Editor's Note
Informed Consent and Communicating Risk and Benefits of Research on Higher-Risk Medications

The Belmont Report formally established ethical principles and guidelines in 1979 for the protection of human research subjects in the United States. Summarizing discussions among the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research from an initial 4-day meeting at the Smithsonian Institution's Belmont Conference Center, as well as several years of subsequent deliberations, 3 core principles were identified in the Belmont Report: respect for persons, beneficence, and justice. While these principles frequently come into play in clinical research, the Belmont Report suggests that when designing a study, careful consideration should be given to informed consent, the assessment of risks and benefits, and selection of participants. To ensure that all conducted research involving human participants is aligned with these ethical principles and guidelines, institutional review boards (IRBs) have been formed across the country, both at academic medical centers and elsewhere. Considerable time and effort are invested by these IRBs, as well as by investigators and research staff, to ensure compliance with the aforementioned principles and guidelines. But how effective have we been? There are few simple ways to measure effectiveness in this area, but Bhattacharya et al suggest one in this issue of JAMA Internal Medicine: what proportion of applicable informed consent forms disclose black box warnings issued by the US Food and Drug Administration (FDA) for study medications?

At a single institution, Bhattacharya et al reviewed 4780 research protocols involving human participants approved by their IRB between January 2010 and December 2012 and determined that for 57 protocols (1.2%), a black box warning had been issued for a study medication. However, nearly two-thirds of informed consent forms for these protocols did not disclose the known safety risk. Studies of these higher-risk medications were infrequent. However, because these studies lacked disclosure of the safety risk, they can neither have ensured true informed consent nor provided a full assessment of the risks and benefits of study participation. Bhattacharya et al should be applauded for publicly examining and reporting on this problem identified at their IRB, but there is no reason to think the problem is an isolated one. Risks and benefits of study medications are difficult to quantify. How have we done? There are few simple ways to measure effectiveness in this area, but Bhattacharya et al suggest one in this issue of JAMA Internal Medicine: what proportion of applicable informed consent forms disclose black box warnings issued by the US Food and Drug Administration (FDA) for study medications?

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Contemporary Nationwide Patterns of Active Surveillance Use for Prostate Cancer

In 2011, the US Preventative Services Task Force discouraged routine prostate cancer screening. Despite an initial decline in prostate-specific antigen (PSA) screening, clinical practice has not changed appreciably. Supporters of PSA screening argue that the potential risks of overdiagnosis are mitigated by active surveillance. Active surveillance—careful monitoring of prostate cancer with selective intervention based on apparent progression—is an option for localized low-risk prostate cancer. While no consensus on active surveillance eligibility exists, it is usually reserved for patients with low-risk disease. We sought to examine active surveillance use and its predictors in American men with low-risk prostate cancer using the National Cancer Data Base, a comprehensive facility-based cancer registry capturing 70% of incident cancer diagnoses in the United States.

Methods | We used 2010-2011 data from the US National Cancer Data Base, the most recent data available that was also unique for its inclusion of an active-surveillance-specific identifier. Institutional review board exemption was granted by University Hospitals Case Medical Center, where the data analysis was conducted. We identified men with biopsy-proven clinical N0/M0 prostate cancer during this period. Low-risk disease was defined by the following known criteria: (1) modified Epstein (clinical stage, ≤T1c; Gleason score, ≤6; PSA level, <10; and ≤2 [or ≤33%] positive biopsy cores); (2) D’Amico (clinical stage, ≤T2a; Gleason score, ≤6; PSA level, <10 ng/mL); and (3) Klotz (clinical stage, ≤T2a; Gleason score, ≤6; PSA level, <10 ng/mL) and ≤70 y). In men who met the modified Epstein criteria, we used multivariate logistic regression to determine the likelihood of undergoing active surveillance, accounting for diagnosis year, race, residential area, income, education, insurance, age, Charlson Comorbidity Index score, hospital type, prostate cancer volume, and geography. Statistical tests were conducted using SAS, version 9.1 (SAS Institute Inc). P <.01 was considered statistically significant.

