Correspondence

The Relative Importance of Unmeasured Covariates in Racial/Ethnic Disparities Research

To the Editor:

Dr. Barnato and colleagues (1) present results from a population-based analysis of race-specific incidence and case fatality in severe sepsis. Using hospital discharge data from six states, the authors determined that the rate of severe sepsis for blacks was almost double that of whites. We commend the authors for documenting this racial/ethnic disparity. Identifying disparities in health outcomes and treatment effects is an important first step in eventually curtailing their occurrence. An important subsequent step involves appropriately identifying the fundamental causes of such disparities. It is here that we take issue with the article.

Confronted with a residual association between race/ethnicity and sepsis incidence after adjusting for measured confounders, the authors acknowledge that unmeasured confounders may be the cause. This is the most obvious conclusion given the crude indicators of social status used in their analysis. However, they are more enthusiastic about a second possibility: unexplained racial disparities in sepsis incidence could be due to “different genetic susceptibility to sepsis between blacks and whites.” The common argument that, after accounting for social/environmental factors, genetic differences are responsible for residual racial disparities in complex diseases is flawed for several reasons (2–4). From a purely probabilistic standpoint, even in situations where social factors can be measured without error, and are appropriately accounted for in the analysis, social/environmental explanations for the higher rates of sepsis among black patients are far more likely than genetic ones (2, 5). This is because the variability in social/environmental factors that influence health across racial/ethnic groups (e.g., education, health insurance, poverty) is orders of magnitude greater than any genetic variability between groups (4). In other words, race is likely to be much more highly correlated with social/environmental factors than with genetic factors.

The authors’ enthusiasm for future research efforts that would determine the genetic basis of racial differences in the pathophysiology of sepsis ignores the fact that race serves as a risk factor for both genetic and environmental effects. Issues of confounding, coupled with the weak correlation between human genetic diversity and racial/ethnic categories, will ultimately limit the promise of such research efforts (6).

While we appreciate the assertion that “hypotheses regarding potential race-associated differences in innate susceptibility do not belie the [importance of] differences in healthy lifestyles,” we feel that the purported genetic and biologic differences between blacks and whites with sepsis are mainly conjecture and detract from the known social and environmental causes that likely explain the vast majority of the difference.

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From the Authors:

We thank Drs. Cooke, Frank, and Frank for their thoughtful letter on our article (1). We regret, though, that they did not take more care to quote us fully when reviewing our discussion. For example, in quoting our statement that genetic factors may play a role in explaining our results, they omitted that we prefaced our point with “for example.” Furthermore, they suggest that we believe enthusiastically that the differences between whites and blacks in the rate of severe sepsis are genetic. Yet, we would contend, as stated in the article (1), that racial differences likely reflect a mixture of environmental and biologic differences. In contrast, it is Cooke and colleagues who appear to vigorously defend the idea that there can only be one realistic explanation for our results—residual confounding due to unmeasured environmental factors that correlate with race.

In defending their position, they cite work by Cooper and coworkers, without noting that Cooper’s opinions have been criticized for straying from “middle ground” (2) or that many of Cooper’s concerns relate to the failure to adjust for a number of environmental factors which, in fact, were accounted for in our analysis. Furthermore, Cooper acknowledges that functional genetic allele frequencies that may influence disease vary significantly across different racial/ethnic groups (3). His concern is that these differences not be overinterpreted as being an “effect of” rather than “association with” race, lest oversimplistic assumptions be made about the link between race, a single gene, and disease in multiattribute non-Mendelian conditions.

We could not agree more. There is very strong evidence of hereditary susceptibility to infection and sepsis (4), yet unraveling the exact genetic basis is a gargantuan task. Variation within different geographic and racial/ethnic populations provides important clues. For example, recent data suggest that *TLR4* haplotypes that appear to increase the risk of sepsis are more prevalent in African populations in part because of evolutionary pressure from malaria, and not simply due to genetic drift (5).

The point here is that there do appear to be important differences in the rates of severe sepsis between different self-identified racial/ethnic groups in the United States. That a large part of these differences is due to differences in environmental factors establishes a clear social and public health agenda. That a large difference persists despite efforts to adjust for environmental factors also leaves open the possibility that not all the difference is environmental, and that continued efforts to explore

the potential causes may not only redress disparities in care but potentially offer insights into the pathogenesis of sepsis.

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Palliation or Euthanasia and End-of-Life Care: Is It in the Eye of the Beholder?

To the Editor:

The American Thoracic Society Clinical Policy Statement on palliative care emphasizes that dosages of opioids that exceed what is necessary to relieve symptoms are illegal and morally suspect, and should be avoided because such circumstances signify some intent other than symptom relief (1). The rule of “double effect” has been misinterpreted when administering medications to blur the line between delivering good palliative care and actively shortening the dying process in end-of-life medical practice. The dying process after withdrawing mechanical ventilation in intensive care patients should not exceed 60 minutes if transplantable organs are to be procured in non-heart-beating organ donation (donation after cardiac death) (2). Administering palliative medications in dosages beyond what is needed to relieve distressing symptoms and to actively shorten the dying process to procure transplantable organs is illegal and morally unacceptable (3). Several cultures, religious affiliations, and ethnic groups strongly oppose and condemn actions intended to actively shorten the dying process or assist in death (4).

Protocols recommending the continuous administration of opioids and benzodiazepines, in the absence of distressing symptoms, with intent to depress spontaneous respiratory rate before withdrawal of mechanical ventilation can effectively

shorten the dying process to less than 60 minutes (5). Administration of medications for terminal sedation to shorten the dying process after withdrawal of mechanical ventilation has been defended as simply compassionate clinical care and not an act of euthanasia (6). In reality, it is euthanasia and physician-assisted death. The medical profession should strongly resist experimentation with physician-assisted death under the veil of delivering compassionate palliative care to intensive care patients. As Giannini and colleagues succinctly say, “the universal imperative ‘not to kill’ is still valid, and we sincerely hope that euthanasia does not become an accepted option for intensive care patients” (6).

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From the Authors:

We thank Drs. Rady, Verheijde, and McGregor for their letter referring to the American Thoracic Society (ATS) Official Clinical Policy Statement concerning palliative care for patients with respiratory diseases and critical illnesses (1). We appreciate their concerns that distinctions between palliative care and euthanasia may become blurred in clinical practice. The statement itself was written to make these distinctions clearer to health care providers, patients, and the public.