Hardaker and colleagues reported differences in pathophysiological determinants of AHR between younger and older patients with asthma (11). In older patients (aged 50–80 yr), AHR was predicted by gas trapping and ventilation heterogeneity in peripheral, diffusion-dependent airways, whereas in younger patients (aged 18–46 yr), AHR was predicted by ventilation heterogeneity in less peripheral conducting airways and by inflammation, as measured by exhaled nitric oxide. They suggested the gas-trapped and diffusion-dependent areas of the lung in older patients may not respond as well to conventional inhaled medications. Interestingly, disease duration was not a factor affecting AHR in either group.

What can we conclude from the present study of Dunn and colleagues (4)? First, it must be recognized that these data were derived from highly standardized randomized clinical trials, in which patients with prior exacerbations and recent need for oral corticosteroids were excluded, and in which compliance with treatment was high, so the results may not be entirely applicable in the real world. Second, although there were significant increases in exacerbations with increasing age over 30 years, projecting these data to older decades is uncertain. The risks could increase or could plateau at an older age. However, these data do resonate with clinical experience. Further studies are needed, including inflammometry to more precisely determine the cellular and molecular nature of asthma in older subjects, as well as assessment of responses to short- and long-acting β -agonists, especially the new ultra-long-acting molecules, inhaled and oral corticosteroids, and the emerging range of biological therapies. Much remains to be learned. ■

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Genomic Insights into Respiratory Outcomes after Preterm Birth

Almost 50 years ago, Northway and colleagues provided the first clinical, radiologic, and pathologic characterization of bronchopulmonary dysplasia (BPD), the chronic lung disease that follows preterm birth (1). This early report first alerted the medical community to the critical problem of severe respiratory morbidities and high mortality in preterm infants, largely as a result of the lack of surfactant therapy and insufficient neonatal respiratory care of that era. With striking improvements in perinatal care, including antenatal corticosteroids, continuous positive airway pressure, surfactant, improved neonatal ventilators and related strategies, nutrition, and other physiologic-based therapies, survival of even the most extremely preterm infants has dramatically increased over time. However, with growing survivors of extreme prematurity, BPD persists as a major problem; the overall incidence of BPD has not declined during the recent decade (2).

However, the nature of the respiratory course and number of infants with severe BPD have clearly changed with these advances in clinical practice. The classic stages of disease, including the prominent fibroproliferative lung histopathology of fatal BPD in the past, appear to be less common now, and BPD is now conceptualized as predominantly a disruption or an arrest of distal lung growth (3, 4). BPD results from complex interactions between the degree of prematurity with early disruption of lung development, the response to acute lung injury, and mechanisms of lung repair and regeneration. Notably, the new BPD primarily occurs in babies born at less than 29 weeks of gestation, with rates ranging from 40 to 60%. Preterm birth near the limits of viability at 23–24 weeks through 28 weeks of gestation disrupts the normal progression of lung development that takes place during the late canalicular, saccular, and alveolar stages of normal lung development. The timing of premature birth clearly precedes the sequential and

rapid increase in airway septation and vessel growth that normally accelerates during late gestation.

General factors commonly implicated in aberrant lung development associated with BPD include a structurally and biochemically immature lung, which enhances susceptibility to hyperoxia, infection, inflammation, oxidative stress, and mechanical injury. However, the “new BPD” often develops in preterm newborns who may have required minimal or even no ventilator support and relatively low inspired oxygen concentrations early after birth. In fact, it is now widely appreciated that the persistence of BPD is strongly linked with factors far beyond postnatal lung injury alone. Importantly, the BPD and related respiratory outcomes clearly have antenatal origins, as reflected by past epidemiologic studies on the effect of chorioamnionitis, preeclampsia, maternal smoking and drug use, and related factors. Growing data support the concept that BPD is at least partly a “fetal disease,” with the subsequent diagnosis of BPD after preterm birth reflected by early changes in placental structure and altered cord blood biomarkers, including decreased circulating progenitor cells and angiogenic markers, increased oxidative stress, and others (5–10).

Studies of preterm twins have further shown that genetic factors are likely linked with an increased susceptibility for BPD (11); however, the actual genetic basis for this association remains unknown. Past studies have identified potential gene candidates and associations of single nucleotide polymorphisms, but more recent genome-wide association studies have failed to identify specific genes that are causally related to BPD (12, 13). This observation likely reflects the multifactorial etiology of BPD, involvement of complex gene–gene and gene–environment interactions, and other biologic factors or lacked sufficient computational power to detect small contributions of genetic variants. Based on numerous laboratory-based studies performed in a wide variety of animal models during the past decades, as well as data from many clinical studies, multiple, interactive signaling pathways are implicated in the pathogenesis of BPD. Importantly, a recent study has suggested that although single-variant analysis failed to identify single nucleotide polymorphisms with genome-wide significance, pathway analysis revealed specific genes associated with BPD risk that were not observed with single-marker strategies (13).

