Table 2. Reasons That EGDs Were Discordant With Evidence-Based Guidelines

Reasons for Discordance	Frequency of Discordance, No. (%)
Inappropriate PPI trial before endoscopy	63 (30.3)
Frequent surveillance for Barrett esophagus within 3 y	59 (28.4)
Chronic reflux symptoms in women	40 (19.2)
Chronic symptoms in patients <50 y of age	20 (9.6)
No designated indication for repeated intervention	11 (5.3)
Mild to moderate erosive esophagitis (grade A)	7 (3.4)
Chronic symptoms in women <50 y of age	5 (2.4)
Duration of chronic symptoms for <5 y	3 (1.4)

Abbreviations: EGD, esophagogastroduodenoscopy; PPI, proton-pump inhibitor.

recommendations may contribute to these high rates.[3-5] No statistical difference in discordance rates existed between EGDs that were referred by primary care physicians vs gastroenterologists. Possible explanations include the relatively recent guideline publication and potential selection bias for greater symptom severity among gastroenterologists.[6] Limitations included our short study duration and inability to capture patient-driven referrals, insurance data, and additional endoscopies performed at other institutions. A multidisciplinary approach of specialist prereview of open-access referrals, incorporation of appropriate indications in referral orders, and continued education may result in improved concordance with the evidence-based guidelines.

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Editor's Note

Promoting Evidence-Based High-Value Health Care

Promoting evidence-based high-value health care remains one of the foremost challenges in medicine today. Increasing scrutiny of the real-world effectiveness, safety, and costs of medical care, including therapeutics, diagnostic tests, procedures, operations, and even decisions regarding whether to admit a patient to the hospital or schedule an outpatient follow-up, have broadened and deepened our understanding of high-quality and high-value care. In response, multiple specialty societies, prompted by the Choosing Wisely campaign,[1] have revised their clinical practice guidelines and recommendations to address not only what care should be provided but also what care should not. But avoiding overtreatment and overdiagnosis are often easier said than done, even at the most prestigious and well-resourced institutions in the world.

In this issue of *JAMA Internal Medicine*, Cai et al[2] reviewed all 550 esophagogastroduodenoscopies performed in adults at Massachusetts General Hospital in the last 4 months of 2013 to evaluate low-risk indications, finding substantial overuse of the procedure. More than one-third were discordant with the American College of Physicians' evidence-based guidelines. Nevertheless, it is always easier to find mistakes and examples of health care that, in retrospect, need not have been provided. This article is a reminder of what we need to do to improve. Guidelines and recommendations are not enough. Practices need to change at the point of care. More steps need to be taken, including checklists before procedures, to review appropriate indications for use; substantive discussions with patients to obtain informed consent to comprehensively review expected benefits, risks, and costs as well as treatment alternatives; and better physician reimbursement policies are needed to provide sufficient financial support for these discussions between patients and their physicians. As patients and physicians grow increasingly aware of the need to promote evidence-based high-value health care, we need to develop the tools to make this care a reality in practice.

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Drug Manufacturers' Delayed Disclosure of Serious and Unexpected Adverse Events to the US Food and Drug Administration

Federal regulations define adverse drug events as those "associated with the use of a drug in humans whether or not considered drug related".[1] Health care professionals and consumers can voluntarily report adverse drug events directly to the US Food and Drug Administration (FDA) or the drug manufacturer. Serious adverse events (AEs) are defined by the regulation as those involving "death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect."[1] Unexpected AEs are defined as those involving "any adverse drug experience that is not listed in the current labeling for the drug product."[1] Serious and unexpected events are classified as *expedited*, and manufacturers receiving any such reports are mandated to forward them to the FDA "as soon as possible but in no case later than 15 calendar days of the initial receipt of the information."[1] The regulation also requests that the manufacturer conduct an investigation and forward findings as follow-up reports to the FDA. Previous studies highlighted that reports by manufacturers to the FDA of serious adverse drug events have increased steadily during the past decade.[2,3] Manufacturer compliance with the regulation to report serious and unexpected AEs to the FDA within 15 calendar days is unknown, although some media coverage has offered anecdotal examples of delays.[4,5] As the FDA uses this information to update drug warnings, delays in reporting can have important public health consequences, particularly if manufacturers selectively delay reporting based on relevant patient outcomes. We investigated patient and event characteristics associated with manufacturers' delayed submission of the expedited reports to the FDA.

