
To the Editor:

We appreciate the comments by Dr. Cogo and colleagues, raising the hypothesis that hypoxemia in itself could play a role in the development of hypopallumemina. However, as in many areas of medicine, is this a cause-effect relationship or simply an association, ie, the inflammatory response is responsible for permeability alterations in the kidney (resulting in hypoalbuminuria) and in the lung (resulting in hypoxemia)?

Moreover, some of our patients required a high fraction of inspired oxygen (sometimes in addition to positive end-expiratory pressure), but we never allow hypoxemia (PaO₂ ≤ 60 mm Hg) to persist in critically ill patients. Hence, we do not believe a low PaO₂ by itself, could have contributed to our findings.

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Lung Cancer Screening Debate

To the Editor:

With respect to the article by Chirikos et al (May 2002)1 and the accompanying editorial by Dr. Grannis (May 2002),2 while the analyses and comments are elegant, they do not address the key issue in the lung cancer screening debate. As noted by Dr. Chirikos, “First and foremost, a cost-effective analysis must assume that effectiveness exists.” Dr. Grannis assumes “a very real possibility that LC [lung cancer] screening, despite high initial cost, can save money as well as lives.” It is problematic that these assumptions are unproven and that considerable data are currently available that, at the very least, suggest that the assumptions are incorrect.

Indeed, in the article following that of Chirikos et al, Lopez-Encuentra et al3 report relatively uniform results in the group of individuals with nodules ≤ 2 cm despite the heterogeneity of nodule sizes within that group including smaller nodules. While the number of cases was relatively small, similar findings have been reported by Patz et al,4 although the nodules evaluated were ≤ 3 cm.

I suspect that this is one of many communications that will be directed toward this issue and with justification. Costs engendered by CT screening are large whenever a nodule is detected, regardless of size. Small nodules may be observed, producing large imaging costs, while larger nodules may undergo biopsies, incurring both cost and patient morbidity. Indeed, the unjustified proliferation of independent centers offering thoracic CT screening services needs to be considered in the context of the number

References
2 Grannis FW. Lung cancer screening: who will pick up the tab? Chest 2002; 121:1388–1390

To the Editor:

In a very sophisticated analysis (May 2002), Chirikos and colleagues1 report that lung cancer screening with low-radiation-dose CT is likely to be cost-effective if it proves to be effective in reducing lung cancer mortality rates. While the authors’ assumptions regarding costs may be conservative, their assumptions regarding effectiveness are very optimistic. It is important to note that, as the incremental benefits of an intervention approach zero, the incremental cost-effectiveness ratio approaches infinity. If low-dose CT leads to only marginal improvements in mortality rates, its cost-effectiveness ratio will be highly unfavorable. In contrast, if the health benefits are large relative to the resources consumed, the intervention will be economically attractive. Thus, it is important to determine not only whether low-dose CT is effective, but also to determine how effective it is. Even if > 50% of cancers are detected at a localized stage, we currently do not know enough about the behavior of screen-detected tumors to determine the magnitude of improvements in life expectancy for these patients.

One might also take issue with the claim that the cost estimates reflect a “worst-case” scenario. Although not stated in the article, the analysis assumes that existing resources and facilities are sufficient to support a program of mass screening. In fact, it is likely that health systems will need to make substantial up-front investments in capital equipment and personnel to support the implementation of new screening programs, because of the large numbers of current and former smokers who might be eligible.
Finally, in an accompanying editorial,2 Grannis asks who will pay the costs for lung cancer screening. Until screening is proved to be effective, individuals will no doubt continue to pay out of their own pockets to have the test performed. Society (taxpayers, persons with private health insurance) will pick up the rest of the tab for costs associated with downstream testing and its complications. In the meantime, we would do better to spend our limited resources on interventions that have been shown to be effective, such as primary prevention through smoking cessation.

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2 Grannis FW. Lung cancer screening: who will pick up the tab? Chest 2002; 121:1385–1390

To the Editor:

We are grateful to Drs. Gould, Blum, and Rinne for their interest in our article1 and for their thoughtful comments. It is critical to differentiate between clinical research investigations of unproven but promising cancer screening strategies and clinical service recommendations for routine use of proven screening modalities. As both letters emphasize, the latter category requires demonstration of cancer mortality reduction from screening. Our article and current clinical research trials of screening for lung cancer with CT fall into the former category.