In this issue of the *Journal*, Li and colleagues (pp. 589–596) provide a novel, important, and exciting new approach to these problems by extracting DNA from newborn blood spots that are routinely obtained from a state screening program to explore the potential contribution of rare genetic variants to the risk for BPD (14). Fifty twin pairs were studied, including 51 subjects who were subsequently diagnosed with BPD. Their report identifies 258 genes with rare nonsynonymous mutations that are related to multiple mechanistic pathways, which were further shown to be involved with lung structure and function during development. Many of these pathways were further supported from data obtained in a mouse model of BPD caused by hyperoxia exposure. Specific genetic pathways that were identified included those involved with collagen fibril organization, morphogenesis of embryonic epithelium, and regulation of Wnt signaling pathways. Thus, in contrast with genome-wide association studies data that failed to identify common variants associated with BPD, this study suggests that rare genetic variants may contribute to high risk for BPD and provides leads into specific pathways

that are likely involved. Importantly, these authors cite essential elements that may link basic studies with potential future therapeutic strategies.

These findings are important for several reasons: from a methodologic perspective, the success of performing genome and exome sequencing from neonatal blood spots that are widely available from large populations illustrates that such a strategy may be readily applicable to many diseases well beyond BPD alone. In addition, this study is an excellent demonstration of a more sophisticated approach that includes the extension of investigation beyond genome-wide association studies to include pathway analysis that further incorporates mechanistic, biologic validation studies in appropriate animal models. These data further support the highly novel concept that rare variants may be of greater importance in disease pathogenesis than previously realized.

Overall, these data further highlight the potential application of genomics toward developing novel strategies for applying “precision medicine” approaches toward improving long-term respiratory outcomes of preterm infants. Such strategies may enable earlier identification of at-risk infants and specific pathways involved with disease pathogenesis, which will allow for earlier and more specific interventions to achieve greater respiratory health after preterm birth (15). ■

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Is Pneumonia a Risk Factor or a Risk Marker for Long-Term Mortality?

Pneumonia is a leading cause of morbidity and short-term mortality (usually measured in the first 30 days after diagnosis) (1–4).

However, the potential long-term consequences of pneumonia remain an area of intense evaluation. Several studies have focused on the long-term risk for mortality among patients with pneumonia. In most studies, patients with more severe pneumonia had a higher risk for long-term mortality relative to patients with less severe pneumonia. As older patients with debilitating comorbidities, including diabetes and glucose homeostasis disturbances, are usually classified in the higher-risk categories, this could explain, at least in part, the higher risk observed among patients with more severe pneumonia (3–8).

Most previous studies have been relatively small in size or with short follow-up, restricted to patients hospitalized with pneumonia, or did not include a comparison group of patients without pneumonia. In this issue of the *Journal*, Eurich and colleagues (pp. 597–604) present a large, prospective cohort study that compares long-term mortality among adult patients enrolled during 2000–2002 with an emergency department visit or hospitalization for pneumonia and an age- and sex-matched comparison group selected among patients without pneumonia from the same settings and period (controls) (9). Investigators also used linked administrative databases to comprehensively monitor subsequent medical encounters for both pneumonia cases and patients without pneumonia. During a median follow-up of 9.8 years, long-term all-cause mortality was significantly higher among patients who had experienced pneumonia compared with controls, with an

adjusted hazard ratio of 1.65 (95% confidence interval, 1.57–1.73). In particular, deaths involving the respiratory system were more common among patients who had experienced pneumonia than among controls (24% vs. 9%).

The increased risk for long-term mortality in patients with pneumonia relative to controls was consistently observed across all age groups and for both hospital and emergency department settings. The study design also allowed the exploration of subsequent hospitalizations and emergency department visits recorded during follow-up. The rates of all-cause and pneumonia hospitalizations and emergency department visits were also increased among patients who had experienced pneumonia relative to matched controls without pneumonia.

Efforts to improve prevention and management of pneumonia are clearly necessary and would reduce the related short-term mortality. However, whether the findings reported by Eurich and colleagues could be used directly to project long-term mortality reductions associated with improvements in pneumonia prevention and management remains unclear. By necessity, these studies are nonexperimental, and accounting for factors that are difficult to measure (e.g., patients' frailty, smoking) is challenging (10). Establishing a causal association between pneumonia and long-term mortality is difficult. The potential effect of pneumonia prevention and management needs to consider whether pneumonia is a risk factor or a risk marker for long-term mortality. This distinction is important because if pneumonia is a causal risk factor, prevention of pneumonia (e.g., through effective vaccination) could indeed improve long-term survival. Alternatively, if pneumonia is only a risk marker of an underlying and possibly unrecognized process that increases the risk for

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