

# Patient Adherence: A Blind Spot in Cost-Effectiveness Analyses?

Allison B. Rosen, MD, MPH, ScD; Alicen B. Spaulding, MPH; Dan Greenberg, PhD; Jennifer A. Palmer, MS; and Peter J. Neumann, ScD

**Background:** Despite evidence that medication adherence can influence cost-effectiveness analysis (CEA) results, the extent to which published CEAs include adherence has not been fully characterized.

**Objectives:** To characterize inclusion of patient adherence in CEAs of self-administered medications and to examine whether industry sponsorship affects adherence inclusion, because adherence exclusion might overstate the interventions' cost-effectiveness.

**Study Design:** Systematic review of the English-language medical literature published between 1998 and 2003 identified 177 original CEAs of self-administered medications.

**Methods:** Two trained readers independently abstracted data. Adherence inclusion was estimated overall and by study characteristics. Predictors of inclusion were assessed with  $\chi^2$  tests and logistic regression.

**Results:** Among 177 CEAs, 30.5% explicitly modeled adherence; of these, only half modeled adherence in both base-case and sensitivity analyses. Only 21% of studies performed sensitivity analysis on adherence; fewer than half of these provided sufficient information to determine the impact on results. Of the remaining 20 studies, 9 were sensitive to adherence. Adherence inclusion varied across clinical areas ( $P = .022$ ). Only 30% of chronic anticoagulation studies, 52% of cardiovascular risk reduction studies, 38% of neuropsychiatric studies, and 32% of HIV antiretroviral studies considered suboptimal adherence. Among 128 CEAs that disclosed study sponsorship, adherence was included in 25.4% of industry-sponsored and 35.1% of non-industry-sponsored studies ( $P = .17$ ).

**Conclusions:** Few CEAs modeled suboptimal medication adherence. As CEAs are meant to model "real world" costs and effects of interventions, investigators would do well to explicitly consider medication adherence in the future.

(*Am J Manag Care.* 2009;15(9):626-632)

For author information and disclosures, see end of text.

Medication adherence is perhaps the most important determinant of the therapeutic effectiveness of medications.<sup>1</sup> Yet suboptimal adherence remains pervasive in the US healthcare system, resulting in substantial adverse health and economic effects.<sup>2,3</sup> Overall, rates of nonadherence are high—fewer than 50% of patients with chronic diseases take their medications as prescribed.<sup>4</sup> In turn, poor adherence is associated with disease progression, complications, avoidable hospitalizations, and death,<sup>1,2,5-7</sup> as well as increased medical costs for some chronic diseases.<sup>6,8,9</sup> Indeed, it has been estimated that suboptimal adherence is responsible for an estimated \$177 billion in total direct and indirect health spending annually in the United States.<sup>1</sup>

Given the substantial impact of adherence on health and spending, inclusion of adherence in economic evaluations may be critical for informing policymakers about the value of therapies in actual practice. Indeed, past studies have shown that adherence can influence the results and recommendations of cost-effectiveness analyses (CEAs).<sup>10-12</sup> Despite the importance of adherence, however, the extent to which published CEAs consider it has not been fully characterized. Our objective was to examine the inclusion of patient adherence in CEAs of self-administered medications. Because the exclusion of adherence might overstate the cost-effectiveness of evaluated interventions, we also examined the relationship between pharmaceutical company sponsorship and inclusion of adherence.

## METHODS

Cost-effectiveness analyses compare alternative approaches to a health problem to determine the relative costs and benefits of each. Cost-utility analyses, the subset of CEAs with health benefits measured in quality-adjusted life-years (QALYs), represent the gold standard for conducting and reporting of CEAs in medicine.<sup>13</sup> For the remainder of this article, we use CEA to refer to cost/QALY studies.

