparent management of COI are essential to ensure the integrity and credibility of published articles and to promote public confidence and trust in the scientific process and the credibility of published articles.[1] Accordingly, all authors of all manuscripts submitted for consideration for publication in *JAMA* and the JAMA Network specialty journals (including research reports, reviews, opinion articles, and letters to the editor) are expected to provide detailed information about all relevant financial interests, activities, relationships, and affiliations including, but not limited to, employment, affiliation, funding and grants received or pending, consultancies, honoraria or payment, speakers' bureaus, stock ownership or options, expert testimony, royalties, donation of medical equipment; or patents planned, pending, or issued.[10,11] As stipulated in the International Committee of Medical Journal Editors (ICMJE) disclosure form, these disclosures should include "Any potential conflicts of interest involving the work under consideration for publication" (during the time involving the work, from initial conception and planning to present), any "relevant financial activities outside the submitted work" (over the 3 years prior to submission), and any "other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing" what is written in the submitted work (based on all relationships that were present during the 3 years prior to submission).[1,10]

Although many universities and other institutions and organizations have established policies and thresholds for reporting financial interests and other COIs, *JAMA* and the JAMA Network journals require complete disclosure of all relevant financial relationships and potential financial COIs, regardless of amount or value. For example, authors of a manuscript about hypertension should report all financial relationships they have with all manufacturers and owners

Peer-Review at JAMA



Frame the Message



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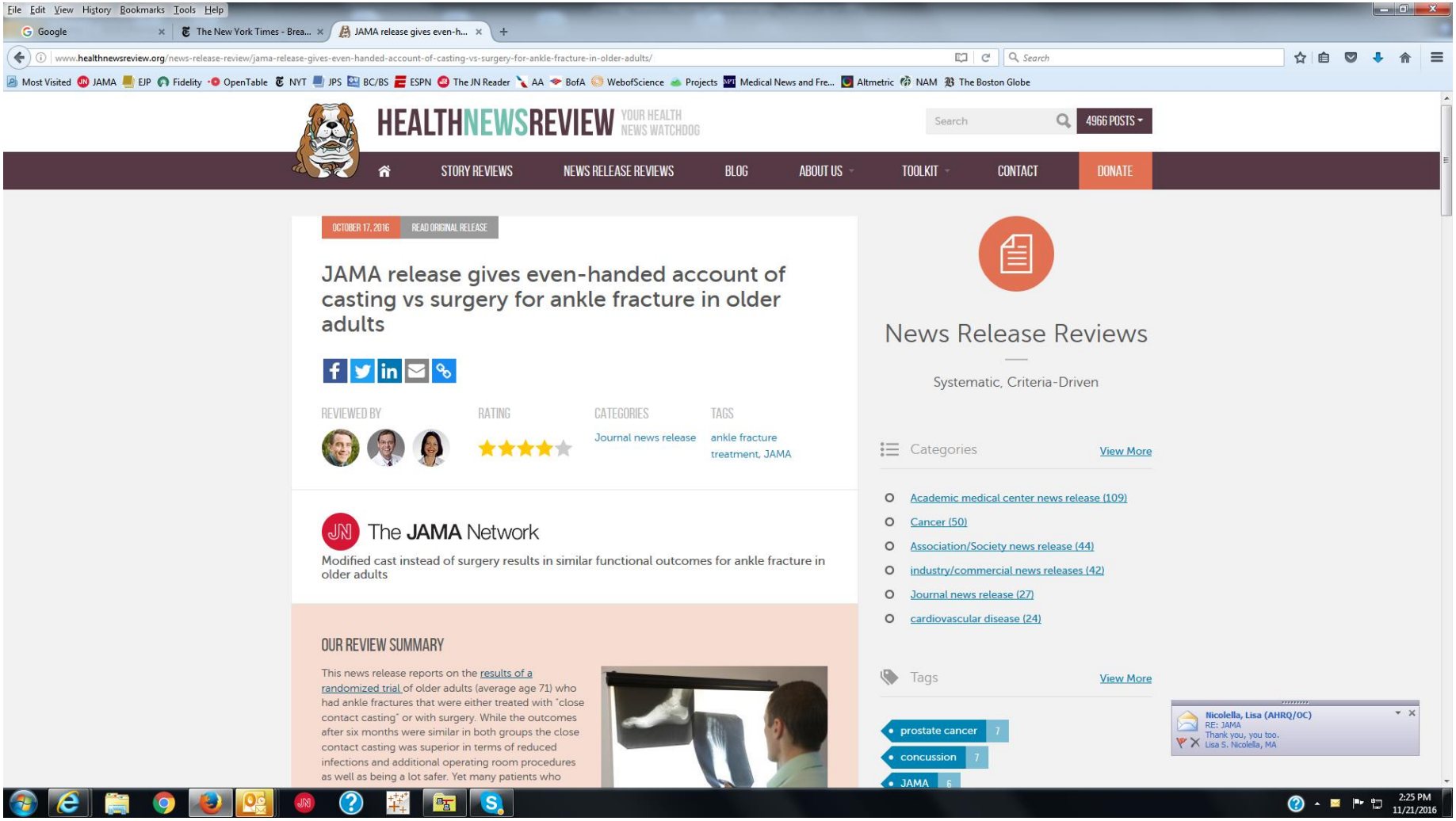

