The World Health Organization estimates that Chronic Obstructive Pulmonary Disease (COPD) will be the third leading cause of death worldwide in 2030. While most COPD patients have a long history of exposure to inhaled cigarette smoke or poor air quality, the majority of people with these exposures do not develop COPD and those who do develop COPD have heterogeneous subtypes such as emphysema, airflow obstruction, or airway inflammation. Our laboratory has used metabolomic, proteomic, and genomic studies in blood and lung to identify the molecular features associated with increased risk and progression of COPD phenotypes. We have identified several important pathways such as those in sphingolipid metabolism, antioxidant defenses, and damage-associated molecular patterns (DAMP). These findings suggest that COPD has both pleomorphic clinical features and molecular basis and that precision diagnostic and treatment strategies are needed to improve treatment outcomes.