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Exhaled nitric oxide (FENO) is a noninvasive easily measurable biomarker that is proving to be an excellent surrogate for eosinophilic inflammation in the lungs of patients who have asthma. Although large-scale normative data are still awaited, preliminary studies have shown FENO to be helpful in diagnosing and assessing severity and control for asthma. FENO levels have also proven helpful in diagnosing and managing several other inflammatory lung diseases.

<b>Exhaled Breath Condensate: An Overview</b>	587
John Hunt	

Exhaled breath condensate (EBC) is a promising source of biomarkers of lung disease. EBC is not a biomarker, but rather a matrix in which biomarkers may be identified, in that way equivalent to blood, sweat, tears, urine, and saliva. EBC may be thought of either as a body fluid or as a condensate of exhaled gas. The field of EBC research has advanced gradually, with the debates surrounding an emerging field helping to pose questions and gradually leading to answers. Conscientious assay technique will likely find in EBC any substance of substantially high enough concentration in the airway lining fluid.

## **Exhaled Breath Condensate pH Assays**

597

John Hunt

Exhaled breath condensate (EBC) is the only currently available, convenient, noninvasive, ethically acceptable method of assessing airway acidity (pH), especially when it comes to repeated sampling from acutely ill patients. It remains necessary to interpret the data cautiously, because acid at any level in the airway can lead to EBC acidification, and an absence of EBC acidification does not exclude the presence of some degree of airway acidification. EBC pH measures remain the most successful manner to date to evaluate the role of airway acidification in respiratory disease.

## **Asthma Biomarkers in Sputum**

607

Joseph D. Spahn

Several inflammatory cells are thought to contribute to the pathogenesis of asthma. Among these, the eosinophil appears to be a major effector cell. This review focuses primarily on the clinical utility of sputum eosinophil counts in asthma. Several studies have shown sputum eosinophils to be associated with both asthma severity and level of asthma control. In addition, the presence of sputum eosinophilia is strongly predictive of a favorable response to glucocorticoid therapy. Conversely, the absence of sputum eosinophilia is predictive of a poor response to glucocorticoid therapy. Sputum eosinophilia also predicts asthma relapse in subjects who have their inhaled glucocorticoid reduced or withdrawn. Lastly, inhaled glucocorticoid therapy can be titrated to keep the sputum eosinophil count at or below 2%.

## **Tissue and BAL Based Biomarkers in Asthma**

623

June Y. Zhang and Sally E. Wenzel

Asthma is a heterogeneous disease with multiple phenotypes. There are no tissue or bronchoalveolar lavage biomarkers that are "specific" for asthma. Markers associated with eosinophilic, neutrophilic, and paucigranulocytic asthma are discussed here, and those for remodeling. Efforts are to compare tissue and lavage biomarkers with less invasive measures, such as sputum, serum, or exhaled breath, to improve the treatment and management of asthma.

## **Bronchoprovocation Testing in Asthma**

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Ronina A. Covar

Bronchial hyperresponsiveness (BHR) is an important feature of asthma and is useful in diagnosis, monitoring, and prognostication. It probably represents inherent elements of the disease process such as genetic predisposition, airway inflammation, and airway

remodeling. Airway inflammation likely accounts for the variable component of BHR, whereas the persistent component of BHR correlates significantly with structural changes in the airway, such as basement membrane thickness and epithelial damage. It might be this component that is resistant or refractory to the effects of available interventions. A few trials of immunomodulatory therapy have shown considerable improvements in markers of airway inflammation, without significantly modifying airway reactivity. Interventions to impact the more permanent feature of BHR are needed.

### **Urinary Leukotriene E<sub>4</sub>**

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Nathan Rabinovitch

Measurement of urinary leukotriene E<sub>4</sub> (LTE<sub>4</sub>) is a sensitive and noninvasive method of assaying total body cysteinyl leukotriene production and changes in cysteinyl leukotriene levels in specific microenvironments, such as the airway. Urinary LTE<sub>4</sub> measurements can be used as sensitive biomarkers of exposure to asthma triggers, such as air pollution and viral infections. Recent studies suggest the potential of using urinary LTE<sub>4</sub> concentrations as predictors of asthma control and markers of susceptibility to treatment with leukotriene receptor antagonists.

### **Pharmacogenetics of the $\beta$ 2-Adrenergic Receptor Gene**

665

Victor E. Ortega, Gregory A. Hawkins, Stephen P. Peters,  
and Eugene R. Blecker

Asthma is a complex genetic disease with multiple genetic and environmental determinants contributing to the observed variability in response to common antiasthma therapies. One focus of asthma pharmacogenetic research has been the  $\beta$ 2-adrenergic receptor gene (*ADR $\beta$ 2*) and its effect on individual responses to beta agonist therapy. Knowledge about the effects of *ADR $\beta$ 2* variation on therapeutic responses is evolving and should not alter current Asthma Guideline approaches, which consist of the use of short-acting beta agonists (SABAs) for as-needed symptom-based therapy and the use of a regular long-acting beta agonist (LABA) in combination with inhaled corticosteroid therapy for those asthmatics whose symptoms are not controlled by inhaled corticosteroid alone. These approaches are based upon studies showing a consistent pharmacogenetic response to regular use of SABAs and less consistent findings in studies evaluating LABAs. The emerging pharmacogenetic studies are provocative and should lead to functional studies. Meanwhile, the conflicting data concerning LABAs may be caused by such factors as small sample sizes of study populations and differences in experimental design.

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