

Priorities for Lung Transplantation Among Patients With Cystic Fibrosis

To the Editor: In her Editorial accompanying our article¹ about prognostic factors for lung transplantation among patients with cystic fibrosis (CF), Dr Maurer² noted that we did not comment on the survivorship effect of the rate of change in the FEV₁%.

We, like others,³⁻⁵ initially made the logical assumption that patients with CF who have rapid deterioration of FEV₁% would have an increased risk of death. It has been hypothesized that the subset of patients with the most rapid decline in FEV₁% would gain a survival benefit from lung transplantation. We created theoretical survival models based on this hypothesis that suggested that we might be able to identify appropriate transplantation candidates several years before the optimal moment for transplantation. This would decrease the number of patients who die while on a waiting list, and optimize the use of donated organs. Unfortunately, none of these models are valid because we also found that the rate of decline in FEV₁% is not a significant predictor of survival.⁶

In our previous work, univariate logistic regression analysis showed that rate of decline of FEV₁% predicted was not a significant predictor of survival.⁶ We now report that, despite the lack of significance, we included the rate of decline of FEV₁% predicted in further multivariate analyses because of its clinical appeal. This variable, whether calculated by linear regression or by linear mixed-effects analysis, again was not statistically significant and was excluded in stepwise analysis of variance when FEV₁% was also included in candidate models. Because we were initially skeptical of this result, we attempted to use the linear mixed effects model of FEV₁% rate

of change to predict future FEV₁%. We identified 12 477 patients in the CF Foundation Patient Registry with 2 to 5 years of pulmonary function data from 1987 through 1992. We generated linear mixed-effects models of the rate of change of FEV₁% for each patient and predicted the change in FEV₁% for 1993 through 1997. The FIGURE shows the complete inability of the FEV₁% rate of change to make that prediction.

Because the rate of FEV₁% decline was not predictive of survival or even of future FEV₁%, as shown here, it was not included in our evaluation of the survival effects of lung transplantation. Based on this additional analysis, we conclude that the rate of decline in FEV₁% is not helpful in the selection of patients with CF for lung transplantation.

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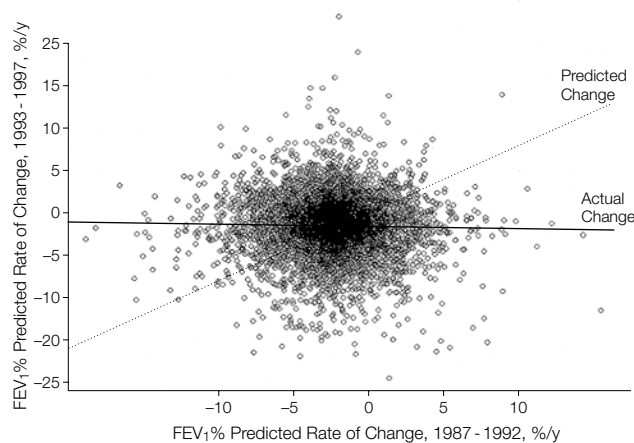
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Figure. Relationship Between FEV₁% Predicted Rate of Change, 1987-1992 and 1993-1997 [N = 12 477]



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Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

1. Liou TG, Adler FR, Cahill BC, et al. Survival effect of lung transplantation for patients with cystic fibrosis. *JAMA*. 2001;286:2686-2689.
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5. Augarten A, Akons H, Aviram M, et al. Prediction of mortality and timing of referral for lung transplantation in cystic fibrosis patients. *Pediatr Transplant*. 2001;5:339-342.
6. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. *Am J Epidemiol*. 2001;153:345-352.

To the Editor: As a 46-year-old with CF awaiting a lung transplant, I would like to comment on the article by Dr Liou and colleagues.¹ While the study does break new ground in identifying an improved multiparameter technique for estimating remaining life expectancy of adults with CF, I am extremely concerned by the conclusion implying that physicians should consider using the results as a basis for recommending to patients whether they should pursue a lung transplant. The unexamined assumption is that a year of survival with a lung transplant is equivalent to one without a lung transplant.

