

COMMENTS AND RESPONSES

Inhaled Long-Acting β -Agonists Versus Anticholinergics in Older Patients With Chronic Obstructive Pulmonary Disease

TO THE EDITOR: Gershon and colleagues (1) describe an increase in death and hospitalizations in patients aged 66 years or older with chronic obstructive pulmonary disease (COPD) who fill a first prescription for the long-acting anticholinergic tiotropium bromide compared with patients who do so for a long-acting β -agonist. These results were based on information from health administrative databases in Ontario, Canada, and contrast with the authors' previous findings (2).

Gershon and colleagues acknowledge the inherent limitations of this retrospective database analysis and conclude that "[f]urther research is needed to confirm these findings . . . in a randomized, controlled trial." We would like to note that this suggested "further research" has already been performed and published in the POET-COPD (Prevention of Exacerbations with Tiotropium in COPD) study (3), a randomized, controlled, double-blind trial that directly compared tiotropium bromide with the long-acting β -agonist salmeterol for 1 year.

The POET-COPD study is the largest head-to-head comparison of these 2 therapeutic regimens and comprised approximately 7400 patients with COPD. This study showed that tiotropium bromide was statistically significantly more effective than salmeterol in reducing exacerbations of COPD. In addition, the incidence of serious adverse events and adverse events leading to the discontinuation of treatment was similar in the 2 treatment groups; furthermore, outcomes were consistent across participants according to age, severity of COPD, and concomitant medication use.

Specifically, all-cause mortality (vital status follow-up to day 360 was 99.1% complete) was not statistically significantly different between the tiotropium bromide (64 deaths [1.7%]) and salmeterol (78 deaths [2.1%]) groups. This finding was independent of subgroup according to age and included patients older than 65 years. In a prespecified subgroup analysis, the hazard ratio (HR) for all-cause mortality was numerically in favor of tiotropium bromide (HR, 0.84 [95% CI, 0.47 to 1.51] for patients between 65 and 75 years) compared with salmeterol (HR, 0.78 [CI, 0.39 to 1.59] for patients aged 75 years or older) (4). This study is another example illustrating that associations observed in retrospective cohort studies are not necessarily confirmed in randomized, controlled trials, which remain the gold standard for proving causality (5).

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Potential Conflicts of Interest: Dr. Fabbri has received consultancy fees from Actelion, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Elevation Pharmaceuticals, Merck Sharp & Dohme, Novartis, Nycomed, Pearl Therapeutics, Roche, and Sigma-Tau and payment for lectures and support for travel expenses from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, EUROMEDIFORM, GlaxoSmithKline, German Centre for Lung Research, Merck Sharp & Dohme, Menarini, Mundipharma International, Novartis, Nycomed, TEVA Pharmaceuticals, Pfizer, and Sigma-Tau. His institution has received grants from Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Italian Ministry of Health, Italian Ministry for University and Research, Merck Sharp & Dohme, Nycomed, and Sigma-Tau. Dr. Vogelmeier has received consulting fees or honoraria and support for travel to meetings from Boehringer Ingelheim; is a board member for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mundipharma, Novartis, and Nycomed; and has received fees for expert testimony and grants from Talecris and payment for lectures or speaking from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Novartis, Nycomed, and Talecris. Dr. Rabe has received consultancy fees and honoraria from, and is a board member for, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Nycomed, and Pfizer and has received grants from Altana, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Roche.

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IN RESPONSE: We thank Dr. Fabbri and colleagues for their comments and congratulate them on successfully conducting the POET-COPD study (1), which was published when our paper was in press. The POET-COPD study adds valuable new evidence to our understanding of the comparative efficacy of long-acting bronchodilators in patients with COPD. However, it is important to recognize that its findings do not necessarily contradict those of our paper because of key differences between the 2 studies—most notably differences in study population, design, and outcomes.

The most salient difference is in study populations. The POET-COPD study, like virtually all such randomized trials about COPD but unlike our study, excluded patients with congestive heart failure, arrhythmias, and recent myocardial infarction (1), who may be the very persons most at risk for adverse events. Also, although our study observed patients from the time of their first use of a long-acting bronchodilator, most patients in the POET-COPD study were already receiving a long-acting bronchodilator at baseline. Because this group tolerated their regimen and volunteered to continue receiving

it in a study, they were more likely to have favorable outcomes. A treatment-naïve subgroup of patients in the POET-COPD study was reported to be similar to the overall cohort with respect to exacerbations, but mortality in this subgroup was not reported (1).

