Dr. Fay Kastrinos

The primary objective of this career development award application is to provide the candidate, Dr. Fay Kastrinos, a gastroenterologist trained in clinical cancer genetics, with the protected time and mentored experience so that she can become an independent investigator of the genetic epidemiology and prevention of
inherited colorectal cancer (CRC) syndromes. Building on her clinical expertise and background in public health, the proposed didactic curriculum will provide her with advanced training in genetic and molecular epidemiology and research methods. Her research projects will focus on Lynch Syndrome, the most common inherited CRC syndrome. Lynch Syndrome is caused by mutations in mismatch repair (MMR) genes and its carriers have a near 80% lifetime risk of CRC and other extracolonic cancers in the absence of medical intervention. While in the last 15 years genetic testing has become available for Lynch Syndrome along with specific preventive measures for patients with gene mutations and their family members, physicians often fail to refer appropriate patients for genetic evaluation and testing. A prediction model analogous to the widely accepted BRCAPRO model for BRCA gene testing in Hereditary Breast Ovarian Cancer Syndrome has not been validated for MMR gene testing in Lynch Syndrome. Also, little is known about the prevalence and penetrance of MMR mutations in nonwhite populations and the utility of prediction models in these patients.

Recently, three clinical prediction models have been developed for Lynch Syndrome: MMRpredict, MMRpro, and PREMM$_{1,2,6}$ (prediction of mismatch repair gene mutations in MLH1, MSH2, and MSH6). The specific aims of the studies in this research proposal are: (1) to compare the performance of the three models
in identifying MMR gene mutation carriers in a multi-centered, international cohort of over 5,000 individuals evaluated for Lynch Syndrome; and (2) to assess the performance of PREMM$_{1,2,6}$ in identifying MMR mutation carriers in over 7,000 African, Asian, Latin/Caribbean American, other nonwhite, and white individuals tested for MMR mutations at Myriad Genetics Laboratories, Inc., and enrolled in the Colon Cancer Family Registry, to determine whether and how to incorporate adjustment for race and ethnicity in the PREMM$_{1,2,6}$ model. These efforts will identify the best clinical tool to provide patients with a personalized assessment of CRC risk and help us determine the true burden of Lynch Syndrome with the ability to promote cancer prevention and control.