Clinical Trials

- Remain the single most important article type (perhaps guidelines have superseded RCTs)
- Occupy the top or contribute to the top of the evidence pyramid
- Clinicians and much of the media understand the importance of clinical trials
- Difficult legacy in the 1980s and 1990s
- Single greatest advance – trial registration
- SAPs, protocols, trial registration
- More conducted in conjunction with industry
- Data-sharing

Clinical Trials

Original Investigation

Effect of Prenatal Supplementation With Vitamin D on Asthma or Recurrent Wheezing in Offspring by Age 3 Years The VDAART Randomized Clinical Trial

Augusto A. Litonjua, MD, MPH; Vincent J. Carey, PhD; Nancy Laranjo, BA; Benjamin J. Harshfield, BA; Thomas F. McElrath, MD, PhD; George T. O'Connor, MD, MS; Megan Sandel, MD, MPH; Ronald E. Iverson Jr, MD, MPH; Aviva Lee-Paritz, MD; Robert C. Strunk, MD, PhD; Leonard B. Bacharier, MD; George A. Macones, MD, MSCE; Robert S. Zeiger, MD, PhD; Michael Schatz, MD, MS; Bruce W. Hollis, PhD; Eve Hornsby, PhD; Catherine Hawrylowicz, PhD; Ann Chen Wu, MD, MPH; Scott T. Weiss, MD, MS

IMPORTANCE Asthma and wheezing begin early in life, and prenatal vitamin D deficiency has been variably associated with these disorders in offspring.

OBJECTIVE To determine whether prenatal vitamin D (cholecalciferol) supplementation can prevent asthma or recurrent wheeze in early childhood.

DESIGN, SETTING, AND PARTICIPANTS The Vitamin D Antenatal Asthma Reduction Trial was a randomized, double-blind, placebo-controlled trial conducted in 3 centers across the United States. Enrollment began in October 2009 and completed follow-up in January 2015. Eight hundred eighty-one pregnant women between the ages of 18 and 39 years at high risk of having children with asthma were randomized at 10 to 18 weeks' gestation. Five participants were deemed ineligible shortly after randomization and were discontinued.

INTERVENTIONS Four hundred forty women were randomized to receive daily 4000 IU vitamin D plus a prenatal vitamin containing 400 IU vitamin D, and 436 women were randomized to receive a placebo plus a prenatal vitamin containing 400 IU vitamin D.

MAIN OUTCOMES AND MEASURES Coprimary outcomes of (1) parental report of physician-diagnosed asthma or recurrent wheezing through 3 years of age and (2) third trimester maternal 25-hydroxyvitamin D levels.

RESULTS Eight hundred ten infants were born in the study, and 806 were included in the analyses for the 3-year outcomes. Two hundred eighteen children developed asthma or recurrent wheeze: 98 of 405 (24.3%; 95% CI, 18.7%-28.5%) in the 4400-IU group vs 120 of 401 (30.4%, 95% CI, 25.7%-73.1%) in the 400-IU group (hazard ratio, 0.8; 95% CI, 0.6-1.0; $P = .051$). Of the women in the 4400-IU group whose blood levels were checked, 289 (74.9%) had 25-hydroxyvitamin D levels of 30 ng/mL or higher by the third trimester of pregnancy compared with 133 of 391 (34.0%) in the 400-IU group (difference, 40.9%; 95% CI, 34.2%-47.5%, $P < .001$).

CONCLUSIONS AND RELEVANCE In pregnant women at risk of having a child with asthma, supplementation with 4400 IU/d of vitamin D compared with 400 IU/d significantly increased vitamin D levels in the women. The incidence of asthma and recurrent wheezing in their children at age 3 years was lower by 6.1%, but this did not meet statistical significance; however, the study may have been underpowered. Longer follow-up of the children is ongoing to determine whether the difference is clinically important.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00920621

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Author Affiliations: Author affiliations are listed at the end of this article.
Corresponding Author: Augusto A.

Original Investigation

Effect of Vitamin D_3 Supplementation During Pregnancy on Risk of Persistent Wheeze in the Offspring A Randomized Clinical Trial

Bo L. Chawes, MD, PhD; Klaus Bønnelykke, MD, PhD; Jakob Stokholm, MD, PhD; Nadja H. Vissing, MD, PhD; Elin Bjarnadóttir, MD; Ann-Marie M. Schoos, MD, PhD; Helene M. Wolsk, MD; Tine Marie Pedersen, MD; Rebecca K. Vinding, MD; Sunna Thorsteinsdóttir, MD; Lambang Arianto, MD; Henrik W. Hallas, MD; Lene Heickendorff, MD, DMSc; Susanne Brix, MSc, PhD; Morten A. Rasmussen, MSc, PhD; Hans Bisgaard, MD, DMSc

IMPORTANCE Observational studies have suggested that increased dietary vitamin D intake during pregnancy may protect against wheezing in the offspring, but the preventive effect of vitamin D supplementation to pregnant women is unknown.