While I have no problem in evaluating the proposed model as an improved method for estimating life expectancy, I cannot accept the authors' implication that only those patients falling into group 1, who exhibit improved life expectancy with a lung transplant, should receive one. The authors have used numerous parameters as input to their model for estimating life expectancy, but they use only 1 parameter, years of survival, as a parameter to indicate benefit from lung transplantation. While this may be all that the available database allows, I feel the discussion of the results is sorely lacking in not bringing up the issues of quality of life that accompany a lung transplant. I fear most physicians will not think of it and will base a discussion on whether to proceed with a transplant based solely on years of survival.

I also question the results, since the survival rate of group 1, having a pretransplant 5-year survival expectancy of less than 30%, had about a 65% posttransplant survival, while groups 2 and 3, having pretransplant 5-year survival expectancies of 30% to 50% and 50% to 70%, respectively, each had about a 50% posttransplant survival. One would expect the opposite, the poorest pretransplant group doing the worst posttransplant.

In my experience, physicians often lose sight of the serious toll on the quality of life that end-stage CF takes from a patient on a daily if not hourly basis. It is significant, and years of survival under abysmal conditions are hardly equivalent to years spent enjoying healthy lungs even if they are fewer than without a transplant. As their lungs give out, adults with CF need more sleep, often 10 or 12 hours per day, and they are still exhausted. Therapy requirements increase, adding further pressure to the available hours in a day. People with CF push through the exhaustion in order to retain a job, working when they should be home in bed. Eventually, however, most must give up their jobs, suffering reduced income and often economic hardship for their families. The resulting social iso-

lation and the reduced self-esteem that accompanies loss of one's career frequently contributes to depression. Lung disease often wipes out a person's appetite, requiring them to force down food 3 times a day and exist on nutritional supplements or to use a feeding tube to survive, all very unpleasant options. And this doesn't even include the secondary issues such as battling with one's providers and insurance companies to correct their numerous billing errors and to ensure appropriate care in this age of fiscal belt-tightening. In short, survival for the sake of survival without a high quality of life cannot come close to comparing with the quality of life available to the transplant recipient. On the other hand, I have met many transplant recipients and they all report their quality of life to be fantastic. Their appetite returns, their lung function is better than it ever has been in their life in many cases, and they are able to work, travel, and vacation with family.

These issues need to be included in a physician's recommendation to a patient considering a lung transplant. Basing a lung transplant decision solely on years of survival is inappropriate, misleading, and unfair to the patient. I feel that the physician's ethical obligation is to provide direction to patients that provides for the best overall quality of life.

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1. Liou TG, Adler FR, Cahill BC, et al. Survival effect of lung transplantation for patients with cystic fibrosis. *JAMA*. 2001;286:2686-2689.

In Reply: It is encouraging that Dr Liou and colleagues carefully considered the potential impact of the rate of fall of FEV₁% in developing their model for predicting survival in patients with cystic fibrosis. They state that despite a variety of iterations of the model they were unable to find an impact on the survival predictions, and they conclude unequivocally that "the rate of decline in FEV₁% is not helpful in the selection of candidates with CF for lung transplantation." However, they also note that this clinical parameter has been identified as a negative predictor by several other authors.¹⁻³ It is important to remember that the model has not yet been validated prospectively in patients with CF who are within their last years of life. The disparity between the model of Liou et al and other published data in predicting 5-year survival likely reflects the different populations studied. Authors who have identified the rate of decrease in FEV₁% as an important predictor have generally not looked at the whole population of patients who might be included in a 5-year survival prediction model, but rather at a smaller subset of patients, a "self-selected" group, who are rapidly deteriorating clinically. In this population, the rate of decline of FEV₁ might indeed be helpful to caregivers and transplant centers in determining appropriate times to wait-list patients. Whether the addition of this type of parameter to the predictions of the model of Liou et al adds useful information for clinicians will become clear as it is evaluated prospectively.