### Development of CEA Registry

We previously reported on the development of a comprehensive registry of CEAs published in the public health and medical literature from

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1976 through 1997.<sup>14-16</sup> The Tufts cost-effectiveness analysis registry is continuously updated and maintained on the Internet as a free, public use resource (<http://www.cearegistry.org>). As part of the updates to this registry, we conducted a systematic review of the English-language medical literature published between 1998 and 2003. We searched MEDLINE for the following medical subject headings and text keywords: “quality-adjusted,” “quality-adjusted life year(s),” “QALY,” “adjusted life year(s),” “cost-utility,” and several variations of these terms. To identify potentially overlooked studies, our search findings were validated to those of the Health Economic Evaluation Database maintained by the British Office of Health Economics.<sup>17</sup> Our search identified 2528 candidate articles published between 1998 and 2003. We then screened titles and abstracts to remove noneligible articles, such as methodologic and review articles, and studies that did not use cost/QALY as their main outcome measure. A final list of 568 published cost-utility analyses were included in the registry for the years 1998 through 2003.

### Study Selection and Data Abstraction

Of the 568 cost-utility analyses, 226 had a medication component in the intervention or comparator. To restrict analyses to studies in which patient adherence was applicable, we excluded studies in which medications were administered by injection or infusion ( $n = 27$ ), in an acute-care setting ( $n = 14$ ), or by someone else (often the physician) for other reasons ( $n = 8$ ). The final sample included 177 CEAs of self-administered medications (available at <https://research.tufts-nemc.org/cear/related/ajmccappendix.pdf>). Each article was reviewed by 2 independent readers, who abstracted select data elements from each article; consensus meetings were held to review and resolve discrepancies. We collected data on a wide variety of elements related to the methods, results, and quality of reporting in the article, along with data on study inclusion of adherence to therapies. In addition, we abstracted data on the source of funding for each study (when reported).

### Definitions

**Adherence.** Readers recorded whether medication adherence was (1) included in the base-case analysis only, (2) included in sensitivity analyses only, (3) included in both the base-case and sensitivity analyses, (4) mentioned in the manuscript but not included in analyses, or (5) not mentioned. If the results of sensitivity analyses on adherence were reported in the text, tables, figures, or an appendix, they were considered “sufficient” to judge the impact of adherence. Of studies

### Take-Away Points

Suboptimal medication adherence remains pervasive in the US healthcare system, resulting in substantial adverse health and economic effects. Despite a growing body of evidence that adherence can influence cost-effectiveness analyses (CEAs), the extent to which published CEAs include adherence has not been fully characterized.

- Fewer than one-third of published CEAs modeled suboptimal adherence.
- In the small subset of studies that varied adherence in sensitivity analyses, the impact on cost-effectiveness often was substantial.
- With payers and policymakers increasingly turning to these studies for guidance, failure to account for nonadherence may lead to suboptimal resource allocation strategies.