OBJECTIVE To determine whether supplementation of vitamin D_3 during the third trimester of pregnancy reduces the risk of persistent wheeze in the offspring.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, single-center, randomized clinical trial conducted within the Copenhagen Prospective Studies on Asthma in Childhood 2010 cohort. Enrollment began March 2009 with a goal of 708 participants, but due to delayed ethical approval, only 623 women were recruited at 24 weeks of pregnancy. Follow-up of the children (N = 581) was completed when the youngest child reached age 3 years in March 2014.

INTERVENTIONS Vitamin D_3 (2400 IU/d; n = 315) or matching placebo tablets (n = 308) from pregnancy week 24 to 1 week postpartum. All women received 400 IU/d of vitamin D_3 as part of usual pregnancy care.

MAIN OUTCOMES AND MEASURES Age at onset of persistent wheeze in the first 3 years of life. Secondary outcomes included number of episodes of troublesome lung symptoms, asthma, respiratory tract infections, and neonatal airway immunology. Adverse events were assessed.

RESULTS Of the 581 children, persistent wheeze was diagnosed during the first 3 years of life in 47 children (16%) in the vitamin D_3 group and 57 children (20%) in the control group. Vitamin D_3 supplementation was not associated with the risk of persistent wheeze, but the number of episodes of troublesome lung symptoms was reduced, and the airway immune profile was up-regulated (principal component analysis, $P = .04$). There was no effect on additional end points. Intrauterine death was observed in 1 fetus (<1%) in the vitamin D_3 group vs 3 fetuses (1%) in the control group and congenital malformations in 17 neonates (5%) in the vitamin D_3 group vs 23 neonates (8%) in the control group.

End Point	Vitamin D_3	Control	Estimate (95% CI)	*P* Value
Persistent wheeze, No. (%)	47 (16)	57 (20)	Hazard ratio (HR), 0.76 (0.52-1.12)	.16
Episodes of troublesome lung symptoms, mean (95% CI)	5.9 (5.2-6.6)	7.2 (6.4-8.1)	Incidence risk ratio (IRR), 0.83 (0.71-0.97)	.02
Asthma at 3 y, No. (%)	32 (12)	47 (14)	Odds ratio, 0.82 (0.50-1.36)	.45
Respiratory tract infections				
Upper, annual mean (95% CI)	5.2 (4.8-5.5)	5.3 (4.9-5.6)	IRR, 0.99 (0.90-1.09)	.84
Lower, No. (%)	94 (32)	95 (33)	HR, 0.96 (0.72-1.27)	.76

CONCLUSIONS AND RELEVANCE The use of 2800 IU/d of vitamin D_3 during the third trimester of pregnancy compared with 400 IU/d did not result in a statistically significant reduced risk of persistent wheeze in the offspring through age 3 years. However, interpretation of the study is limited by a wide CI that includes a clinically important protective effect.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00856947

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Author Affiliations: Author affiliations are listed at the end of this article.
Corresponding Author: Hans Bisgaard, MD, DMSc, Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Ledreborg Allé 34, DK-2820

Accompanying Editorial

EDITORIAL

Editorials represent the opinions of the authors and JAMA and not those of the American Medical Association.

Inconclusive Results of Randomized Trials of Prenatal Vitamin D for Asthma Prevention in Offspring
Curbing the Enthusiasm

Erika von Mutius, MD, MSc; Fernando D. Martinez, MD

Related articles pages 353 and 362

In most large cities in the Northern hemisphere in the late 19th and early 20th centuries, rickets was an enormous public health problem, mainly because exposure to sunlight was limited, particularly for children.[1] German physicians noticed that daily administration of a tablespoon of cod liver oil could reverse rickets, a finding that led to the discovery of vitamin D, its structure, and function. In the United States, most of the milk supply is now voluntarily fortified with vitamin D, whereas fortification of infant formula with vitamin D is mandatory.[2] In many European countries, food fortification with vitamin D is not required by law,[3] but vitamin D administration to infants and pregnant women is recommended. This public health intervention has been highly suc-

ing prior to age 3 years progress to develop asthma, but no biomarker exists to precisely identify individuals at risk.