A second difference is that participants in the POET-COPD study who were randomly assigned to receive tiotropium bromide were precluded from adding or switching to long-acting β -agonist therapy, and vice versa (1), whereas our study involved no such restriction. In real-life practice, such switches and additions of drug therapy happen routinely in keeping with the recommendations of current COPD guidelines (2). Therefore, although the findings of the POET-COPD study may apply to specific clinical situations, our study is probably more representative of what usually happens in actual clinical practice.

Finally, mortality was the primary outcome in our study, whereas exacerbations of COPD were the primary outcome in the POET-COPD study. The POET-COPD study was not adequately powered to find small differences in mortality because it comprised 7376 patients in contrast to the 46 403 patients included in our study.

We agree with Dr. Fabbri and colleagues that a randomized trial provides the highest level of evidence for causal associations, but observational research often plays an essential role in identifying unintended consequences of therapy that in actual practice may differ from findings observed in the idealized context of a randomized trial (3). We remain concerned that, in current clinical practice, the choice of initial long-acting bronchodilator therapy may lead to different outcomes, including death. The POET-COPD study does not fully allay these concerns for the reasons described earlier.

We think that to confirm or refute our findings would instead require a pragmatic randomized trial in which patients were assigned to either class of long-acting bronchodilator (and would ideally also include a group assigned to both agents) and allowed to add or switch to other drug therapies without restriction. However, we anticipate that such a trial would be very large and expensive, which would present substantial barriers to feasibility.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-1643.

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An Update on the Comparative Effectiveness and Safety of Medications for Type 2 Diabetes

TO THE EDITOR: We concur with the recent article by Bennett and colleagues (1) that metformin should be the preferred first-line therapy for type 2 diabetes. However, important safety issues regarding dipeptidyl peptidase-4 (DPP-4) inhibitors have recently emerged (2), bolstering disturbing signals raised several years ago in premarket studies with these agents. It is therefore disconcerting that the American Association of Clinical Endocrinologists and the American College of Endocrinology recommend treatment with a DPP-4 inhibitor as an option for initial monotherapy of type 2 diabetes (1).

Examination of the U.S. Food and Drug Administration (FDA) database of reported adverse events for the DPP-4 inhibitor sitagliptin from 2004 to 2009 revealed a nearly 3-fold increase in pancreatic cancer (odds ratio, 2.72; $P = 0.008$) among patients receiving sitagliptin compared with other therapies (2). Other types of cancer were not associated with sitagliptin, but these cancers may have been underreported in the voluntary reporting system, unlike pancreatic cancer, which would be reported because of the pancreas's involvement in the pathogenesis of diabetes.

It is noteworthy that DPP-4 has many functions beyond regulating glucose homeostasis, including modulating cellular growth and differentiating and stimulating immune function; therefore, it is not surprising that experimental evidence has shown that DPP-4 down-regulation is related to increased metastatic potential of melanoma and prostate and colon cancer (3). Furthermore, DPP-4 inhibition increases pancreatic ductal cell turnover and metaplasia, which are risk factors for pancreatic cancer (3).

Premarket studies of sitagliptin were done on relatively few persons and were short-term—typically 6 months (4, 5). Although statistically nonsignificant, data submitted to the FDA revealed a numerical increase in risk for cancer among individuals exposed to sitagliptin compared with those who were not exposed (4). Patients receiving higher doses of sitagliptin had about a 1% annualized absolute increase in overall cancer risk. Data submitted to the European Medicines Agency also demonstrated a statistically nonsignificant 1% annualized absolute increase in risk for cancer among the sitagliptin-exposed persons (5).

Sitagliptin and newer DPP-4 inhibitors have become popular agents for the treatment of type 2 diabetes. The premarket studies of these increasingly used and heavily advertised drugs have been inadequate in size and duration to rule out a cancer risk when taken long-term. Physicians therefore need to be extra vigilant in reporting to appropriate agencies any new cancer or unusually rapid cancer promotion among their patients taking these drugs.

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Potential Conflicts of Interest: None disclosed.