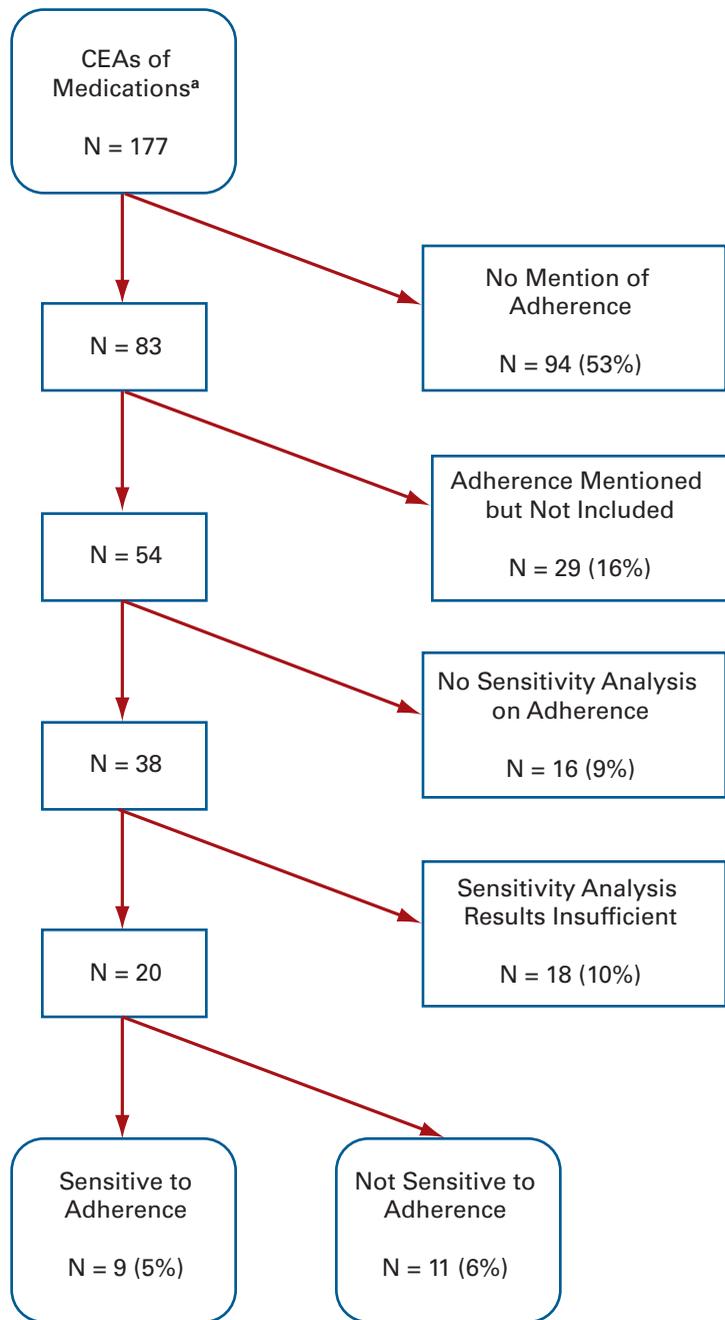
with sufficient data, we report whether the authors describe the results as sensitive to adherence. In practice, adherence has many different definitions, measurement approaches, and even names (eg, compliance, persistence).<sup>2</sup> For the purposes of this analysis, we included any form of adherence regardless of whether or how it was defined.

**Additional Covariates.** Readers abstracted data from each study on the expected duration of intervention therapy, study sponsorship, and the clinical condition of interest. Intervention medications were classified as short term if therapy duration was expected to be less than 1 month. Study sponsorship was categorized as unknown if no funding source was listed, industry-sponsored if at least 1 funding source or 1 author’s affiliation was a pharmaceutical or medical device company, and non-industry-sponsored if all funding came from governments, foundations, or other nonindustry sources. Study settings included the United States, the United Kingdom, Canada, and an “other country” category that included any country that served as the CEA setting in 10 or fewer studies. Studies were grouped into the following clinical categories: cardiovascular risk factors and disease (CVD), cancers, HIV and AIDS, other infectious diseases, hepatitis, other gastrointestinal conditions, musculoskeletal conditions (including osteoporosis), neurologic conditions, psychiatric conditions, pulmonary diseases, and an “other disease” category that included any clinical conditions examined in fewer than 5 CEAs. Additionally, a separate anticoagulation category was included because of the large number of CEAs published in this area. To assess whether the inclusion of adherence in CEAs has improved over time, we also created a variable indicating whether the study was published earlier (1998-2000) or later (2001-2003) in the 6-year study window.

### Statistical Analyses

We examined the frequency with which adherence was included in CEAs, as well as the extent to which it was included. The kappa interrater reliability score for adherence inclusion was 0.84, representing strong agreement between reviewers.<sup>18</sup> Associations between adherence inclusion and

■ **Figure 1.** Flow Chart of Adherence Inclusion in Cost-Effectiveness Analyses of Self-Administered Medications



CEAs indicates cost-effectiveness analyses.

