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| **eMERGE Network: Proposal for Analysis**  Project/Manuscript Concept Sheet | |
| **Reference Number** | NT245 |
| **Submission Date** | 7/19/2017 |
| **Project Title** | Penetrance, cancer types, and outcomes of cancers associated with germline mutations in hereditary breast cancer genes and the impact of return of results of mutations for hereditary breast cancer on medical utilization and health outcomes. |
| **Tentative Lead Investigator** *(first author)* | Katherine Crew |
| **Tentative Senior Author**  *(last author)* | Wendy Chung |
| **All Other Authors** | Julia Wynn, Meghna Trivedi |
| **Sites Involved** | All sites |
| **Background / Significance** | Breast cancer (BC) affects 1 in 8 women in the United States, and 30% of women with BC have a family history of BC. Recent advances in methods to efficiently analyze hereditary breast cancer genes promises options of personalized medicine with the ability to tailor prevention and treatment of individual patients based on their genotype and to translate those recommendations into modified patient behaviors that will improve health outcomes. Thus, genetic screening for disease susceptibility, including cancer, holds great promise for informing tailored risk reduction and increased surveillance, thereby reducing morbidity and mortality. Many women with a personal and/or family history of breast cancer have mutations in BRCA1/2 or in one of any increasing number of rarer genes associated with high breast cancer risk (TP53, PTEN, PALB2, STK11) or one of the hereditary cancer genes associated with moderate risk (ATM, CHEK2, PMS2, POLE, POLD1). Many of the prior studies of these rarer or moderate risk genes have been performed in studies of high risk women and may have skewed the frequency and risk associated with mutations in these genes. They are likely to carry other genetic factors increasing the risk of breast and possibly other cancers in their families. Yet, the clinical utility of moderate penetrance genes, such as these, remains unknown. |
| **Outline of Project** | Our goal is to use the eMERGE cohort that is currently undergoing full sequence analysis and return of results for many of these hereditary breast cancer genes to study the penetrance, types of cancer, and outcomes in a less biased cohort and to understand the impact of returning this information on their medical care (cancer screening and risk reducing medications/procedures) and mortality in the short term. We will focus the screening studies on breast cancer screening in women. |
| **Desired Variables**  *(essential for analysis*  *indicated by* ***\*****)* | \*Current age, race/ethnicity, gender, and vital status  \*Cancer status (type of cancer, stage of cancer, age at diagnosis)  Family history of cancer (if feasible)  \*Breast cancer subtype (hormone receptor-positive, HER2-positive, triple-negative)  \*Type of cancer treatment (surgery, chemotherapy, hormonal therapy, HER2-targeted therapy, and radiation therapy)  \*Type of breast cancer screening (mammogram, breast ultrasound, breast MRI) and frequency prior to and after return of results; breast radiology results (according to BIRADS category) and mammographic density  \*Genetic test results for BRCA1/2, PALB2, PMS2, POLD1, POLE, PTEN, TP53, ATM, CHEK2, STK11  \*Genetic information returned to participant  \*Date of return of results  \*Diagnosis of anxiety or depression, use of anxiolytics or antidepressants |
| **Desired Data** | eMERGESeq cohort |
| **Planned Statistical Analyses** | Determine age related cancer penetrance associated with mutations in each gene (men and women)  Determine breast cancer mortality with and without germline cancer mutations, controlling for age at diagnosis, race/ethnicity, pathology, stage, and cancer treatment (men and women).  Quantify the medical impact of returning breast cancer genetic results by gene on breast cancer screening, cancer risk reduction actions, and psychiatric diagnoses (women only). We will compare change in health behaviors within a year of return of results among: 1) women with vs. without pathogenic mutations; 2) women with pathogenic mutations in moderate vs. high-penetrance genes; 3) women with pathogenic mutations vs. VUSs (for sites that report VUSs). |
| **Ethical Considerations** | None |
| **Target Journal** |  |
| **Milestones\*\*** | 9/1/17: study approval  10/1/18: delivery of data  3/1/19: first draft of paper  6/1/19: second draft of paper  8/1/19: submission of manuscript |

***\*\**** *This section should include the timeline for completion of project, including: approval, project duration, first and second draft of the paper and submission.*