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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT430 |
| **Submission Date** | 08/11/2021 |
| **Project Title** | Carfilzomib-related cardiotoxicity |
| **Tentative Lead Investigator** *(first author)* | Marwa Tantawy |
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| **All Other Authors**  |  |
| **Sites Participating** |  |
| **Background / Significance** | Cardiotoxicity, such as heart failure (HF), related to the proteasome inhibitor carfilzomib, is an increasingly recognized adverse event that contributes to the symptom burden and poor outcomes of multiple myeloma (MM) patients. Identification of risk factors for carfilzomib-associated cardiotoxicities could enable preemptive ascertainment of at-risk patients who would benefit from management options, including prioritizing the use of alternative agents or managing risk factors. Given the knowledge gap in the understanding of carfilzomib-related cardiotoxicity, a pharmacogenomic approach may identify predictive pharmacogenomic/metabolomic biomarkers of cardiotoxic adverse effects and provide an opportunity to improve cardiovascular outcomes of cancer patients in a personalized manner. Our long-term goal is to identify and institute preventive strategies for MM patients at high risk for carfilzomib-related HF, *prior to carfilzomib administration*, in order to prevent or minimize such risk. The proposed work will provide tools to enable the stratification of MM patients for cardiotoxicity risk based on pharmacogenomic and provide the basis for clinical translation of these biomarkers. Ultimately, our research will potentially lead to a paradigm shift in current clinical practice to better prevent cardiotoxicity and improve outcomes in the MM patient population and HF patients in general. |
| **Outline of Project** | 1. GWAS/WES analysis of carfilzomib-related cardiotoxicity.
2. GWAS/WES analysis of anthracycline-related cardiotoxicity.
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| **Desired Data - Common Variables\*** *(Available from the CC)* | [x] Demographics [x] ICD9/10 codes[x] CPT codes[x] Phecodes[x] BMI | [x] Common Variable Labs[x] Common Variable Meds[ ]  Geocoding 2015 ACS variables[x] Other: Case/Control status  |
| **Other Desired Data *(Available from participating sites)*** | *Please specifically list out any data elements that participating sites would collect or extract from clinical or other sources for this project (i.e. not common variables above)*  |
| **Desired Genetic Data** | [x] eMERGE I-III Merged set (HRC imputed, GWAS)[ ] eMERGE PGx/PGRNseq data set [ ] eMERGEseq data set (Phase III)[ ] eMERGE Whole Genome sequencing data set[x] eMERGE Exome chip data set[ ] eMERGE Whole Exome sequencing data set[ ] Other (not listed above): |
| **Does project pertain to an existing eMERGE Phenotype?** | [x] Yes, if so please list phenotype ID: 147, heart failure [ ] No |
| **Planned Statistical Analyses** | 1. GWAS/WES analysis of carfilzomib-related cardiotoxicity (HF).
2. GWAS/WES analysis of anthracycline-related cardiotoxicity (HF).
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| **Ethical Considerations** | IRB to be applied |
| **Target Journal** | JACC-CardioOncology |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | Estimated dates:-approval: by 10/31/21-Project duration: Sep 2021-Aug 2023-draft completion for preliminary analysis: Sep 2022-draft submission for abstracts: Sep 2022-draft submission for manuscript: Sep 2023 |

**\*Common Variables available across all datasets:**

* Demographics: sex, year of birth, decade of birth, race, ethnicity
* Codes: (repeated values & age at event): ICD, CPT, Phecodes
* BMI: (repeated value & age at event) height, weight, BMI
* Labs: (lab name, repeated lab value & age at event) Serum total cholesterol, LDL, HDL, Triglycerides, Glucose fasting/non-fasting/unknown, & White Blood Cell count
* Medications: (medication name, repeated, & age at event) Cerivastatin sodium, Rosuvastatin, Simvastatin, Fluvastatin, Pravastatin, Lovastatin, Atorvastatin, & Pitavastatin
* Other: Case/Control status on Phase I and Phase II phenotype: only on GWAS dataset participants