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IN RESPONSE: We appreciate Drs. Goldstein and Mascitelli's letter. We acknowledge growing concerns about the association of diabetes medications and cancer risk (1), and we therefore evaluated cancer as an outcome in our report (2). As Drs. Goldstein and Mascitelli point out, DPP-4 inhibitors have been linked with reports of pancreatic cancer in the FDA's database of reported adverse events (3). Because Elashoff and colleagues examined spontaneous reports to the FDA, they lacked data on the number of patients exposed to DPP-4 inhibitors and could not report on the rate of this outcome (3).

Our study included 4 trials and 1 observational study that reported cancer outcomes, and the results were inconclusive (2). Two of these studies included comparisons with the DPP-4 inhibitor sitagliptin. The first was a 26-week, open-label, randomized, controlled trial that reported 1 case of cancer in the combination liraglutide and metformin group ($n = 221$) and 1 case in the combination sitagliptin and metformin group ($n = 219$) (4).

The second study was a 30-week trial with 190 patients randomly assigned to sitagliptin therapy or placebo in addition to metformin therapy (5). Three cases of cancer were reported in the group receiving metformin alone, whereas no cases were reported in the group receiving metformin and sitagliptin (5).

Our report was limited in its assessment of cancer as an outcome because of the paucity of long-duration trials. Well-designed observational studies are needed to assess the association between diabetes medications and cancer. We note that the FDA's Sentinel Initiative is under development as a national electronic drug-safety tracking system that is expected to improve postmarketing active surveillance and will allow the querying of large databases for rapid investigation of safety concerns, such as this (6).

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The Potential for Increasing Quality and Reducing Costs

TO THE EDITOR: I read the recently published simulation study by Eddy and colleagues (1) with great interest. In the simulation, hypertension treatment based on individualized guidelines powered by the authors' proprietary computer model reduced myocardial infarctions (MIs), strokes, and the cost of care when compared with treatment based on a traditional guideline—the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The reductions in MI and stroke resulting from the model were particularly impressive. The effects were on par with pharmaceuticals we traditionally use to treat hypertension and cardiovascular risk, but I was surprised that the authors described their potential conflicts of interest at the end of the study as “none.”

I reviewed the company's Web site, and the authors' computer model seems to be a product marketed to clients worldwide, including health care systems, industry professionals, and foundations (2). Much like I would expect a pharmaceutical company publishing on the effectiveness of a drug it manufactures to disclose potential conflicts of interest, I would expect a company publishing on the effectiveness of a decision-support tool it developed to be held to the same standard. It is unclear whether this was a simple oversight or if it represents a more pervasive issue in published literature examining the effects of computer programs on health care, where potential conflicts may not be as easily recognized or identified as traditional pharmaceutical industry conflicts. In this new era of comparative effectiveness research, where drugs are compared alongside other treatment methods, including surgical procedures, medical devices, behavioral interventions, and computerized clinical decision-support systems, it's important that we as authors, reviewers, and editors be mindful about disclosing such potential conflicts (3).

In addition, with increasing investments in health information technology fueled by the HITECH (Health Information Technology

for Economic and Clinical Health) Act and “meaningful use” (4), we’re likely to see even more studies examining the effect of computerized decision-support programs by those who have created them—ranging from simple evidence-based information resources to complex differential diagnosis generators. Disclosing potential conflicts of interest alongside a published study can help readers fully appraise the study’s validity and apply the results to patient care. As journals consider methods to standardize the reporting of potential conflicts by authors, particular attention should be paid to disclosures around the study of less traditional interventions, such as computerized decision-support systems (5).

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Potential Conflicts of Interest: Dr. Umscheid collaborates with multiple organizations on the development of traditional clinical practice guidelines.

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TO THE EDITOR: The recent article by Eddy and colleagues (1) proposes to guide treatment on the basis of the individual’s underlying risk for the primary outcome. Identifying individuals who will derive more benefit than harm from treatment is the primary goal of evidence-based medicine. Medicare spends a fortune each year on procedures whose benefits for the recipient are highly questionable (2). One fifth of all implantable cardiac defibrillators are placed in patients who will not clearly benefit from them (3). Therefore, we welcome the authors’ proposal, which is sensible and has face validity. There is a fundamental problem, however: How accurately can we determine an individual’s underlying risk for the primary outcome?

