with the pathological structure of BPD, as seen in the lungs of preterm infants who died and in animal models (3, 7).

As the authors note, this study was limited in that the subjects with BPD were stable outpatients younger than 3 years who did not require oxygen therapy at the time of the study. Whether their findings hold true in infants with persistent severe BPD, including those with chronic ventilator-dependent hypoxemic respiratory failure, is not clear. In addition, BPD classification was based on clinical decision making, rather than a physiologic assessment such as the oxygen reduction test (11).

In an earlier article, members of this group studied D_{LCO} and its components, D_M and Vc, in full-term infants without lung disease and showed that D_{LCO} and Vc (but not D_M) correlated with the level of proangiogenic circulating hematopoietic stem/progenitor cells (pCHSPCs) (12). However, this study did not include preterm infants with or without BPD. Both pCHSPCs, also referred to as circulating progenitor cells, as well as late-outgrowth endothelial colony-forming cells, are decreased in the cord blood of preterm infants who later develop moderate or severe BPD (13, 14). Together, these findings suggest that early disruptions in the number and function of angiogenic progenitor cells, possibly by maternal complications of pregnancy known to be associated with BPD risk, may lead to impaired development of the pulmonary vasculature and sustained impaired gas exchange in preterm infants with BPD.

This study shows how a physiologic assessment, such as infant pulmonary function testing, may be used in the clinical setting to provide an estimation of impaired gas exchange in preterm infants with varying degrees of lung injury. Combining functional assays such as this with measurement of pCHSPCs and other angiogenic biomarkers in the cord blood, as well as novel imaging techniques such as quantitative pulmonary magnetic resonance imaging (15), will lead to improved disease phenotyping of preterm infants at risk for BPD. Given the spectrum of disease severity among infants with severe BPD (as determined by the currently accepted diagnostic criteria), novel methods such as these will help identify preterm neonates more accurately, permit targeted therapies for the most severely affected infants, and provide quantitative evidence of the efficacy of these interventions in young children after preterm birth (16). ■

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An Expression of Clinical Significance: Exploring the Human Genome to Understand the Variable Response to Rhinovirus

Rhinoviruses are ubiquitous respiratory pathogens that have coevolved with humans for millennia. Although historically associated with benign conditions such as the common cold, it is now appreciated that human rhinoviruses (HRVs) contribute to the pathogenicity of several major respiratory illnesses (1–7). Two recent surveillance studies identified HRV as the most common cause of community-acquired pneumonia in U.S. adults and the second most common in U.S. children (8, 9). An extensive body of

literature implicates HRV as a leading precipitant of asthma exacerbations, and mounting evidence suggests that recurrent HRV infection drives chronic airway remodeling and primary disease development in asthma (2). HRV is also the leading viral precipitant of chronic obstructive pulmonary disease exacerbations and the most frequently isolated virus in patients admitted to intensive care units with severe lower respiratory tract infection (1, 6, 7). The broad range of disease states associated with HRV may reflect a multifactorial contribution to pathogenesis involving clade-specific virulence, interactions with airway microbial communities, and the host immunologic response (7, 10, 11).

High-sensitivity molecular diagnostics have not only established a role for HRV in severe respiratory illness but also revealed that asymptomatic individuals can incidentally harbor HRV in their airways (12, 13). This has led many clinicians to question the value of a positive HRV polymerase chain reaction assay, as detection of virus may not equate to clinical significance (13). Given the wide spectrum of respiratory conditions and disease severity associated with HRV, this lack of clarity poses a significant diagnostic dilemma. There is a need for precision assays to delineate the significance of airway HRV and allow for efficient triage and patient care.

In this issue of the *Journal*, Heinonen and colleagues (pp. 772–782) directly address this need by leveraging transcriptional profiling to define the molecular signature of symptomatic HRV infection and characterize the HRV-associated host response (14). The authors identify a reproducible HRV-associated transcriptional signature in an otherwise healthy pediatric population that accurately predicts symptomatic infection when compared with healthy controls. This transcriptional signature endures across a spectrum of illness severity and includes gene expression alterations typical of the viral host response. They importantly go beyond the symptomatic versus healthy comparison to show that asymptomatic children with an HRV-positive polymerase chain reaction do not display the same host transcriptional response as symptomatic children.

The authors were able to compensate for low participant numbers in the asymptomatic HRV group by using multiple analyses that capitalized on the high dimensionality of whole-genome profiling. More specifically, the asymptomatic host response was found to be more similar to the healthy than the symptomatic response, using cluster-based methods, pathway analyses, and differential expression of a metric that summarized transcriptional response. This work highlights the limitations of our current diagnostics in identifying HRV significance. Future work could focus on validating a signature that differentiates asymptomatic from symptomatic disease in the setting of a positive HRV polymerase chain reaction.