<sup>a</sup>CEAs of medications refer to the 177 published cost-utility analyses of self-administered medications available at <https://research.tufts-nemc.org/cear/related/ajmccappendix.pdf>.

duration of therapy, study sponsorship, publication window, study setting (country), and disease categories were assessed with  $\chi^2$  tests. Logistic regression was performed with inclusion of adherence in either the base-case or sensitivity analyses as the dependent variable, and therapy duration, study

sponsorship, publication window, and disease category as independent variables. Analyses were conducted using SAS version 9.1 (SAS Institute, Inc, Cary, NC).

## RESULTS

Among the 177 CEAs of self-administered medications, only 30.5% ( $n = 54$ ) explicitly modeled patient adherence to therapy, whereas an additional 16.4% mentioned but did not model medication adherence (Figure 1). Of the 54 studies that did model adherence, only half (14.7% of all studies, or 26 studies) modeled adherence in both the base-case and sensitivity analyses. In those studies that included adherence in the base case, the most common base-case assumption was that medication nonadherence and/or discontinuation rates were the same as those rates reported in clinical trials. Adherence was equally likely to be considered in CEAs of long-term versus short-term drug therapy (29.6% vs 30.3%; not significant).

Study inclusion of adherence varied significantly across clinical areas ( $P = .022$ ). Only 30% of chronic anticoagulation studies, 52% of cardiovascular risk reduction studies, 38% of neuropsychiatric studies, and 32% of HIV antiretroviral studies included suboptimal adherence in either the base-case or sensitivity analyses. Figure 2 shows the extent to which adherence inclusion varied across clinical areas.

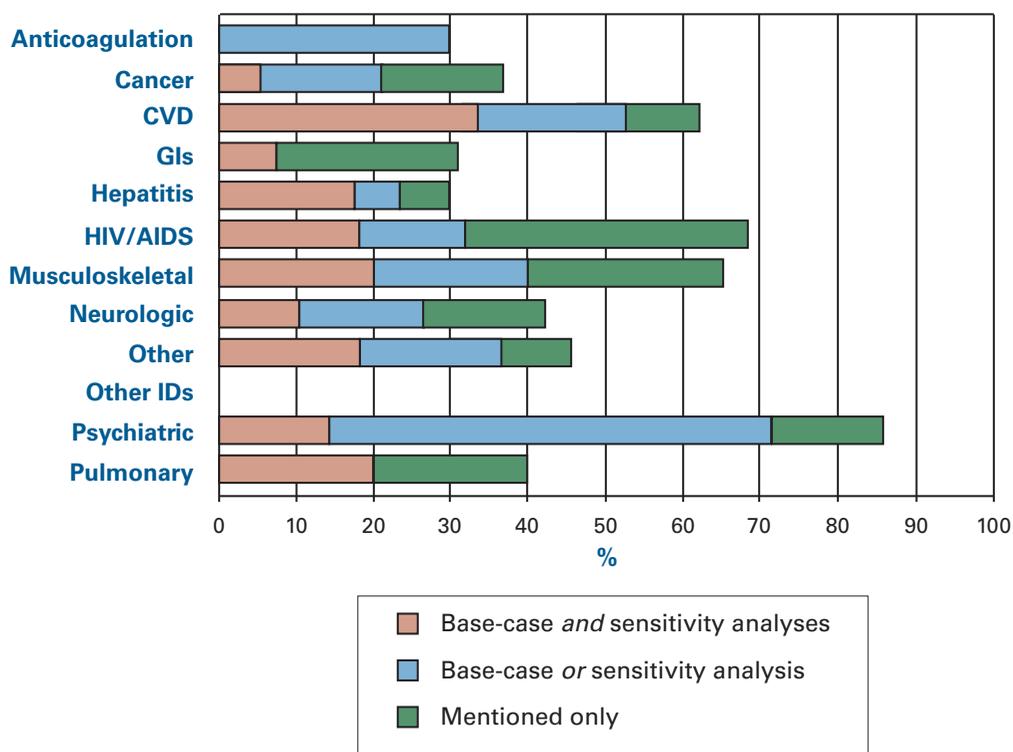
Eighty-four CEAs were set in the United States, 23 in the United Kingdom, 19 in Canada, and 10 or fewer in all other countries. In 35% of studies set in the United States, 30% of those set in the United Kingdom, 32% in Canada, and 25% of studies set in other countries, adherence was included in either the base-case or sensitivity analyses (differences were nonsignificant).