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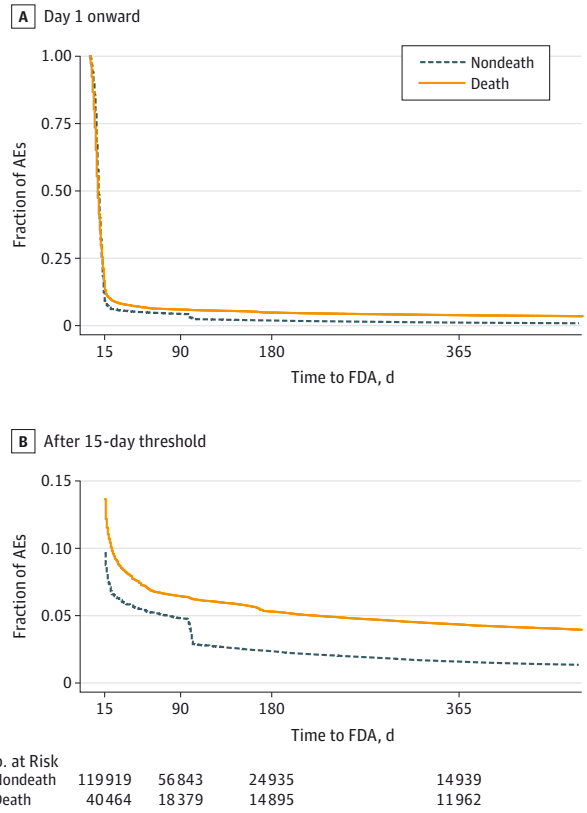
Methods | We extracted the quarterly FDA Adverse Event Reporting System data files of AE reports received between January 1, 2004, and June 30, 2014. We excluded direct reports to the FDA (about 5%) in which drug manufacturers are not involved. Our final sample included only the initial reports (excluding follow-ups) characterized by the FDA as expedited, and therefore subject to the regulation requiring the reports to be submitted within 15 calendar days. Analysis was conducted from May 2014 to May 2015. The University of Minnesota Institutional Review Board determined that this study does not meet the regulatory definition of human subjects research.

Our categorical outcome variable indicated whether the number of calendar days between the date the manufacturer received the report and the date the FDA received the same report from the manufacturer ("days to FDA") was: 15 days or fewer, 16 to 90 days, 91 to 180 days, or more than 180 days. We estimated a multivariable ordered logit model to examine the association between the categorical outcome variable and whether the AE involved patient death, adjusting for the number of unique drugs the patient was taking, the source of the report to the manufacturer (ie, consumer, physician, pharmacist, lawyer, or other), whether the report was electronically submitted, and patient age, sex, and weight. We included an indicator for the missing values of patient age, sex, and weight. To account for time trends, we included quarter and year indicators, and to account for systematic differences across manufacturers, we included indicators for manufacturers. We clustered standard errors at the drug level to account for correlation within drugs.

Figure. Kaplan-Meier Survival Estimates



Survival estimates of the number of days between the date the manufacturer received the adverse event (AE) report and the date the US Food and Drug Administration (FDA) received the same report from the manufacturer. Log-rank, $P < .001$. A, Kaplan-Meier estimates from day 1 onward. B, Kaplan-Meier estimates from day 15 onward.

Results | The study included 1 613 079 AE reports. Kaplan-Meier estimates show that 9.94% of reports (N = 160 383; 40 464 with patient death and 119 919 without patient death) were not received by the FDA by the 15-day threshold (**Figure**). Results of the log-rank test rejected the equality of the survivor functions by patient death ($P < .001$). In multivariable analyses, patient death was associated with delayed reporting (**Table**). A larger adjusted rate of events without patient death