Ultimately, randomized clinical trials (RCTs) are essential to determine if associations present in observational studies can be translated into specific clinical indications. For nonskeletal disorders apart from asthma, a recent, comprehensive meta-analysis of trials concluded that there was little or no evidence to suggest a protective relationship that would be sufficient to justify preventive administration of vitamin D.[11]

In this issue of *JAMA*, the results of 2 RCTs assessing the effect of vitamin D supplementation during pregnancy (beyond usually recommended doses) in relation to asthmalike symptoms in the first 3 years of life are presented. Chawes and colleagues[12] randomly assigned 623 pregnant Danish women who were receiving 400 IU/d of vitamin D as part of usual care

Based on the results reported in the trials by Chawes et al and Litonjua et al, what should clinicians do? Given the lack of any major unwanted effects observed in either of these trials, prescribing a higher than recommended vitamin D–containing supplement during pregnancy to mothers who are at high risk of having children with asthma (ie, with a history of asthma, eczema, or allergic rhinitis) seems to be a reasonable strategy, especially if the pregnant woman has evidence of vitamin D deficiency. However, the data in these 2 RCTs do not support the use of very high-dose vitamin D: the effects reported by Litonjua et al[13] were similar to those reported by Chawes et al,[12] with the latter study using an almost 50% lower total dose of vitamin D (ie, 2800 IU/d). Moreover, these studies provide support for a larger adequately powered study of the role of vitamin D supplementation during pregnancy for asthma prevention that includes plans for rigorous outcome assessment and long-term follow-up. Then it may be possible to know whether maternal vitamin D supplementation can reduce the risk of childhood asthma.

The Influence of Opinion

VIEWPOINT

Evaluating the Risks of Electric Uterine Morcellation

Kimberly A. Kho, MD, MPH
Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas.

Ceana H. Nezhat, MD
Atlanta Center for Minimally Invasive Surgery and Reproductive Medicine, Atlanta, Georgia.

Gynecologic surgeons, like many other surgical specialists, have embraced laparoscopic surgical techniques because they offer quicker recovery, less postoperative pain, and fewer wound complications than open procedures. The removal of large pieces of tissue through the small incisions of laparoscopy is difficult. However, this problem can be overcome by tissue morcellation, a technique of fragmenting tissue into smaller pieces that often prevents the need to enlarge established incisions. Surgeons have long used manual morcellation with a scalpel or scissors to remove masses abdominally and vaginally, but use of the technique has increased with wide adoption of laparoscopic approaches and with the introduction of laparoscopic electric morcellators in 1993.

Intracorporeal (ie, intra-abdominal) electric morcellation also rarely disseminates occult malignancies, including uterine sarcomas and ovarian, renal, and endometrial carcinomas.[2] While cervical and endometrial cancer can be screened for preoperatively, there are no good methods to detect uterine sarcomas; these tumors usually are identified incidentally after review of the surgical specimen. Retrospective single-institution tissue fragments from being inadvertently dispersed throughout the peritoneal cavity; these fragments may then implant anywhere and cause symptoms and morbidity requiring intervention. Numerous reports have documented ectopic leiomyoma, endometriosis, adenomyosis, ovarian tissue, and fragments of spleen and kidney as a result of morcellation.

VIEWPOINT

Stealth Research
Is Biomedical Innovation Happening Outside the Peer-Reviewed Literature?

John P. A. Ioannidis, MD, DSc
Stanford Prevention Research Center (SPRC) and Meta-Research Innovation Center at Stanford (METRICS), Stanford, California.

Author Reading at jama.com

Information about Theranos, a privately held biotechnology company that has developed novel approaches for laboratory diagnostic testing, has appeared in *The Wall Street Journal*, *Business Insider*, *San Francisco Business Times*, *Fortune*, *Forbes*, *Medscape*, and *Silicon Valley Business Journal*—but not in the peer-reviewed biomedical literature. As of January 5, 2015, a search in PubMed using *Theranos* as a search term identified affiliations for only 2 unrelated articles coauthored by Theranos Inc employees, although these 2 reports do not offer insights about their company.

Conversely, according to the non–peer-reviewed of venipuncture.[5] Several patents have been filed and approved. A search in the JUSTIA patent database using *Theranos* as a search term yielded 71 items retrieved as of January 5, 2015.[6] However, it is practically impossible to judge the validity of the science based only on patents with titles such as "Methods and Systems for Assessing Clinical Outcomes."

Theranos is just one example among many for which major efforts and major claims about biomedical progress seem to be happening outside the peer-reviewed scientific literature. Many of these efforts and claims have a biotechnology flavor, and the people involved often include a blend of engineers, physical scientists, and vop

VIEWPOINT

Reconsideration of the Lifetime Ban on Blood Donation by Men Who Have Sex With Men

I. Glenn Cohen, JD
Harvard Law School, Cambridge, Massachusetts; and Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics, Cambridge, Massachusetts.

Jeremy Feigenbaum, JD
Harvard Law School, Cambridge, Massachusetts.

Eli Y. Adashi, MD, MS
Warren Alpert Medical School, Brown University, Providence, Rhode Island.