Study sponsorship came from industry in 40.1% ( $n = 71$ ) of CEAs, from sources other than industry in 32.2% ( $n = 57$ ), and could not be determined in the remaining 27.8% ( $n = 49$ ) of studies. Among the 128 CEAs for which study sponsorship was disclosed, 25.4% of industry-sponsored studies and 35.1% of non-industry-sponsored studies incorporated adherence into their models ( $P = .17$ ). There was no

change over time in the inclusion of adherence (31% for both time periods) in CEAs, and no significant difference over time in whether industry-sponsored versus non-industry-sponsored studies included adherence.

Among the 38 CEAs that performed sensitivity analysis on adherence, nearly half (47%, n = 18 studies) did not provide sufficient information in the study methods or results for reviewers to determine whether varying adherence had a significant impact on the cost-effectiveness ratios. Among the 20 remaining CEAs, 45% (n = 9) were reported as sensitive to changes in adherence, whereas 55% (n = 11) were not.

■ **Figure 2.** Adherence Inclusion in CEAs by Clinical Area<sup>a</sup>



CEAs indicates cost-effectiveness analyses; CVD, cardiovascular disease and cardiovascular disease risk factors; GIs, gastrointestinal conditions; IDs, infectious diseases.

<sup>a</sup>The bars denote the percentage of CEAs in a given clinical area that included adherence, as well as the extent to which it was included: in both the base-case and sensitivity analyses, in either the base-case or sensitivity analyses, or mentioned in the text but not modeled. The right-most portion of each clinical area (with no bar) represents the percentage of CEAs within that clinical area that neither modeled nor mentioned adherence in the text. For example, there is no bar corresponding to the “other IDs” clinical category because none of these studies mentioned or modeled adherence.

## DISCUSSION

Despite the potential importance of medication adherence, few CEAs incorporate it into analyses, although the level of incorporation varies substantially across clinical areas. Of the small subset of CEAs that varied adherence in sensitivity analyses, half provided insufficient information for the reader to clearly discern whether or how adherence impacted the cost-effectiveness ratios, and close to half of the remainder reported that results were sensitive to adherence. Although industry-sponsored studies included adherence less frequently than did non-industry-sponsored studies, this finding was not statistically significant, perhaps because of small sample sizes.

Although prior studies have indicated the important impact suboptimal adherence may have on cost-effectiveness,<sup>10-12</sup> this is the first study to our knowledge to document the extent to which adherence is actually included in published CEAs. The low rate of adherence inclusion was surprising given the substantial health and economic impact of medication non-

adherence in practice. Further, even when studies performed sensitivity analysis on adherence, insufficient reporting of the methods and/or results precluded determination of the true sensitivity of the results to medication adherence.

Among the CEAs that did model adherence, their assumptions about the level of adherence were frequently not consistent with the published literature. Many studies, for example, used adherence rates from clinical trials, which notoriously overestimate adherence found in the general population. Still others modeled adherence levels that were higher than those reported in the literature. For example, a study by Marchetti and colleagues reported that screening for factor V Leiden followed by 2 years of anticoagulation therapy was cost-effective compared with standard 6-month therapy for individuals diagnosed with first deep venous thrombosis.<sup>19</sup> However, the base-case results (\$12,833/QALY) supporting this conclusion relied on an assumption of 100% warfarin adherence, and sensitivity analyses (which varied adherence from 85% to 100%) indicated that this strategy only remained cost-effective (de-

defined as a ratio below \$50,000 per QALY) as long as warfarin adherence remained above 94%.<sup>19</sup> However, the literature suggests that warfarin adherence in practice falls far below that threshold; in a recent warfarin adherence study, patients were nonadherent (ie, took fewer than 80% of prescribed doses) 36% of the time.<sup>20</sup>