I understand and empathize with Mr Maish's comments regarding length vs quality of life. End-stage lung disease, re-

ardless of the diagnosis, is devastating in virtually all aspects of daily life to both the patient and his or her family. Unfortunately, since the number of people on the waiting list for lungs exceeds the number of donors per year by 3 to 4 times, physicians are rarely allowed the luxury of recommending transplants for quality of life issues alone.

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1. Augarten A, Akons H, Aviram M, et al. Prediction of mortality and timing of referral for lung transplantation in cystic fibrosis patients. *Pediatr Transplant.* 2001; 5:339-342.
2. Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *J Pediatr.* 1997;131:809-814.
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In Reply: We appreciate Mr Maish's comments about our work and the important issue of quality of life (QOL). We found that only the sickest patients with CF had a survival benefit from lung transplantation. To answer Maish's specific question, we previously examined the apparent superior survival of transplanted patients from group 1 compared with groups 2 and 3 (Figure 1 in our article) and found no statistical difference.

The greater issue is his concern that physicians might lose sight of the toll that CF has on QOL. The principle *primum non nocere* (first, do no harm) requires physicians to consider risks before recommending any procedure. Our study provides the first estimate of survival risks and benefits of lung transplantation for patients with CF stratified by predicted survival. We focused on survival because it is an indisputable end point for measuring the benefit of therapy.

We agree, however, that QOL is important, and we are acutely aware of the physical, psychosocial, and economic burdens that CF places on individuals.^{1,2} Several studies show a positive impact of lung transplantation on QOL.^{1,3} However, interpretation of these works requires caution. Some patients evaluated both before and after transplantation experienced no improvement in QOL.⁴ In all studies, patients who died shortly after transplantation were not evaluated. The QOL benefit was not uniform, and accurate prediction of individual outcomes is impossible.

A study examining the relationship between predicted survival and QOL would improve the individual estimates of potential QOL benefits from lung transplantation. As we surmised in our article, patients with the poorest predicted survival likely have the poorest QOL. One might assume these patients would reap the greatest QOL benefit from lung transplantation. If true, then transplantation of the sickest patients might maximally improve both survival and QOL.

There may, however, be a group with high predicted survival but poor QOL. Should these patients undergo transplantation? Because the donor organ shortage constrains lung transplantation, preferentially performing lung transplants in patients with potentially improved QOL and longer survival seems wiser

than performing transplants in patients with improved QOL but unchanged or decreased survival. If the organ supply should increase, then studies of QOL relative to predicted survival tempered by the known rigors of lung transplantation² may help guide the latter group to estimate the potential trade-off between survival and QOL. For now, we agree with Maish that discussions about lung transplantation must include both survival as well as QOL risks and benefits.

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1. Trulock EP. Lung transplantation. *Am J Respir Crit Care Med.* 1997;155:789-818.
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Relationship Between Kaposi Sarcoma-Associated Herpesvirus and HIV

To the Editor: Dr Osmond and colleagues¹ found that the prevalence of Kaposi sarcoma-associated herpesvirus (KSHV) in 1978 and 1979 was 26.5% among homosexual men who later enrolled in the San Francisco City Clinic Cohort (SFCCC) study. This finding is important for understanding the subsequent epidemic of Kaposi sarcoma and its relationship with human immunodeficiency virus (HIV) in San Francisco. It was inappropriate, however, for Osmond et al to infer that the incidence of KSHV has not changed from 1978 through 1996 based on cross-sectional prevalence data from 3 heterogeneous studies, and to use these data in an ecological analysis of how behavior change might affect KSHV transmission.

