on these results, we can state that solving the sarcoidosis conundrum is possible. ■

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Noninvasive Quantitative Imaging–based Biomarkers and Lung Cancer Screening

Lung cancer is the leading cause of cancer-related death among men and women globally and in the United States (1, 2). Despite improvements in patient survival in recent years for many other cancer types, there have been few improvements in non-small cell lung cancer patient survival, mainly because by the time a diagnosis is made, the tumor is often well advanced and treatment options are limited. Approximately 57% of all lung cancers are diagnosed at a distant stage, for which 5-year survival is 4% (1). Because of the large number of affected individuals and poor outcomes, screening and early detection could have a significant effect on increasing patient survival, as by identifying the cancer at an earlier stage, patients have a better possibility of a surgical cure. Until recently, however, no screening method has been shown to decrease mortality rates for non-small cell lung cancer. The National Lung Screening Trial (NLST) compared

low-dose computed tomography (LDCT) and standard chest radiography for three annual screens and found a 20% reduction in lung cancer mortality for CT compared with standard chest radiography (3). On the basis of the findings from the NLST, in December 2013 the U.S. Preventive Services Task Force (4) issued a recommendation for annual screening for lung cancer with LDCT, and in February 2015, the Centers for Medicare & Medicaid Services made the determination that LDCT is appropriate for eligible beneficiaries (5).

Although the NLST demonstrated a clear benefit for lung cancer and all-cause mortality reduction, LDCT screening also identifies large numbers of false positives and indeterminate pulmonary nodules, of which only a fraction actually develop into cancer. Further, LDCT screening detects indolent neoplasms, which are generally adenocarcinoma, that may not otherwise cause

clinical symptoms or death (6). Overdiagnosis is an important problem because the work-up and treatment of these cancers incur additional costs, patient anxiety, and morbidity for disease that may pose no mortality threat if not otherwise treated (6, 7). Because of the current limitations in lung cancer screening, clinically relevant approaches are needed to distinguish indolent tumors versus more biologically aggressive cancers by using molecular, genetic, and quantitative imaging-based biomarkers (8, 9). As such, the report in this issue of the *Journal* by Maldonado and colleagues (pp. 737–744) is notable for its important and novel approach, in using a noninvasive, imaging-based risk stratification of patients with lung cancer in the NLST (10). Their previously described Computer-Aided Nodule Assessment and Risk Yield (CANARY) tool (11) is an innovative and promising noninvasive method to risk stratify pulmonary nodules of the adenocarcinoma spectrum. In their most recent report (10), the authors used data and images from patients with lung adenocarcinoma in the NLST to validate the CANARY tool. Specifically, they grouped 294 prevalent (detected at the baseline screen) and incident (detected on follow-up screening rounds) lung adenocarcinomas into three prognostic CANARY classes: good (accounting for 13.9% of the cases), intermediate (accounting for 62.6% of the cases), and poor (accounting for 23.5% of the cases). Overall, patients in the poor CANARY class exhibited significantly poorer progression-free survival compared with those in the good and intermediate classes, and this finding was consistent when restricted to stage I patients and in multivariable analyses. Interestingly, the CANARY classes were not prognostic for stage II, III, and IV tumors. Thus, the stratified and multivariable analyses provide compelling evidence that the observed associations are not likely attributed to biases and confounding.

The CANARY tool successfully identified a potentially vulnerable subset of lung adenocarcinomas that harbor a more aggressive tumor. As such, the findings may support more aggressive treatment of these patients, as current evidence indicates that adjuvant chemotherapy confers a survival advantage for patients with non-small cell lung cancer who have high-risk disease (12, 13). Additional research will be needed to understand the biology of these tumors, to determine whether these findings are consistent across screening populations, to understand how to personalize cancer management in these vulnerable patients, and to begin the development of analogous tools for other lung cancer histological subtypes. Nonetheless, the work presented by Maldonado and colleagues (10) shows the potential of imaging-based risk stratification as a complimentary approach in the identification and management of patients with high-risk lung cancer. Moving forward, in the context of improving lung cancer screening, inclusion of patient-specific risk factors (14, 15) and additional quantitative imaging-based biomarkers, known as radiomics (16), could also provide noninvasive methods to better discriminate benign nodules/indeterminate pulmonary nodules from malignant tumors, predict future risk of lung cancer incidence, and inform screening time intervals.