In 2013, the US Supreme Court took a historic step in *United States v Windsor* by striking down the Defense of Marriage Act on the grounds that it imposed a "disability on the class [of gay Americans] by refusing to acknowledge a status the State finds to be dignified and proper."[1] This milestone in gay rights stands in stark contrast to the ongoing lifetime ban imposed in 1983 on blood donation by men who have ever had sex with men (MSMs) even once.[2] As it stands, the US Food and Drug Administration (FDA) continues to uphold this 30-year-old policy, unaltered, on the grounds that MSMs remain at increased risk of contracting transfusion-transmissible pathogens such as human immunodeficiency virus (HIV).[2]

This indefinite and indiscriminate policy has hardly gone unchallenged. The American Red Cross, America's Blood Centers, and the American Association of Blood Banks have opposed the ban as "medically and scientifically unwarranted." More recently, the American Medical Association and the American Osteopathic Association prospective blood donors served a useful purpose at a point in time when the ascertainment of HIV status was not possible. However, much has changed over the last 3 decades. First, modern nucleic acid diagnostic technology has advanced to a point enabling ascertainment of HIV infection within weeks of the inciting exposure. Second, effectively designed screening tools focused on risk stratification and individualization are now practicable, thereby permitting the ascertainment of safe-sex practices, monogamy, or HIV status. Third, the current policy is increasingly incompatible with international norms. Indeed, several nations have recently limited their deferral periods for sexually active MSMs to 5 years (Canada), 1 year (United Kingdom), and 6 months (South Africa). Fourth, the current policy is both inconsistent and inequitable. While sexually active MSMs face a lifetime ban, men who have had sex with commercial sex workers or with HIV-positive women are deferred for no more than 12 months since that sexual encounter before regaining eligibility.[7] The same holds true for women who have had sex with HIV-positive men.[7]

> Viewed in the aggregate, the current FDA policy may be perpetuating outdated homophobic perceptions.

Viewed in the aggregate, the current FDA policy may be perpetuating outdated homophobic perceptions. Even

Curb Your Enthusiasm

VIEWPOINT

Seven Questions for Personalized Medicine

Michael J. Joyner, MD
Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota.

Nigel Paneth, MD, MPH
Department of Epidemiology and Biostatistics, College of Human Medicine, Michigan State University, East Lansing; and

Personalized or precision medicine maintains that medical care and public health will be radically transformed by prevention and treatment programs more closely targeted to the individual patient. These interventions will be developed by sequencing more genomes, creating bigger biobanks, and linking biological information to health data in electronic medical records (EMRs) or obtained by monitoring technologies. Yet the assumptions underpinning personalized medicine have largely escaped questioning. In this Viewpoint, we seek to stimulate a more balanced debate by posing 7 questions for the advocates of personalized medicine.

are offered enhanced screening and preemptive surgery. In the 25 years since *BRCA1/2* was discovered, breast cancer mortality in the United States has declined by nearly one-third; however, little of this decline stems from the discovery of *BRCA1/2*. Moreover, *BRCA1/2* is a unique story because the gene variants account for such a substantial amount of the variance in

VIEWPOINT

Avoiding the Unintended Consequences of Screening for Social Determinants of Health

Arvin Garg, MD, MPH
Department of Pediatrics, Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts.

Renée Boynton-Jarrett, MD, ScD
Department of Pediatrics, Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts.

Paul H. Dworkin, MD
Department of Pediatrics, University of Connecticut School of Medicine, Farmington; and Office for Community Child Health, Children's Medical Center, Hartford, Connecticut.

Screening for social determinants of health, which are the health-related social circumstances (eg, food insecurity and inadequate or unstable housing) in which people live and work, has gained momentum as evidenced by the recent Centers for Medicare & Medicaid Services innovation initiative of $157 million toward creation of accountable health communities.[1] Funding will allow grantees to test a novel model of health care that includes identifying and addressing social determinants of health for Centers for Medicare & Medicaid Services beneficiaries. The initiative promotes collaboration between the clinical realm and the community through screening of beneficiaries to (1) identify unmet health-related social needs and (2) assist high-risk beneficiaries (ie, >2 emergency department visits and a health-related social need) with accessing available community services.

Some health policy makers have embraced screening of social determinants as the next hope for achieving the triple aim of better health, improved health care delivery, and reduced costs because social and environmental factors are thought to contribute half

ment) requires effective care coordination and cross-sector collaboration. The relatively few exemplary, evidence-based models (eg, WE CARE, Health Leads, Project DULCE, Safe Environment for Every Kid, Help Me Grow) that use such strategies are limited in scope and reach and must be expanded to address the needs of diverse patient populations.[6]

The sensitive nature of such issues as food insecurity, unemployment, and interpersonal violence also poses unique challenges. Physicians may be uncomfortable routinely inquiring about adverse social circumstances, given their lack of personal experience with such needs and inadequate training on how to respectfully elicit and respond to patients' concerns. In addition, the absence of available services means that needs are often difficult to address, given the tenuous capacity of community resources such as affordable housing, behavioral health services, workforce development and employment, and public transportation.

Thus, despite the potential benefits of identifying and addressing adverse social determinants, there is the potential for unintended harm. Such screening could yield expectations that, if unfulfilled, could lead to frustration for patients and physicians alike. Furthermore, patients' perceptions of physicians as judgmental, presumptuous, or even callous could erode the patient-physician relationship. However, several key principles could guide physi-

> Screening for any condition in isolation without the capacity to ensure referral and linkage to appropriate treatment is ineffective and, arguably, unethical.