Determining KSHV incidence from prevalence data is problematic² and requires assumptions that are not met in this analysis. One is that there was no net migration of KSHV-uninfected homosexual men into San Francisco during this period and no excess deaths among KSHV-infected men already in San Francisco, either of which would decrease KSHV prevalence. A second assumption is that the 3 cohorts represent unbiased samples of the same population. The SFCCC enrolled subjects in a public sexually transmitted diseases clinic from 1978 through 1980, while the San Francisco Men's Health Study (1984-1985) and the San Francisco Young Men's Health Study (1995-1996) had population-based designs. Subjects in the SFCCC likely had higher rates of sexually transmitted infections, including KSHV, than would have been found in a contemporaneous population-based study. The SFCCC had an even higher proportion of KSHV-infected subjects because it retrospectively included 97% of the 699 deceased subjects, but less than half of the remaining 6006

subjects.¹ Deceased subjects were much more frequently infected with HIV-1 at entry into SFCCC,³ and KSHV and HIV infections are strongly linked in this cohort.¹ Finally, there may be relevant temporal differences among SFCCC enrollees: subjects in the first phase of the hepatitis B virus (HBV) study on which SFCCC is based had a higher prevalence of HBV seromarkers than subsequent enrollees,³ which suggests that early enrollees had more sex partners. All of these biases could have obscured an increasing prevalence of KSHV among homosexual men in San Francisco during 1978 through 1985. Even so, KSHV prevalence in SFCCC actually increased by 34% between the January through June 1978 and the September 1979 through December 1980 periods.¹

Closed cohort studies are not limited by the above problems. Such studies demonstrate that KSHV incidence peaked during the early 1980s among homosexual men in New York, Copenhagen, and Washington, DC.^{4,5} Therefore, the conclusion that KSHV incidence was not changing during the onset of the HIV epidemic among homosexual men in San Francisco (and, by inference, in the rest of the United States) is doubtful.

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1. Osmond DH, Buchbinder S, Cheng A, et al. Prevalence of Kaposi sarcoma-associated herpesvirus infection in homosexual men at beginning of and during the HIV epidemic. *JAMA*. 2002;287:221-225.

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5. Melbye M, Cook PM, Hjalgrim H, et al. Risk factors for Kaposi's-sarcoma-associated herpesvirus (KSHV/HHV-8) seropositivity in a cohort of homosexual men, 1981-1996. *Int J Cancer*. 1998;77:543-548.

To the Editor: Dr Osmond and colleagues¹ noted the lack of consensus as to the route of KSHV transmission in homosexual men. Recent studies¹⁻³ have suggested that KSHV, also known as human herpesvirus 8 (HHV-8), is primarily transmitted among homosexual men through deep kissing or oral sex. While this hypothesis is consistent with much of the data, it fails to explain why HHV-8 is much more prevalent in homosexual than in heterosexual men, since deep kissing and oral sex are common in both groups. Nor can differences in HHV-8 prevalence be solely attributed to numbers of sex partners, because even commercial sex workers have a lower prevalence of HHV-8 than do homosexual men.⁴ Thus, the higher preva-

lence of HHV-8 among homosexual men may be related to sexual practices, such as anal sex, that are more prevalent among this population. Several findings of Osmond et al are consistent with this hypothesis.

First, HIV-seropositive homosexual men had significantly higher rates of KSHV seroprevalence than did HIV-seronegative subjects. While the seropositive group might have had higher numbers of sex partners, HIV-seropositive subjects are also more likely to have practiced unprotected receptive anal sex, which thus may be an important route of KSHV transmission.

Second, as the authors noted, there was limited information about the relationship between specific sexual behaviors and KSHV seroprevalence. The study only identified associations at an ecological level, meaning that an individual's sexual behavior could not be linked to his HHV-8 status. In addition, HHV-8 seroprevalence was measured at only 2 time points when behavioral data were available (1984-1985 and 1995-1996), so that there were no data to indicate whether KSHV seroprevalence remained constant during the interim. It is possible, for example, that when the prevalence of unprotected receptive anal sex was lowest (1987-1992), KSHV seroprevalence decreased correspondingly. Without additional information, the relative contributions of oral and anal sex in KSHV transmission cannot be determined.