Our findings were consistent with those of Hughes and colleagues,<sup>11,12</sup> which suggested that the impact of suboptimal adherence on the cost-effectiveness of medications can be substantial. Indeed, several of the CEAs reviewed for this study confirmed the critical impact of adherence on medications' cost-effectiveness or lack thereof. A study by Mar and Rodriguez-Artalejo demonstrated large variations in the cost-effectiveness of hypertension treatment by patient age, sex, hypertension stage, and drug class used; however, treatment adherence had by far the biggest impact on health benefits and, in turn, cost-effectiveness.<sup>10</sup> Phillips and colleagues demonstrated that increasing beta-blocker use after myocardial infarction would lead to impressive health gains and potential cost savings.<sup>21</sup> Clark and colleagues demonstrated that Canadian provincial coverage of angiotensin-converting enzyme inhibitors for patients with type 1 diabetes with nephropathy could be highly cost-effective but this cost-effectiveness hinged critically on adherence; indeed, the cost-effectiveness ranged from a savings of \$899 to expenditures of more than \$1 million per QALY with adherence rates of 67% and 51%, respectively.<sup>22</sup>

Recognizing the importance of patient adherence for the value of medical spending, a number of private payers have begun to overhaul their prescription drug benefit designs. Rather than setting enrollees' cost-sharing levels based on the cost of the drugs, these payers have linked copayments to the value (ie, cost-effectiveness) of each therapy. These so-called value-based insurance designs<sup>23</sup> are premised on the fact that cost-sharing should neither inhibit access nor discourage adherence to high-value medications. Although these experiments are generally too recent to be fully evaluated, a number of studies that model copayment changes (and the subsequent increase in adherence) have generated a number of important findings. A recent study by Rosen and colleagues, for example, found that Medicare first-dollar coverage of angiotensin-converting enzyme inhibitors for beneficiaries with diabetes appeared to both extend life and reduce Medicare program costs. The long-term health and economic benefits to Medicare far surpassed the initial increase in medication spending because of improved patient adherence.<sup>24</sup> A subsequent study by Choudhry and colleagues suggested that a typical insurer could prevent heart attacks, saving lives and money, if the insurer paid the full costs of secondary prevention medications after myocardial infarction.<sup>25</sup> A clear un-

derstanding of the way in which adherence moderates the cost-effectiveness of therapies (and the way in which cost-sharing affects adherence) is critical to efficient targeting of these incentive programs. Including adherence information in CEAs will considerably help with this first aim.

Because adherence can play such an important role in CEAs, why is it not addressed more often in these studies? One possibility is the historical backdrop for CEAs. They first started appearing in the medical literature in the early 1970s, which was a time when the magnitude and import of suboptimal adherence to therapy were not as well recognized or characterized as they are today. In turn, the most widely cited standards for performing and reporting CEAs, those developed by the Panel on Cost-Effectiveness in Health and Medicine in 1996,<sup>13</sup> do not explicitly recommend modeling suboptimal adherence in CEAs, potentially allowing journal editors, reviewers, and authors to implicitly overlook adherence. This problem is compounded by the absence of standard definitions of and measurement standards for adherence. Recently, Hughes and colleagues at the International Society for Pharmacoeconomics and Outcomes Research published a set of proposed standards for incorporating adherence into economic evaluations,<sup>26</sup> but it is too early to assess the impact of these recommendations on actual practice. Another possible reason for the poor inclusion of adherence in CEAs is the source of data. Although CEAs often are used to inform real-world practice, their estimates of effect most often come from clinical trials, which demonstrate efficacy rather than effectiveness. The recent COURAGE trial provides a perfect example of just how different these constructs can be. Of participants enrolled in COURAGE (individuals with stable coronary artery disease), more than 90% (in both arms) remained on beta-blockers, statins, and aspirin at 5 years.<sup>27</sup> By contrast, in the real world, 50% of individuals with coronary artery disease stop these therapies by 2 years.<sup>28</sup>

