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Project Abstract
The interstitial lung diseases (ILDs) are a family of closely related lung conditions characterized by alveolar inflammation, injury, and/or fibrosis not due to infection or neoplasia. Idiopathic pulmonary fibrosis (IPF), a fibrotic ILD affects nearly 1 in 200 older adults and carries a poor prognosis. Therapeutic options are limited, and to date no study has tested interventions that prevent the development of a fibrotic ILD. We are conducting studies that are preparatory to and requisite for future clinical trials of preventative IPF and ILD interventions. To move toward this goal, in the previous award period, we established the construct validity of a novel quantitative computed tomographic (CT)-based measure, termed high attenuation areas (HAAs), as an imaging biomarker of early, mild alveolar inflammation, injury, and fibrosis in a large cohort of community dwelling adults enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA), an ongoing NHLBI-funded prospective cohort study of 6,814 adults age 45 and older at enrollment in 2000 through 2002. These data strongly support HAA as a novel and relevant quantitative biomarker of the earliest biological changes in the lung parenchyma that later lead to ILD, yet additional work is required to move these findings into future clinical trials and into the clinic. In the current application, we propose to examine the pulmonary histopathology and biology of HAA in first-degree relatives of adults with clinically diagnosed ILD. To achieve these goals, we will initiate the Families At-Risk for ILD (FAR-ILD) study, a prospective study of adults with ILD and their first- degree relatives designed to identify adults with subclinical ILD and those at-risk for incident ILD. We will also use the MESA cohort to develop a clinical prediction model for incident radiologic ILD. Our study will provide strong evidence that will inform future studies of preventative interventions for adults at high risk of ILD. Our results will also help identify potential targetable pathways for prevention in at-risk adults and inform future phase 2 trial of a preventative intervention, such as pirfenidone, nintedanib, or N-acetylcysteine (which may be effective in subsets of individuals), or perhaps by targeting a pathway identified through our study of the biology of early subclinical ILD.