Although smoking rates in the United States have steadily declined since the 1960s (17), today nearly 18% of adults in the United States currently smoke cigarettes (18). Even after smoking cessation is successfully accomplished, former smokers remain

at significant risk of developing lung cancer. As such, lung cancer will likely remain a major public health burden for decades to come, and improvements in early detection will be remain relevant and important to improve patient outcomes of this disease. ■

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Associations between Obstructive Sleep Apnea and Glucose Metabolism More Than Meets the Eye

Sleep health has taken on a dimension of public health importance (1). The effect of sleep and sleep-disordered breathing on glucose homeostasis has, in particular, garnered much attention. To date, studies addressing the independent association of obstructive sleep apnea (OSA) and glucose metabolism have revealed conflicting results. Apart from methodological differences that pose limitations on the comparison of data from different studies, the pathogenesis of diabetes mellitus and its spectrum of preceding dysmetabolism is governed by multiple interacting endogenous and exogenous factors, as well as additional insults such as, in this context, inappropriate sleep duration or OSA, leading to many permutations of possible outcomes. Using data from the Multi Ethnic Study of Atherosclerosis (MESA) (2), a population-based study involving four ethnic groups in six U.S. centers, in this issue of the *Journal*, Bakker and colleagues (pp. 745–753) reported a significant association of moderate to severe OSA (but not sleep duration) with abnormal fasting glucose in African Americans, independent of obesity and sleep duration, of a magnitude similar to that observed in white individuals, an association not observed in the Hispanic and Chinese subgroups (3). This work is timely in light of a National Institutes of Health imperative underscoring the need for investigation of the contribution of sleep disorders to health disparities (4). Although the relationship between OSA and abnormal glucose metabolism has been described, the salient new knowledge is that the magnitude of association is equally strong in African American and white individuals (twofold higher odds) and occurs irrespective of degree of hypoxia considered (i.e., 3% vs. 4% hypopnea desaturation). Bakker and colleagues should be commended, as this work leverages a unique pairing of a multiethnic cohort and integration of polysomnogram and actigraphy-based objective sleep measures to examine sleep and metabolism.

To explain this difference among the ethnic groups, OSA may confer lesser additional risk in those already at very high background risk for dysglycemia. In support of this premise, the highest overall

prevalence of abnormal fasting glucose in this cohort appeared in Hispanics, followed in descending order by Chinese, African American, and white individuals (3). The relative prevalence of abnormal fasting glucose in those without OSA in the four ethnic groups, despite the relatively small numbers, was consistent with a previous report on incident diabetes in the 20-year follow-up of the Nurses' Health Study (5), with higher incidence in Asian, Hispanic, and black individuals than in white individuals. Furthermore, MESA is composed of participants with a mean age of about 69 years, and advancing age is a known type 2 diabetes risk factor.

Both diabetes and OSA are strongly related to obesity, and Asians have lower anthropometric thresholds for the definition of obesity, attributed to a higher percentage body fat and an increased risk for cardiovascular disease and diabetes mellitus compared with age-, sex-, and body mass index (BMI)-matched white subjects (6). In this study, the Chinese group had the lowest mean BMI and waist circumference, yet the overall prevalence of abnormal fasting glucose was the second highest among the four ethnic groups, in keeping with the consensus of the World Health Organization consultation. Whether ethnic differences in the relationship of OSA and dysglycemia would persist when adjusted for percentage body fat instead of BMI or waist circumference remains unclear.

When ethnic differences in prevalence of a disease are observed in residents from the same population, it is intuitive to consider genetic differences, with the assumption of a similar external exposure. A healthy diet high in cereal fiber and polyunsaturated fat, and low in trans-fat and glycemic load, was more strongly associated with a lower risk for diabetes among minorities than among white individuals (5). In the current study, although diet was taken into consideration in the multiethnic comparison, it would be interesting to investigate the influence of diet within each ethnic group. Lifestyle factors may vary even for the same ethnic group in different geographic locations and may change substantially over time within one community.