Our study had several limitations. First, we only examined CEAs that reported outcomes in cost/QALY; therefore, our findings may not fully represent the handling of adherence by the broader universe of cost-effectiveness studies. Second, we may have overestimated the number of studies that included adherence by very liberally defining inclusion of adherence. For example, if a study explicitly stated that it addressed adherence by using intention-to-treat estimates from a clinical trial, it was considered to include adherence. On the other hand, if researchers used clinical trial estimates of effect but did not mention or discuss adherence anywhere in the paper, the study was considered not to include adherence. Third, because this analysis was restricted to self-administered medications, the inclusion of adherence in nonpharmaceutical CEAs remains to be investigated.

Finally, it is important to recognize that traditional sensitivity analyses of adherence may not be the only or even the most appropriate way to consider the relationship between adherence and cost-effectiveness. Sensitivity analyses can capture how uncertainty about adherence impacts uncertainty in the incremental cost-effectiveness ratio. However, even if adherence were known for certain, it is a modifiable parameter. Interventions (eg, reducing copayments, providing medication counseling) can increase adherence through the investment of additional resources. As such, sensitivity analyses may be far more informative if CEAs include both adherence and the relationship between additional spending and changes in adherence.

## CONCLUSION

This study demonstrates how infrequently medication adherence is addressed in published CEAs. As national efforts to contain rising healthcare costs via increased consumer cost-sharing move forward, a profound impact on medication adherence is likely.<sup>29</sup> Because adherence can so markedly impact cost-effectiveness, it has become more important than ever to adequately address suboptimal adherence in CEAs. With payers and policymakers increasingly turning to these studies for guidance, failure to account for nonadherence may lead to suboptimal resource allocation strategies, worsening the value of healthcare spending in a system that is already plagued with inefficiencies.

### Acknowledgments

The authors would like to thank Patricia Stone, PhD, for thoughtful comments on project conceptualization, and Susan Goold, MD, and Justin Timbie, PhD, for thoughtful comments on an earlier version of this manuscript.

**Author Affiliations:** From the Departments of Internal Medicine and Health Management and Policy (ABR), University of Michigan, Ann Arbor, MI; the Division of Epidemiology and Community Health (ABS), University of Minnesota, Minneapolis, MN; the Department of Health Systems Management (DG), Ben Gurion University of the Negev, Beer-Sheva, Israel; and the Center for the Evaluation of Value and Risk in Health (JAP, PJN), Tufts Medical Center, Boston, MA.

**Funding Source:** This study was funded by National Library of Medicine grant 1G08LM008413-02. Dr Rosen was supported by National Institutes of Health grant K12RR17607.

**Author Disclosures:** The authors (ABR, ABS, DG, JAP, PJN) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article. Dr Rosen had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analyses.

**Authorship Information:** Concept and design (ABR, ABS, DG, PJN); acquisition of data (ABR, ABS, DG, JAP, PJN); analysis and interpretation of data (ABR, ABS, DG, PJN); drafting of the manuscript (ABR, ABS, DG); critical revision of the manuscript for important intellectual content (ABR, ABS, DG, JAP, PJN); statistical analysis (ABR); provision of study materials or patients (JAP); obtaining funding (ABR); and administrative, technical, or logistic support (ABS).

**Address correspondence to:** Allison B. Rosen, MD, MPH, ScD, Departments of Internal Medicine and Health Management and Policy, University of Michigan, 300 N Ingalls, Ste 7E10, Ann Arbor, MI 48109. E-mail: abrosen@umich.edu.

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## ■ METHODS ■

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