Multiple studies have noted that race/ethnicity influences disease expression and outcome in systemic sclerosis (SSc, scleroderma; for review see Reveille\(^1\)). For example, compared to white Americans, African Americans have earlier disease onset, more frequently have diffuse cutaneous involvement, have increased severity of lung disease, and less frequently have anticentromere antibody positivity, which is a marker of more mild disease\(^2\text{–}^5\). Looking specifically at mortality, Laing, et al found that black women with scleroderma had a worse age-adjusted survival rate than did white women with scleroderma\(^6\). Similarly, Medsger, et al reported as early as 1971 that African Americans had significantly worse survival than Caucasians\(^8\).

In this issue of The Journal, Nietert and colleagues report that African Americans and other non-Caucasians in South Carolina, USA, have a significantly greater risk of in-hospital death than do Caucasians, and they analyze several factors that could contribute to this difference\(^9\). For this study, they used the South Carolina state hospital database to identify admissions of scleroderma patients, and to link them with length of stay, comorbid conditions, certain procedures, complications, and outcome. Strong points of this study include the large number of cases (\(n = 727\)), the large number of hospitalizations and emergency room visits (\(n = 2574\)), and the relatively complete record of events in the study period (1996–2000) covering all participating South Carolina hospitals (excluding only federal and military hospitals).

However, this state hospital database was established for administrative purposes and some relevant socioeconomic and clinical details were not available in the dataset. To overcome these limitations, the authors used surrogate markers to infer these features. Income and education level were assigned using data from zip code (postal code) of residence and US Census data and Bureau of Labor Statistics data regarding these features among area residents. This approach has been used in multiple other studies and is considered legitimate, reliable, and robust. Perhaps more problematic, scleroderma-specific disease characteristics that have been identified in other studies as predictors of prognosis had to be inferred from surrogate markers of disease severity such as age at admission, total number of admissions, comorbid conditions, length of stay, etc.

Indeed, the challenge for any epidemiology study using existing databases is to find the appropriate balance between the need for large numbers to accomplish the study objectives on the one hand, and the loss of individual subject detail on the other hand. Recently, this has been made even more difficult in the United States by regulations in the Health Insurance Portability and Accountability Act (HIPAA) that limit access to individual records containing patient identifiers without prior authorization of the subject.

Thus researchers in these studies have to deal with “dirty data,” collected for administrative purposes, recorded by non-study personnel, and which frequently lack specific demographic or disease features that are important to the study.

### USE OF SURROGATE VARIABLES

To overcome these limitations, researchers have developed several strategies to infer patient and clinical features that are not identified explicitly in administrative databases. The reliability of a study’s conclusions depends to a large extent on the careful selection, analysis, and interpretation of these surrogates.

### RESULTS AND INTERPRETATION

The main result of this study, confirming several earlier studies as noted above, is that even after adjustment for markers of socioeconomic status (SES), disease severity, and comorbidities, African Americans and other non-Caucasian subjects had significantly greater odds of death than did whites.

*See Demographic and clinical factors associated with in-hospital death among patients with SSc, page 1888*
Did the adjustment for markers of SES adequately eliminate this factor as a predictor of worse outcome? Nietert and colleagues admit that this adjustment may be inadequate because the quality of medical and societal resources may still not be equivalent among groups.

Did the adjustment for disease severity and comorbidities adequately eliminate these factors as predictors of worse outcome? Although some surrogate markers for disease severity may have been inadequate, other features such as longer length of stay, greater number of hospitalizations, and being transferred from another hospital have such strong face validity that it is difficult to question their legitimacy.

FINAL QUESTION
So why do African Americans and other non-Caucasians with SSc have a worse prognosis (all other factors being made as equal as the data permit)? If race and ethnicity are themselves surrogates for a shared gene pool, are hereditary factors the key difference?

A growing body of evidence suggests this may be at least part of the answer. A study of scleroderma among Choctaw Native Americans found an increased prevalence of disease in this group, as well as striking disease homogeneity, with the majority of cases having diffuse disease, pulmonary fibrosis, and antibodies to topoisomerase I10. Among the Choctaw, SSc was associated with a unique HLA haplotype.

In another study, particular HLA-DRB1 alleles were associated with anti-topo-I antibody production in patients with SSc, but the specific DRB1 alleles were different in Caucasians, African Americans, Japanese, and Choctaws4.

Differences have been seen in non-HLA genes as well. Hudson, et al reported that particular polymorphisms in the cytotoxic T lymphocyte associated antigen 4 (CTLA4) gene were associated with SSC in African-American patients but not in Caucasians11. Multiple other genetic polymorphisms have been reported in case-control studies of SSc, but most of these have been done in predominantly Caucasian populations and thus do not address racial differences (for review see Reveille1).

Well, is it nature or nurture? The answer, it seems, is “yes.”

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