**Application number/Title:** 40946 - Understanding the Pathophysiology of Cystic Fibrosis Gene Modifiers

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**Keywords provided by the Applicant PI to describe the research project:**
GWAS, cystic fibrosis, hybrid imputation, modifier genes, mutation carriers, phewas

**Application Lay Summary:**

Genome-wide association studies (GWAS) in Cystic Fibrosis patients have identified several modifier genes. These modifier genes explain the variability in disease severity seen in Cystic Fibrosis patients with the same mutation in the causal CFTR (cystic fibrosis transmembrane conductance regulator) gene. The mechanism and physiological relevance of these modifier genes outside of CF, however, is not well understood, nor is the phenotype of CF carriers. The aim with data from the UK Biobank is to understand the impact of variation in modifier genes in individuals with functional CFTR; determine if the modifier genes show different effects in individuals who carry mutations in CFTR; and better understand the health of CFTR carriers and the genes that contribute to variability in health in carriers. We estimate these aims will require a minimum of 3 years to achieve. Defining the CFTR-carrier phenotype could have significant public health impact since 1 in 25 Europeans are carriers. Current therapies in CF may be applicable to a severe carrier phenotype, but current CF therapies that are approved or under development target CFTR or modifier genes. Therefore, the current study could contribute significantly to our understanding of the applicability and impact of these therapies in both CF and CFTR-carriers.