Risk prediction models tend to generalize poorly. A main reason for this is that the risk for an outcome is typically governed by numerous risk factors, each of which contributes only a small amount to the overall risk. Typically, only a small proportion of the overall variation in survival can be explained, even with inclusion of several risk factors. Furthermore, the risk models are sensitive to the joint distribution of risk factors in the sample in which the models are developed, hence, they tend not to predict well when applied to a population with a different multivariate distribution of risk factors. If we can identify a few blockbuster risk factors, we can hope to develop more generalizable prediction models, but this is seldom the case in primary prevention.

Eddy and colleagues seem to have sidestepped this problem by using the same ARIC (Atherosclerosis Risk in Communities) Study

sample to estimate the risk for MI and stroke and to evaluate the effect of allocating treatment on the basis of the estimated risk. This strategy does not test the generalizability of their risk calculator. It is no surprise then that their risk-based treatment-allocation strategy convincingly beats the externally derived guideline-based strategy. By not using an external risk calculator, which is what a clinician would have access to in routine practice, the authors portray an overly optimistic picture of the risk-based strategy. A more relevant test of their strategy would be to allocate treatment on the basis of an external risk calculator and then compare it with guideline-based allocation.

Although we welcome Eddy and colleagues’ proposal to guide treatment allocation on the basis of underlying risk for the primary outcome, our enthusiasm is tempered by the fundamental challenge of obtaining accurate risk estimates in clinical settings.

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Potential Conflicts of Interest: None disclosed.

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IN RESPONSE: We share Dr. Umscheid’s concerns about conflicts of interest and took several steps to avoid them. As described in the article, we created a relatively simple cardiovascular risk calculator specifically for this analysis, to transparently illustrate the concept of individualized guidelines—not to promote a particular model. We also stressed that our general conclusions do not depend on any particular model. We are developing methods for more accurately calculating the benefits that individuals can expect from various treatments, and for implementing individualized guidelines in practice settings. However, none of the concepts or methods in the paper is proprietary.

We agree with Drs. Varadhan and colleagues that the success of individualized guidelines depends on the development of externally valid risk models. However, we disagree that this constitutes a “fundamental problem,” implying that it is not possible to develop such models.

Creation of risk models does not require a “blockbuster” risk factor. Risk models can include as many risk factors as desired and for which there is good evidence. Because the risk calculator we used in this analysis was purposefully kept simple (Cox proportional hazard) and included only a small number of factors, it underestimates what can be achieved with models that include more variables and are physiologically more realistic. Even this simple model was validated not only against data from the ARIC Study but data from

those of 3 other sources—none of which was used to build the model.

The external validity of our results can be further tested by using Framingham tables to rank the portion of the ARIC Study population to which the tables can be applied. For that subpopulation, the study produced a “relative benefit ratio” only slightly lower than that of the cardiovascular risk calculator (1.38 and 1.43, respectively). The weakness of the Framingham tables is not their accuracy but their narrow span. No matter which risk model is initially used, when individualized guidelines are actually implemented, their accuracy in any particular setting can be continuously improved by tracking actual outcomes over time and gradually tuning the model to the setting.

We want to emphasize that to be superior to traditional guidelines, risk models do not have to be perfectly accurate—they only need to rank individuals more accurately than traditional guidelines, which sort people into 2 groups: “treat” and “don’t treat.”

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Potential Conflicts of Interest: None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-0352.

Measuring Blood Pressure for Decision Making and Quality Reporting

TO THE EDITOR: I read with great interest the article by Powers and colleagues (1). I agreed with most of the article, but I wondered why the authors did not discuss the proper technique of taking blood pressure. Maybe what I was taught is out of date, but is not the position of the arm, the level of the arm in relation to the heart, and the size of the cuff important to obtaining an accurate reading?

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Potential Conflicts of Interest: None disclosed.

Reference

1. Powers BJ, Olsen MK, Smith VA, Woolson RF, Bosworth HB, Oddone EZ. Measuring blood pressure for decision making and quality reporting: where and how many measures? *Ann Intern Med.* 2011;154:781-8, W-289-90. [PMID: 21690592]

TO THE EDITOR: The article by Powers and coworkers (1) is not only clinically important, it is directly relevant to the ongoing evolution of the health care system. Hypertension is the most common cardiovascular disease in the United States and is often the initial insult on the road to coronary artery disease and heart failure (2). As such, it is not surprising that blood pressure is a common quality measure used by the National Committee for Quality Assurance, the Centers for Medicare & Medicaid Services, and various insurers (3).