Results | Of 189,768 patients with prostate cancer, 75,546 (39.8%), 54,070 (28.5%), and 20,377 (10.7%) were determined to be eligible for active surveillance by the Klotz, D’Amico, and modified Epstein criteria, respectively. In practice, 6.5%, 7.4%, and 12.1% of these men received active surveillance (Figure). Increasing age was most strongly associated with active surveillance use (60-64 y vs <50 y: OR, 1.87; 95% CI, 1.35-2.22; 65-69 y vs <50 y: OR, 2.38; 95% CI, 1.80-3.16; >70 y vs <50 y: OR, 3.83;
95% CI, 2.88-5.11). Being uninsured or treated in the Northeast also predicted its use (OR, 3.26; 95% CI, 2.33-4.54 and OR, 2.16; 95% CI, 1.90-2.46, respectively) (Figure 2). Additional positive predictors of active surveillance use included diagnosis in 2011 (OR, 1.45; 95% CI, 1.32-1.59) and treatment at an academic hospital (OR, 1.84; 95% CI, 1.44-2.35) or a hospital with a high volume of patients with prostate cancer (OR, 1.33; 95% CI, 1.16-1.54). Being healthy, African-American, or more educated were significantly but less strongly associated with its use (OR, 1.56; 95% CI, 1.33-1.82; OR, 1.23; 95% CI, 1.05-1.43 and OR, 1.32; 95% CI, 1.07-1.62, respectively).

**Discussion** | Only 12.1% of men (2466 of 20377) with very-low-risk prostate cancer received active surveillance. Expanding
on prior evidence that observation is used infrequently in men with low-risk disease, this study establishes that active surveillance use is low. Usage increases as the inclusion criteria for surveillance become more stringent, ie, less likely to miss significant disease. While active surveillance is aptly applied to elderly men, its use is sporadic, confined to academic and regional hospitals, and strongly influenced by nonclinical factors, including the patient’s insurance provider. Patient preference may influence use, especially in certain demographic groups. Despite ongoing adoption, use of active surveillance must increase substantially to effectively reduce the overtreatment of screening-detected prostate cancer.

This study has several limitations. Selection bias related to the National Cancer Data Base’s hospital-based data set may cause potential underrepresentation of active surveillance use in the outpatient setting. Because the data set is somewhat dated, it may not accurately reflect recent urological patterns. Nonetheless, this study represents, to our knowledge, the most up-to-date analysis of active surveillance trends, and its predictors, in a large nationally diverse cohort. Uniquely, our study is generalizable to men of all ages, including younger men who may benefit more in the long term with active surveillance. Last, the treatment-specific identifier that we used minimizes misclassification bias.

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Reporting of Limitations of Observational Research

Observational research is abundant and influences clinical practice, in part via publication in high-impact journals and dissemination by news media. However, it frequently generates unreliable findings.1 Inherent methodologic limitations that generate bias and confounding mean that causal inferences cannot reliably be drawn. Study limitations may be inadequately acknowledged and accompanied by disclaimers that diminish their importance.2 We assess the reporting of limitations of observational studies published in major internal medicine journals and associated news stories, specifically focusing on inference of causality.

Methods | Using MEDLINE, journal websites, Eurekalert!, and Factiva, we collated 81 prospective cohort and case-control studies with clinical outcomes published between January 1, 2013, and June 30, 2013, in the Annals of Internal Medicine, BMJ, JAMA, JAMA Internal Medicine, Lancet, New England Journal of Medicine, and PLoS Medicine; 48 accompanying editorials; 54 journal press releases; and 319 news stories generated within 2 months of publication. We analyzed the Abstract and Discussion sections of the source articles as separate documents. For each of the resulting 583 documents, we determined whether any study limitation was reported and whether there was an explicit statement that causality could not be inferred. If a causality limitation was reported, we determined whether it was accompanied by a disclaimer, defined as a statement that undermines or downplays the limitation. Data were extracted independently by 2 of us (M.T.M.W. and A.G.), and differences were resolved by consensus.

Results | Any study limitation was mentioned in 70 of 81 (86%) source article Discussion sections, 26 of 48 (54%) accompanying editorials, 13 of 54 (24%) journal press releases, 16 of 81 (20%) source article abstracts (of which 9 were published in the Annals of Internal Medicine), and 61 of 319 (19%) associated news stories. An explicit statement that causality could not be inferred was infrequently present: 8 of 81 (10%) source article Discussion sections, 7 of 48 (15%) editorials, 2 of 54 (4%) press releases, 3 of 81 (4%) source article abstracts, and 31 of 319 (10%) news stories contained such statements (Figure). Among the 51 source documents that included a causality limitation, 23 (45%) were accompanied by a disclaimer.

Of the 13 source articles that generated at least 1 news story containing a causality limitation, 8 (62%) contained the limitation in the Abstract or Discussion, editorial, or journal press release. In comparison, only 10 of 68 (15%) source articles that did not generate at least 1 news story with a causality limita-