Finally, Osmond et al found KSHV seroprevalence to be greater than 25% prior to widespread HIV infection. This important observation makes it clear that HIV is not primarily responsible for differences between homosexual and heterosexual subjects in KSHV prevalence. Thus, other factors, including behaviors such as anal sex, may be responsible for these differences. These factors might best be identified in longitudinal studies of KSHV-discordant, monogamous couples.

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1. Osmond DH, Buchbinder S, Cheng A, et al. Prevalence of Kaposi sarcoma-associated herpesvirus infection in homosexual men at beginning of and during the HIV epidemic. *JAMA*. 2002;287:221-225.

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4. Cannon MJ, Dollard SC, Smith DK, et al. Blood-borne and sexual transmission of human herpesvirus 8 in women with or at risk for human immunodeficiency virus infection. *N Engl J Med*. 2001;344:637-643.

To the Editor: Dr Osmond and colleagues¹ reported that KSHV infection was already highly prevalent among homosexual men in San Francisco when the HIV epidemic began, and that its prevalence did not change through 1996. On the other hand, the rapid increase in the incidence of HIV-associated Kaposi sarcoma (KS) in the early 1980s and its decline in the United States prior to the era of highly active antiretroviral therapy (HAART) suggests that KSHV alone does not cause KS. If KSHV infection does play an etiologic role in KS, then one would expect KS to "spread" to heterosexuals dually infected with HIV,

which has not yet been observed. Furthermore, the decline in KS prior to HAART has not been explained.

Use of nitrite inhalants should be considered a third factor that is consistent with the unique epidemiology of HIV-associated KS. Homosexual men used "poppers" more commonly than did heterosexuals prior to the AIDS epidemic and use has been declining since. Additional pharmacological and epidemiologic evidence supports the connection of nitrite inhalant use to KS.^{2,3} The decline in the incidence of KS in the United States⁴ parallels a similar decrease in the use of nitrite inhalants.⁵ The epidemic of HIV-associated KS provides a unique opportunity to decipher the pathogenesis of a malignancy that appears to be multifactorial in origin.

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1. Osmond DH, Buchbinder S, Cheng A, et al. Prevalence of Kaposi sarcoma-associated herpesvirus infection in homosexual men at beginning of and during the HIV epidemic. *JAMA*. 2002;287:221-225.
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In Reply: We agree with Dr O'Brien and colleagues that it can often be problematic to infer incidence from prevalence data. As we noted, our data are not inconsistent with some increase in KSHV prevalence with the first wave of HIV infection. Our principal objective in documenting the robust prevalence of KSHV in 1978 in HIV-uninfected men, however, was not to make a strict comparison with 1984 and 1985, but rather to show that KSHV infection was probably not introduced recently in homosexual men. This has implications for understanding KSHV transmission. If acts that are practiced by both homosexuals and heterosexuals, such as kissing, are significant routes of KSHV transmission, KSHV would likely be widespread in heterosexual populations, but actual prevalence estimates range from 0% to 9%.¹⁻³ Low prevalence in heterosexual groups despite spread by kissing would be plausible if KSHV were recently introduced, but our data from 1978 do not support this.

O'Brien et al also point out that a closed cohort is a more appropriate study design in which to examine changes in KSHV incidence. Again we agree with the theoretical point but note

that the published cohort studies are not in agreement. O'Brien et al⁴ cite their own cohort analysis and a study by Melbye et al⁵ as showing declining KSHV incidence, but Goudsmit et al⁶ report declining HIV incidence and no decline in KSHV incidence during the 1980s. An apparent decline in KSHV incidence early in the follow-up of a closed cohort could be an artifact of serological testing based on a specific but insensitive assay. It is generally acknowledged that the immunofluorescence assay for antibodies against KSHV latency-associated nuclear antigen is an insensitive assay, identifying about 80% of KS patients as positive on a single test.¹ Repeating the test on subsequent samples is likely to identify many of the 20% of truly infected persons missed on the baseline test as early "seroconverters." As follow-up time increases, this source of seroconverters would diminish substantially, producing a pattern of declining incidence that is an artifact of the assay characteristics. Our own experience testing longitudinal samples (with the assay used by O'Brien et al⁴) is similar to that reported by Quinlivan et al,⁷ who found an inconsistent pattern of positive results that make it difficult to determine with confidence when seroconversion occurred. We therefore remain skeptical that published incidence rates from cohort studies have settled the question.