As the country moves to public reporting for outcomes and physicians and systems begin organizing into accountable care organizations with a focus on quality, it is important that quality indicators, such as blood pressure, be based on science. In the ACCORD

(Action to Control Cardiovascular Risk in Diabetes) trial, findings showed that the current blood pressure target of less than 130/80 mm Hg was inappropriate in many diabetic patients and actually led to increased cardiac events (4). Despite this, a blood pressure target of less than 130/80 mm Hg is the metric used by the National Committee for Quality Assurance and others as a marker of “quality.” This metric is based on a single reported blood pressure measurement. In their work, Powers and coworkers conclude that “[q]uality metrics based on a single clinical measurement potentially misclassify a large portion of patients” (1).

It is imperative that stakeholders and policymakers acknowledge that quality in medicine does not always lend itself to a hard number that can be applied to all patients. Should such entities continue to do so, patient outcomes will suffer, and physician’s actions will be based on treating a number instead of the patient.

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IN RESPONSE: As Dr. Logan Silva pointed out, the common errors of a poorly fitting cuff, instrument miscalibration, and sloppy technique all contribute to imprecise blood pressure measurement. Unless we insist on high standards for blood pressure measurement, the reported value may not mean much (1). In addition, terminal digit preference (for example, the tendency to report manual readings with 0 or 5) and remeasurement of blood pressure when the initial value is high but never when it is normal are common biases. There is substantial room for improvement in our implementation of standards for blood pressure measurement.

However, we believe that our data also suggest that focusing only on the technical aspects of clinic measurement misses the point, that no matter how carefully blood pressure is measured, it can vary substantially, from day to day or hour to hour. Over our 18-month study, the coefficient of variation was nearly identical for blood pressure measured in the clinic, research setting, or home. This argues against technique as the primary source of variation. Home blood pressure measurement eliminates white-coat effects; is a much stronger predictor of vascular risk than clinic readings (2, 3); and more practically, it allows for decision making based on multiple measurements. Although we can significantly improve how blood pressure is measured, it is even more important that future guidelines emphasize where it is measured and how that information should be used for clinical decisions. Current evidence suggests that decisions made on

the basis of home blood pressure measurements result in use of fewer medications and lower overall treatment costs without an apparent increase in end-organ damage (4).

We agree with Dr. Wexler's comment about the importance of quality metrics actually reflecting high-quality decision making. Although these metrics were created primarily to evaluate the practice of medicine, it is clear that they also influence it. When hypertension quality metrics promote treatment decisions on the basis of a single clinical reading, they risk more than just inaccurate assessment of quality, but also patient harm. Future guidelines should include recommendations on where blood pressure should be measured and how many measurements should be averaged to guide treatment decisions for patients and their physicians.

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Analysis of Health Benefits and Cost-Effectiveness of Mammography for Breast Cancer

TO THE EDITOR: Schousboe and colleagues (1) have contributed to the mammographic screening debate by calculating the cost-effectiveness ratio of annual screening compared with biennial screening for all ages as more than \$340 000 per quality-adjusted life-year (QALY), from a "national payer" perspective. The American Cancer Society and some professional groups who benefit from screening advocate this aggressive annual schedule.

Unfortunately, this cost-effectiveness ratio understates the case by ignoring indirect costs in the societal perspective, including substantial time and travel costs (2). Screening mammograms and recall examinations cause anxiety, and this harm should have been included in the base-case analysis and varied in the sensitivity analysis as presented in Table 2 in the article (1). Finally, an overdiagnosis rate of invasive breast cancer of 30% rather than 0% or 10% is a more reasonable estimate (3). Overdiagnosis causes overtreatment, and these excess interventions from surgery and radiation result in

disfigurement and increased mortality that the authors should reflect in the QALY analysis.

Most women in the United States do not have a "national payer"—they have insurance companies. Medicare fee schedules do not necessarily reflect resource costs (2), and future cost-effectiveness analyses should use more accurate median reimbursement information from insurance databases. According to the U.S. Food and Drug Administration, digital technology penetration is now 78% (4), so using median Medicare film reimbursement is outdated. Because of the link between digital technology and computer-aided detection, a direct screening resource cost greater than \$200 per mammogram is more appropriate than \$108, and should have at least been included in a sensitivity analysis.