VIEWPOINT

What Happens When Underperforming Big Ideas in Research Become Entrenched?

Michael J. Joyner, MD
Laboratory of Human Integrative Physiology and Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota.

Nigel Paneth, MD, MPH
Departments of Epidemiology and Biostatistics and Pediatrics and Human Development, College of Human Medicine, Michigan State University, East Lansing.

John P. A. Ioannidis, MD, DSc
Stanford Prevention Research Center, Department of Medicine and Meta-Research Innovation Center at Stanford, Stanford University, Stanford, California.

For several decades now the biomedical research community has pursued a narrative positing that a combination of ever-deeper knowledge of subcellular biology, especially genetics, coupled with information technology will lead to transformative improvements in health care and human health. In this Viewpoint, we provide evidence for the extraordinary dominance of this narrative in biomedical funding and journal publications; discuss several prominent themes embedded in the narrative to show that this approach has largely failed; and propose a wholesale reevaluation of the way forward in biomedical research.

Primacy of the Narrative

In 2016 approximately $15 billion of the $26 billion of extramural research funding sponsored by the National Institutes of Health (NIH) could be linked to some version of search terms that include gene, genome, stem cells, or regenerative medicine.[1] These topics have also increased geometrically in their representation among published articles. Between 1974 and 2014 the annual number of published articles indexed in PubMed increased by 410% (from 234 613 to 1 196 110), but those identified with genome increased by 2127% (2705 to 60 246). Between 1994 and 2014, the annual number of articles indexed in PubMed increased by 175% (from 435 376 to 1 196 110), but articles identified with gene therapy or stem

mats. As of April 2016, the Centers for Medicare & Medicaid Services had paid $34 billion in financial incentives to service providers for implementing electronic health record (EHR) systems.[4] EHRs are an important aspect of this narrative because they are thought to provide the structural underpinnings of precision medicine. It has been suggested by some that some combination of these 8 big ideas will yield substantial cost savings for health care.

Expectations that a few DNA variants explain most common diseases have faded as the genetic architecture of most diseases has proved to be formidably complex. Apparently, hundreds or even tens of thousands of genetic variants are involved in each common disease. The function of these variants is difficult to decipher. Very few genes have found undisputed roles in preventive efforts or pharmacogenetic testing.

Continued enthusiasm for gene therapy ignores what is known from classic single-gene disorders such as sickle cell anemia. The complex biological processes set in motion by a single amino acid substitution that leads to painful crises, stroke, and other complications are not predictable from the genomic defect, but only by appreciating the complexity of biological systems at the level of tissues and organs. Sixty years after the discovery of the genetic defect, no targeted therapy has emerged for sickle cell anemia.

Use Language Carefully

- Causal language used only for clinical trials including in abstract, throughout the article, and in all press releases
- Absolute differences presented with relative differences, for both outcomes and adverse events (often can make any difference feel significant)
- Adverse events included in reporting of clinical trials
- Conclusion and relevance – our last section – reflects the data in the abstract

Careful Use of Language

JAMA | Original Investigation

Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty
The GIFT Randomized Clinical Trial

Brian F. Gage, MD, MSc; Anne R. Bass, MD; Hannah Lin, BA; Scott C. Woller, MD; Scott M. Stevens, MD; Noor Al-Hammadi, MBChB, MPH; Juan Li, MPH; Tomás Rodríguez Jr, MS; J. Philip Miller, AB; Gwendolyn A. McMillin, PhD; Robert C. Pendleton, MD; Amir K. Jaffer, MD, MBA; Cristi R. King, BS; Brandi DeVore Whipple, BS; Rhonda Porche-Sorbet, MS; Lynnae Napoli, BS; Kerri Merritt, BA; Anna M. Thompson, BA; Gina Hyun, MD; Jeffrey L. Anderson, MD; Wesley Hollomon, MD, MBA; Robert L. Barrack, MD; Ryan M. Nunley, MD; Gerard Moskowitz, PhD; Victor Dávila-Román, MD; Charles S. Eby, MD

IMPORTANCE Warfarin use accounts for more medication-related emergency department visits among older patients than any other drug. Whether genotype-guided warfarin dosing can prevent these adverse events is unknown.

OBJECTIVE To determine whether genotype-guided dosing improves the safety of warfarin initiation.

DESIGN, SETTING, AND PATIENTS The randomized clinical Genetic Informatics Trial (GIFT) of Warfarin to Prevent Deep Vein Thrombosis included patients aged 65 years or older initiating warfarin for elective hip or knee arthroplasty and was conducted at 6 US medical centers. Enrollment began in April 2011 and follow-up concluded in October 2016.