Although we cannot directly infer incidence rates from our cross-sectional data, we believe they are relevant in understanding the relative incidence of HIV and KSHV infections between the 1984 through 1985 and the 1995 through 1996 periods, for which we have identical population-based samples. Restricting comparison to the groups of 25- to 29-year-old subjects, HIV prevalence dropped from 48.6% to 21.9% while KSHV stayed nearly steady at 21.8% and 25.8%. Other explanations are possible, but the most likely explanation for the discrepant patterns of seroprevalence is that the incidence of the 2 viral infections differed in the population of young homosexual men during this period. For example, these men were too young for deaths from AIDS to have had much effect on prevalence. Although we acknowledged that our data do not establish a cause-and-effect relationship, we think the most plausible explanation for the prevalence patterns is that there are significant differences in the way the 2 viruses are transmitted. Finally, we note that O'Brien et al⁴ found a nearly constant KSHV incidence between 1984 and 1990 (the last year sampled), which is consistent with the constant seroprevalence we found when comparing the period 1984 through 1985 with 1995 through 1996.

We suggested that the difference in seroprevalence patterns could be due to penile-oral intercourse playing a greater role in KSHV than in HIV transmission. Drs Cannon and Pellett note that if KSHV were transmitted by deep kissing and oral sex, it would be common in heterosexuals. We agree with respect to deep kissing but point out that the specific route of transmission in oral sex may be from infected saliva to mucosal cells of the penis, that is, from the receptive to the insertive partner, as the virus is found frequently in saliva but rarely in semen. Hence transmission to female partners would be unlikely to

occur to female partners in penile-oral intercourse. We certainly cannot rule out transmission by penile-anal intercourse and note that a high proportion of the homosexual men we have studied report using saliva as a lubricant during penile-anal intercourse,⁸ raising the possibility of transmission to the receptive partner even if the insertive partner is using a condom. We do not know why saliva may be less infectious during kissing, but the mouth may be less hospitable to an infecting virus than is other less well-defended mucosal tissue.

Drs Haverkos and Kopstein use national surveillance data for the occurrence of KS in patients with AIDS to identify a decline in KS incidence prior to HAART that they believe has not been explained. While we agree that there has been an overall decline in KS incidence in the United States prior to HAART, the more pertinent question is whether there has been a decline in KS incidence among HIV-infected homosexual men (the group at most risk for KSHV infection) who were infected with HIV at different times in the HIV epidemic. If such a decline were seen between men seroconverting for HIV in the early 1980s compared with the late 1980s, this would need to be explained. Veugelers et al⁹ found no differences in KS incidence in 407 men who seroconverted for HIV throughout the 1980s. This is consistent with the nearly constant prevalence of KSHV that we found in homosexual men between 1984 and 1995. These data, however, do not rule out a role for other cofactors, such as nitrite use. Indeed, only about half of the men in the San Francisco Men's Health Study who were KSHV and HIV positive developed KS, so there may well be one or more other factors that are important in KS pathogenesis.

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1. Kedes DH, Operskalski E, Busch M, Kohn R, Flood J, Ganem D. The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. *Nat Med*. 1996;2:918-924.
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Measurement of Serum Estradiol

To the Editor: Dr Cummings and colleagues¹ found that serum estradiol levels may be useful to identify women who would be most likely to benefit from prophylactic use of raloxifene to prevent breast cancer. Application of their results, however, which used a "sensitive" assay, may not be directly applicable to the commercially available assays for serum estradiol that are generally used in clinical practice. The apparent average value for estradiol in their population of postmenopausal women using this assay was 2.93 pg/mL, which is much lower than the range of 10 to 20 pg/mL used in daily clinical practice.² Thus, their results must be adjusted before they can be applied to clinical practice.