Cost-effectiveness analysis is a useful tool and shows the opportunity cost of aggressive annual screening mammography in this case. Medical resources are limited and have better alternative uses. Physicians ultimately should take the patient perspective and promote informed medical decision making and personalized risk-based screening. In the case of screening mammography, physicians should obtain individual informed consent given the substantial harms from overdiagnosis.

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Potential Conflicts of Interest: None disclosed.

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IN RESPONSE: We thank Dr. Keen for his thoughtful comments regarding our cost-effectiveness modeling study of mammography. We agree that the costs relative to health benefits gained of performing annual compared with biennial screening mammography are very high, and our analyses may have underestimated these costs. From the societal perspective, additional costs of mammography could be included, among them time and travel costs to and from a breast imaging facility. However, advanced breast cancer may result in more disability, and one must also account for the cost of replacing disabled women in the workplace (1). If more frequent mammography detects breast cancer at earlier stages, there may be lower labor-replacement costs. This exclusion would tend to overestimate the costs per QALY gained.

We are unaware of any evidence that Medicare reimbursement underestimates the true cost of mammography, or that private insurer reimbursement rates are a more accurate indicator of its true

cost. We agree, however, that if the true cost of screening film mammography is higher than the median Medicare reimbursement, then our calculated costs per QALY gained of more frequent mammography compared with less frequent or no mammography are underestimated.

There is no consensus that the rate of overdiagnosis of invasive breast cancer is 30% (2). Recent evidence has shown that overdiagnosis is most prominent in the first few years of mammography when long-standing, nonprogressive lesions are first discovered, and even during that period the overdiagnosis rate may be 11% to 12% (3). After a period of repeated mammography, the ongoing overdiagnosis rate may be under 3%.

We chose to model the use of film mammography because most women in the Breast Cancer Surveillance Consortium were screened with that technique between 1996 and 2006, allowing reliable estimates for the influence of breast density on the stage at diagnosis by screening interval. Although digital mammography is more expensive, it may improve detection of breast cancer in women with high breast density and in younger women. As stated in our article, based on the cost-effectiveness study of digital compared with film mammography by Tosteson and colleagues (4), digital mammography every 2 years would probably be more cost-effective than mammography every 3 to 4 years or not at all for women of all ages with high breast density (BI-RADS [Breast Imaging Reporting and Data System] category 3 or 4). In addition, digital mammography seems to be less cost-effective for women with average or low breast density compared with our results. Therefore, our conclusions about the value of including breast density as a factor in determining the frequency of screening mammography would be strengthened.

We agree that anxiety induced by mammography probably represents a transient reduction in quality of life for a subset of women. We chose not to include this in the base-case analysis because of the lack of empirical data regarding its duration and the true quantity of the associated loss of quality of life. As noted in our sensitivity analysis, mammography becomes quite expensive if this anxiety is substantial. There is also the theoretical possibility that true-negative mammography results are reassuring to some, and if true, the cost of mammography relative to the gain in health benefits would be lower. All of these points lead us to agree with Dr. Keen that personalized, risk-based mammography screening while providing the patient with full information regarding harms and benefits of screening is paramount.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-2871.

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OBSERVATION

Herpes Simplex Virus Type 2 Mimicking Necrotizing Fasciitis

Background: Necrotizing fasciitis is a life-threatening condition characterized by infection of deep layers of skin, subcutaneous tissue, and fascia. It rarely involves the face. The most common causes are group A β -hemolytic *Streptococcus*, *Staphylococcus aureus*, and *Clostridium perfringens*.

Objective: To report what we believe is the first published case of nasal reactivation of herpes simplex virus type 2 (HSV-2) that mimics necrotizing fasciitis.

Case Report: A 49-year-old man developed a tiny papule on the tip of his nose. During the next 4 days, his nose became painful and swollen. The lesion increased in size despite treatment with trimethoprim-sulfamethoxazole. Nineteen days before his symptoms began, he received the measles, mumps, and rubella vaccine in preparation for deployment to Afghanistan. He has had the same female sexual partner for 2 years and had no history of oral or genital HSV infection.

His temperature was 38.4 °C (101.1 °F), but he did not have a toxic appearance. He had an eschar that had no sensation on the tip of his nose and distal nasal bridge (**Figure, left**). He had no oral, labial, genital, or perianal ulcers.