INTERVENTIONS Patients were genotyped for the following polymorphisms: *VKORC1-1639G>A*, *CYP2C9*2*, *CYP2C9*3*, and *CYP4F2 V433M*. In a 2 × 2 factorial design, patients were randomized to genotype-guided (n = 831) or clinically guided (n = 819) warfarin dosing on days 1 through 11 of therapy and to a target international normalized ratio (INR) of either 1.8 or 2.5. The recommended doses of warfarin were open label, but the patients and clinicians were blinded to study group assignment.

MAIN OUTCOMES AND MEASURES The primary end point was the composite of major bleeding, INR of 4 or greater, venous thromboembolism, or death. Patients underwent a screening lower-extremity duplex ultrasound approximately 1 month after arthroplasty.

RESULTS Among 1650 randomized patients (mean age, 72.1 years [SD, 5.4 years]; 63.6% women; 91.0% white), 1597 (96.8%) received at least 1 dose of warfarin therapy and completed the trial (n = 808 in genotype-guided group vs n = 789 in clinically guided group). A total of 87 patients (10.8%) in the genotype-guided group vs 116 patients (14.7%) in the clinically guided warfarin dosing group met at least 1 of the end points (absolute difference, 3.9% [95% CI, 0.7%-7.2%], $P = .02$; relative rate [RR], 0.73 [95% CI, 0.56-0.95]). The numbers of individual events in the genotype-guided group vs the clinically guided group were 2 vs 8 for major bleeding (RR, 0.24; 95% CI, 0.05-1.15), 56 vs 77 for INR of 4 or greater (RR, 0.71; 95% CI, 0.51-0.99), 33 vs 38 for venous thromboembolism (RR, 0.85; 95% CI, 0.54-1.34), and there were no deaths.

CONCLUSIONS AND RELEVANCE Among patients undergoing elective hip or knee arthroplasty and treated with perioperative warfarin, genotype-guided warfarin dosing, compared with clinically guided dosing, reduced the combined risk of major bleeding, INR of 4 or greater, venous thromboembolism, or death. Further research is needed to determine the cost-effectiveness of personalized warfarin dosing.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01006733

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Supplemental content

Author Affiliations: Washington University in St Louis, St Louis, Missouri (Gage, Lin, Al-Hammadi, Li, Rodríguez, Miller, King, Whipple, Porche-Sorbet, Thompson, Hyun, Barrack, Nunley, Moskowitz, Dávila-Román, Eby); Hospital for Special Surgery, New York, New York (Bass, Merritt, Hollomon); University of Massachusetts, Worcester (Lin); Intermountain Healthcare, Salt Lake City, Utah (Woller, Stevens, Anderson); University of Utah, Salt Lake City (Woller, Stevens, McMillin, Pendleton, Napoli, Anderson); New York Presbyterian Queens Hospital, New York, New York (Jaffer); University of Central Florida College of Medicine, Orlando (Thompson); Saint Louis University, St Louis, Missouri (Hyun).

Corresponding Author: Brian F. Gage, MD, MSc, General Medical Sciences, Washington University in St Louis, 4523 Clayton Ave, St Louis, MO 63110 (bgage@dom.wustl.edu).

Ensure Accuracy of Scientific Record

- Corrections
- Retractions
- Retractions with Replacements

Correcting the Medical Literature: "To Err Is Human, to Correct Divine"

Stacy Christiansen, MA; Annette Flanagin, RN, MA

Corrections are important to the integrity of the medical literature and clinical decision making. Those who use the content as a source for replication of findings or as the basis of new research rely on accurate data, which requires corrections of errors in published articles. These errors may range from relatively minor, inconsequential errors to major errors that invalidate the results and the underlying science (**Table**). Corrections of errors in published articles protect the reputation of authors, journals, and others involved in biomedical publication by demonstrating their willingness to publicly amend content in the best interests of science.

JAMA and the JAMA Network journals use numerous checks for quality from manuscript submission through publication, but errors still occur. Many errors originate with the content, inaccuracies that even astute peer reviewers, editors, and journal staff would not necessarily recognize (eg, a study participant improperly analyzed in the wrong treatment group). Reports of errors in published research reports originate from myriad sources: readers, the original investigators while engaged in subsequent analyses, investigators trying to replicate the research, journal staff, and members of the news media. These sources are the most frequent discoverers of errors that are reported to the JAMA Network journals.

According to the International Committee of Medical Journal Editors, "corrections are needed for errors of fact" and "matters of debate are best handled as letters to the editor, as print or electronic correspondence, or as posts in a journal-sponsored online forum."[1] The US National Library of Medicine has a useful guide for managing corrections to the literature and notes that it "does not differentiate between errors that originate in the publication process and those that result from errors of scientific logic or methodology."[2] The Council of Science Editors has provided a list of questions to consider when a potential error is reported.[3] Issues to consider include the nature of the error reported, the most appropriate method to correct the literature, and if any statute of limitations should