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1. Cummings SR, Duong T, Kenyon E, Cauley JA, Whitehead M, Krueger KA. Serum estradiol level and the risk of breast cancer during treatment with raloxifene. *JAMA*. 2002;287:216-220.
2. Speoff L, Glass RH, Kase NG, eds. *Clinical Gynecologic Endocrinology and Infertility*. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 1999:658.

This letter was shown to Dr Cummings and colleagues, who declined to reply.—ED.

Value of Ophthalmologic Examination in Diagnosing Temporal Arteritis

To the Editor: In their Rational Clinical Examination article about temporal arteritis, Drs Smetana and Shmerling¹ suggest that a temporal artery biopsy is important but fail to consider the role of the ophthalmologist. A more rational approach would include a complete ophthalmic examination by an ophthalmologist, neuro-ophthalmologist, or retina specialist. The eye findings could point toward the correct diagnosis (and might suggest other reasons to proceed with the contemplated temporal artery biopsy).

Because many patients with temporal arteritis have ocular manifestations,² a complete eye examination is most useful in any patient suspected of having temporal arteritis. When performed in a timely fashion, such an examination, along with evaluation of the erythrocyte sedimentation rate (ESR) and C-reactive protein laboratory tests can allow for a presumptive diagnosis of temporal arteritis. Such a patient can be started on high doses of systemic corticosteroids and a temporal artery biopsy can be scheduled to be performed shortly thereafter to make a definitive diagnosis.

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1. Smetana GW, Shmerling RH. Does this patient have temporal arteritis? *JAMA*. 2002;287:92-101.
2. Hayreh SS, Podhajsky PA, Zimmerman B. Ocular manifestations of giant cell arteritis. *Am J Ophthalmol*. 1998;125:509-520.

In Reply: The primary purpose of our article was not to determine the incremental value of ophthalmologic examination in the diagnosis of temporal arteritis, but rather to determine the diagnostic value of the history, physical examination, and ESR among patients with suspected temporal arteritis. We agree with Dr Blodi that an ophthalmologic examination may be particularly useful for the subset of patients with suspected temporal arteritis who have visual symptoms at the time of presentation (37% in our review). If clinicians can arrange such evaluation promptly, it is reasonable to request this consultation while awaiting the results of the ESR measurement. However, we do not believe that clinicians should withhold empiric systemic corticosteroid therapy or defer biopsy in patients with a high clinical probability of temporal arteritis (as suggested by multiple typical features or the presence of a high likelihood feature as determined by our review), in order first to obtain the results of an ophthalmologic examination.

Such consultation would be particularly helpful in the absence of compelling clinical features that would suggest temporal arteritis, and when clinicians would thus be more likely to entertain diagnostic evaluation for carotid artery stenosis or other alternate considerations. For example, in a patient with transient visual loss and suspected temporal arteritis whose ESR proves to be normal, the likelihood of temporal arteritis would

be sufficiently reduced (likelihood ratio, 0.2) that the physician should consider alternate diagnoses. An ophthalmologic examination would be particularly important in such a case.

We are aware of no evidence to suggest that all patients with suspected temporal arteritis, including those without visual complaints, should receive a complete eye examination as part of the diagnostic strategy. In fact, our review suggests otherwise. The finding of a normal funduscopic examination in such a patient would not alter the likelihood of temporal arteritis. In our review of 745 patients who had a complete funduscopic examination, the negative likelihood ratio for any funduscopic abnormality was 1.0. Likewise the finding of an abnormal funduscopic examination did not substantially increase the likelihood of positive temporal artery biopsy results (positive likelihood ratio, 1.1). Therefore, we find that the risk of potential delay in diagnosis or of institution of appropriate empiric therapy while awaiting temporal artery biopsy would likely outweigh the benefit of ophthalmologic consultation for patients without visual symptoms for whom a clinical suspicion of temporal arteritis exists.

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