The work by Heinonen and colleagues is a proof-of-concept study, and although it is of limited direct clinical applicability, it represents an important foundation for future work in complex populations with disproportionate severe HRV susceptibility (14). This study focused on a generally healthy and limited population (<2 yr old, evaluated at four hospitals), using a cross-sectional design. One could argue that among the target population, clinical exam alone could identify symptomatic individuals, but by defining the host transcriptional response of true symptomatic HRV infection in a study population with few confounding variables, the authors lay the groundwork for subsequent studies in more complex populations, where HRV confers significant disease burden.

With this in mind, patients with underlying immune compromise would be a key target population for future studies. Substantial infection may present atypically in this growing demographic, which is disproportionately susceptible to severe HRV-mediated disease and complications such as secondary bacterial infections (4). Longitudinal studies will also be essential. If prognostic transcriptional biomarkers identify who will develop severe infection early, this could have important implications for triage and treatment, especially as new antivirals currently in clinical trials become available (6).

Another area in which an HRV-specific transcriptional signature may prove useful is in the setting of bacterial coinfection, a well-described complication of primary HRV disease (4, 7, 11). An HRV-specific signature that rules out bacterial coinfection would allow for more targeted treatments that reduce unnecessary antibiotic use. Furthermore, transcriptional profiling holds promise for overcoming the limitations of current respiratory infection diagnostics, which are unable to identify causative pathogens in the majority of cases (8, 9, 13).

The transcriptional signature of HRV infection may also serve as a tool for investigating mechanisms of pathogenesis. Although blood provides a straightforward and relatively noninvasive medium for analysis, respiratory fluids (e.g., sputum, tracheal aspirate, bronchoalveolar lavage) would likely provide a more accurate reflection of host response at the site of active infection. Transcriptional analyses that incorporate a metagenomic deep sequencing (MDS) platform may be particularly valuable for such studies (15), as they allow for simultaneous high-throughput analyses of host and microbial transcripts as well as RNA viral genomes.

MDS has other advantages, including that it provides an opportunity to identify causative pathogens without a need for culture. Unlike microarrays (a probe-based technology), MDS is not limited to studying prespecified transcripts, and thus could even identify novel pathogens. In addition, this approach could aid in understanding the molecular basis for the disproportionately severe outcomes associated with HRV clades A and C, which our current diagnostics do not distinguish (2, 5, 10). MDS also captures commensal microbial community structure and could identify ecological changes that signal outgrowth of colonizing bacterial pathogens in the setting of an otherwise mild HRV infection. This could lead to early identification of bacterial coinfections and allow for pathogen-targeted interventions in advance of clinical deterioration.

HRVs are among the most frequently encountered and clinically significant viral pathogens in adults and children. Although most often associated with innocuous conditions, HRV can also induce severe infection and precipitate exacerbations of chronic airway diseases. Here, Heinonen and colleagues leverage an innovative approach to evaluate differential host transcriptional responses that occur in patients with asymptomatic versus pernicious HRV infection (14). This work provides a platform for both mechanistic studies of host–microbe interactions in pulmonary illness and future clinical studies of HRV infection in medically complex populations. ■

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Does Age Matter? The Relationship between Sleep-disordered Breathing and Incident Atrial Fibrillation in Older Men

The prevalence of sleep-disordered breathing (SDB) is increased in older people. Although estimates vary considerably due to the diagnostic criteria applied and methodology used, the heterogeneity of older populations also often includes comorbidity. The mechanisms for the age-related increase in SDB include a reduction in pharyngeal muscle function (1) and upper airway reflex sensitivity (2) in older people. This is in addition to age-related differences in pharyngeal morphology, including a decrease in the size of the upper airway lumen in older people (3), associated with an age-related lengthening of the pharyngeal airway (4) and a descent of the hyoid bone (5). This leads to increase in airway resistance and a predisposition to airway collapse (6), with the critical closing pressure being lower in older people than in younger people, independent of body mass index (1).

Interestingly, the central control of breathing is relatively stable in older people (7), although arousal frequency increases with age and the genioglossus response to hypoxia is reduced (8), as is the ventilatory sensitivity to hypercapnia measured during wake and sleep (9). Increased arousal rates lead to hyperventilation and relative hypocapnia, which can promote respiratory instability if arterial P_{CO_2} falls below the hypercapnic apneic threshold.

The anatomical and physiological predisposition for developing SDB with increasing age does matter because, as May and colleagues (pp. 783–791) have shown in this issue of the *Journal*, SDB, and in particular, indices of central sleep apnea (CSA) were associated with an increased risk for atrial fibrillation (AF) (10). Thus, their findings point to SDB in older people being a potential target to modify the pathophysiological consequences of aging (11).

In another prospective cohort (12), 939 older patients (⩾65 yr) with obstructive sleep apnea (OSA) were followed for 69 months. The authors of this study found that patients with untreated severe OSA had increased all-cause and cardiovascular mortality. When the cohort was further divided, patients with severe disease who