Table. JAMA Network Corrections, Pervasive Errors, and Retractions

Type	Definition	Publication Response
Minor error	Inconsequential error (eg, typographical error that could result in misunderstanding)	**Article corrected online:** An indication of correction and date of correction are added to the article information (html and PDF versions).
Substantive errors	Errors requiring a Correction notice (eg, author name misspelled, incorrect numbers, important missing information)	**Correction notice published:** The article is corrected online with indication of correction and date of correction added to the article information (html and PDF versions). The Correction notice and corrected article are reciprocally linked.
Pervasive errors	Inadvertent errors that result in the need to correct important or numerous data in the abstract, text, tables, and figures (eg, a coding error)	**A. Letter and Correction:** If none of the conclusions or interpretations are affected and there are no statistically significant changes in the results, a Letter of explanation from the authors and a Correction notice are published; the article is corrected online with indication of correction and date added to article information (html and PDF versions). The Letter, Correction notice, and corrected article are linked to each other. **B. Retraction and Replacement:** If the direction or significance of the results, interpretations, and conclusions change—and the science is still valid—a Letter of explanation from the authors is published as a Notice of Retraction and Replacement; the corrected article is replaced online with indication of correction and date added to article (html and PDF versions); a PDF copy of original article with the errors highlighted and a PDF copy of the replacement article with the corrections highlighted are published in an online supplement to the corrected, replaced article; the replacement article includes a prominent note: "This article has been retracted and replaced with a corrected version." The Letter and replacement article are reciprocally linked. **C. Retraction:** If the results, interpretations, and conclusions change—and the science is no longer valid—a Notice of Retraction is published (see below).
Scientific or research misconduct or Pervasive errors that should not be corrected or replaced	Fabrication, falsification, or plagiarism or Pervasive errors that invalidate the results, interpretations, conclusions, and the underlying science	**A. Retraction:** If confirmed, a Notice of Retraction as either a Letter from the authors or an Editorial from the editors is published. A prominent note and watermark are added to the retracted article (html and PDF versions). "This article has been retracted." The Notice of Retraction and the retracted article are reciprocally linked. **B. Expression of Concern:** If not officially confirmed by the authors or authors' institution or funders, but evidence of scientific or research misconduct is substantial, a Notice of Expression of Concern may be published as an Editorial from the editors. A prominent note is added to the html and the PDF versions of the article: "An Expression of Concern has been published about this article." The Notice of Expression of Concern and the article of concern are reciprocally linked.

Retracting, Replacing, and Correcting the Literature for Pervasive Error in Which the Results Change but the Underlying Science Is Still Reliable

Stephan Heckers, MD; Howard Bauchner, MD; Annette Flanagin, RN, MA

In this issue of *JAMA Psychiatry*, Lopes and colleagues[1] request retraction and replacement of their article titled "Gamma Ventral Capsulotomy for Obsessive-Compulsive Disorder: A Randomized Clinical Trial."[2] After an error was discovered by Baethge,[3] as also reported in a letter herein, the authors reviewed the data and confirmed an important but inadvertent error had occurred. As the authors explain in their letter to the editor,[1] this error involved a miscomputation of a treatment response for 1 of the 8 trial participants in the treatment group. This error resulted in an erroneous Yale-Brown Obsessive-Compulsive Scale score of 36 instead of 30 for that participant, which the authors counted as a responder to the treatment rather than a nonresponder. Thus, the number of responders in the treatment group at 12 months (as per the primary outcome reported in the trial protocol) is 2 of 8 participants rather than the originally reported 3 of 8 participants.

Related articles pages 1257 and 1258

Because of this error, the authors reconducted the analysis and provided a corrected article with corrections to the Abstract; Results, Discussion, and Conclusions sections of the article; and relevant tables and figures in the article and online supplement. The authors have confirmed that there are no additional errors. The corrected article has been reviewed and we have confirmed that the primary outcome has changed as stated in the corrected article: "Two of 8 patients randomized to active treatment responded at 12 months, and none of the 8 sham-GVC patients responded (the absolute difference was not statistically significant: 0.25; 95% CI, 0.05-0.55; $P = .11$)."[2]

Retractions are typically reserved for articles that have resulted from scientific misconduct, such as fabrication, falsification, or plagiarism, or from pervasive error for which the results cannot be substantiated.[4-6] In scientific publication, a pervasive error could result from a coding problem or a miscalculation and results in extensive inaccuracies throughout an article (eg, abstract, methods, results, discussion, conclusions, tables, and figures). Publication of pervasive incorrect data resulting in a major change in the direction or significance of the results, interpretations, and conclusions, as occurred with the trial reported by Lopes et al,[2] is a serious matter. However, in this case, the error was inadvertent and the underlying science is still reliable and important. Thus, we now publish this notice of retraction and replacement with explanation from the authors[1] and a corrected replacement article[2] as we believe it is important for readers, investigators, and clinicians to have access to correct results of this trial. We have included a version of the original retracted article showing the original errors and a version of the replacement article showing what was corrected in the online supplement of the corrected replacement article.[2]

Trust in Biomedical Journals

- A primary responsibility of editors
- More important than ever
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No legacy is so rich as honesty.
William Shakespeare

The goal of education is the advancement of knowledge and the dissemination of truth.
John F. Kennedy