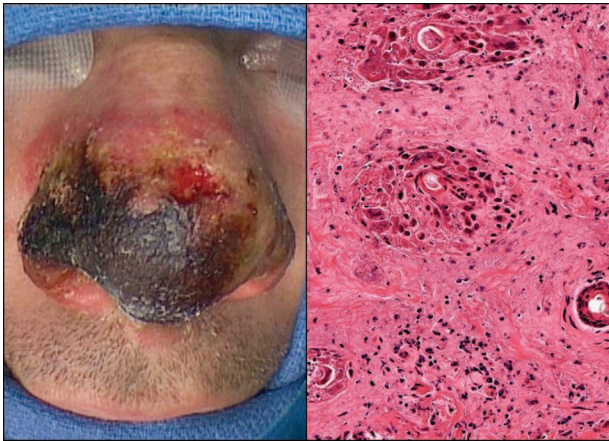
Nasal endoscopy revealed a normal nasal septum. Surface cultures of the lesion yielded scant coagulase-negative *Staphylococcus* and *Propionibacterium acnes*. Blood cultures were sterile. An assay for HIV-1 antibodies and p24 antigen was negative. An assay for serum IgG antibodies to HSV-1 was negative, but an assay for serum IgG antibodies to HSV-2 was positive. Polymerase chain reaction performed on a surface swab specimen of the nose was positive for HSV-2 DNA and negative for HSV-1 and varicella-zoster virus DNA.

Frozen specimens of nasal tissue obtained by surgical debridement revealed extensive necrosis and vascular thrombosis consistent with necrotizing fasciitis. Further pathology examination of these specimens revealed the effects of herpes infection (**Figure, right**).

The patient received additional debridement and acyclovir, 10 mg/kg of body weight every 8 hours for 10 days. After 4 weeks, he had almost complete reepithelialization of his nose.

Discussion: Infection with HSV α 2 is a common sexually transmitted disease, and 50 million persons in the United States are HSV-2-seropositive (1). Herpes simplex virus 2 is an α -herpesvirus that infects mucocutaneous epithelia before establishing latent infection in the neurons of the sensory ganglia. Serum IgG develops 21 to 42

Figure. Reactivation of herpes simplex virus involving the nose.



Left. Photograph of the patient's nasal lesion caused by herpes simplex virus reactivation mimicking necrotizing fasciitis. **Right.** Photomicrograph of the nasal tissue (hematoxylin–eosin stain; original magnification, $\times 200$) obtained by surgical debridement revealing the effects of infection with herpes virus.

days after infection; therefore, this case probably represents HSV-2 reactivation (2).

Although HSV-2 principally causes anogenital ulcers, it also can cause orolabial, cutaneous, and central nervous system infections. With orolabial infection, latency occurs in the trigeminal ganglion. Triggers for reactivation include sunlight, stress, febrile illness, menstruation, and immunosuppression. In this case, a temporal association existed between the measles, mumps, and rubella vaccination and the patient's illness. Although this association may be coincidental, events that activate the immune system, such as inoculation with live virus vaccines, can trigger reactivation of herpesviruses.

To the best of our knowledge, nasal reactivation of HSV-2 has not been previously reported. In contrast, varicella-zoster virus reactivates in the nasociliary branch of the trigeminal nerve and is known

as herpes zoster ophthalmicus. This condition can cause vesicles to develop on the nose, which are known as Hutchinson sign; vesicles can also develop on the forehead and periocular area (3). In addition, 2 cases of severe nasal HSV-1 have been reported (4, 5).

Necrotizing fasciitis due to group A β -hemolytic *Streptococcus* occurs as a complication of infection with varicella virus (chickenpox) in children and as a complication of infection with varicella-zoster virus (shingles) in adults. However, we could not identify a causative bacterium in this case. Although HSV-2 causes necrosis of infected cells, why it causes extensive necrosis and tissue destruction only in rare cases is unclear.

Conclusion: Infection with HSV-2 is a lifelong condition that many persons have. This case report describes a novel manifestation of HSV-2 and should alert clinicians that herpesvirus reactivation can occur in unusual anatomical locations and mimic necrotizing fasciitis.

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Potential Conflicts of Interest: None disclosed.

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