We agree that the effectiveness of screening for lung cancer with CT is unproven. We stated this in both the “Introduction” and “Discussion” sections of our article. We did not recommend routine CT screening for lung cancer. The purpose of our article was to estimate if cost-effectiveness considerations were so unfavorable that it might be wise even to consider further clinical investigations to prove effectiveness. As we stated, “our estimates appear to be sufficiently reasonable and economically feasible to argue that cost factors should not be used to rule out more definitive controlled trials of the use of CT scans to screen for lung cancer.”1

Drs. Blum and Rinne believe that, as effectiveness is unproven, cost-effectiveness analysis is interesting but not applicable. We disagree. Before considering whether to conduct appropriate clinical research investigations to prove or disprove effectiveness, some preliminary estimates of costs and cost-effectiveness must occur, especially when the screening test itself, CT, is virtually the poster child for high-cost, high-technology medicine. Our article is such a preliminary analysis. As we stated, we can refine our data and our conclusions as more information is known.

Drs. Gould states that it is important to determine not only effectiveness, but its magnitude. We agree. However, questions of proof and magnitude of effectiveness will not be definitively answered for another decade, at great expense, from appropriately designed, randomized clinical trials, with several years of screening and additional years of follow-up. A preliminary study such as ours must deal with limited available clinical information, and those limitations were stated.

Drs. Gould notes that we do not know enough about the behavior of screen-detected tumors to determine the magnitude of benefits; he believes that, while we were conservative in estimating costs (the numerator of a cost-effectiveness ratio), we were too optimistic in estimating effectiveness (the denominator). Drs. Blum and Rinne state that the concept of lead-time bias has not been resolved. We did not attempt to adjust our findings for lead-time bias (clinical outcome observations not adjusted for the timing of the diagnosis), length sampling bias (clinical outcome observations not adjusted for the rate of progression of disease), or overdiagnosis bias (clinical outcome observations not adjusted for disease that would remain clinically covert until death from other causes), as the extent and effect of these biases have not been sufficiently quantified for CT screening. We specifically stated that we didn’t adjust for biases, and we limited our estimate of outcomes to those derived from existing survival figures adjusted for age, stage at diagnosis, gender, and treatment modality. All three types of biases may artificially inflate survival estimates.2–10 The uncertainty surrounding the effectiveness denominator term accounts for our extremely conservative cost estimates. For example, Marshall, et al.11,12 did adjust for lead-time bias in their cost-effectiveness model, but they gauged costs less conservatively, so their estimate of their cost-effectiveness ratio is not appreciably different from ours. We refer to our paragraphs in the “Discussion” section describing the limitations in our estimates of the ratio between cost numerator and effectiveness denominator terms.1

Dr. Gould believes our analysis implies that existing resources are sufficient to support a program of mass screening. We disagree. We made no such statement or implications, and we do not believe it to be true. As noted in the accompanying editorial to our article,13 in the first year alone, the costs for screening CT studies and incurred diagnostic CT examinations would probably total at least 19 billion dollars, an amount almost equal to the costs of all radiology and medical imaging in 1990.14 Current resources are not sufficient to support a program of mass screening—but who is recommending such a program? Certainly not us—not until the effectiveness of CT screening is demonstrated. Once again, it is important to differentiate between research investigations of unproven strategies and clinical service recommendations for routine use of proven screening.

As for the responsiveness for our health care system to provide access, capital, and capacity for new services proven to be effective, we are more optimistic. As Drs. Blum and Rinne comment, CT screening centers currently flourish, often charging less than the Medicare rates used in our analysis. If such centers can succeed economically, we have no doubt that the rest of the system could adapt, if screening were shown to be effective in reducing the death rate from lung cancer. However, if effectiveness and cost-effectiveness are eventually demonstrated for CT screening, our society will need to decide, through our usual imprecise methods, if we are willing or able to spend the additional money to achieve the additional outcomes.

Drs. Blum and Rinne decry the proliferation of centers offering screening CT services without proof of effectiveness. We agree. We believe strongly that the best way to respond is to encourage scientifically valid clinical research trials to demonstrate whether or not such screening is effective. We believe our stance is consistent with the current recommendations of the American Cancer Society, the American College of Radiology, and the American Thoracic Society concerning lung cancer screening with CT.

Dr. Gould rephrases the question posed in the editorial accompanying our article11—“who will pay the costs?”—and replies that individuals will pay out of their own pockets for unproven screening CT services. We agree. People also pay out of their own pockets for aromatherapy and laetrile treatments; we cannot stop people from spending their money as they want. However, we believe that recommendations for clinical CT screening services, and for health insurance or