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| **eMERGE Network: External Collaborator Manuscript Concept Sheet** | | |
| **Reference Number**  *(to be assigned by CC)* | NT412 | |
| **Submission Date** | 11/17/2020 | |
| **Project Title** | Developing a holistic platform for skin cancer management in organ transplant recipients | |
| **Tentative Lead Investigator** *(first author)* | Lee Wheless, VUMC | |
| **Tentative Senior Author**  *(last author)* | Adriana Hung, VUMC | |
| **eMERGE Site Sponsor & Contact** | Dan Roden (VUMC) | |
| **All Other Authors** | Mary-Margaret Chren, VUMC  Allison Hanlon, VUMC  Kelly Birdwell, VUMC  LaVar Edwards, VUMC  Shilin Zhao, VUMC  Others: TBD | |
| **Sites Participating** | VUMC, others TBD | |
| **Background / Significance** | Skin cancer is the most common malignancy in the United States. Organ transplant recipients are at an increased risk of developing multiple, aggressive skin cancers, although these risks are heterogeneous even among high-risk phenotype Caucasian patients. It is not known how much of this risk is due to immunosuppressant medications, genetic variants, or the interaction between these two. Most genetic studies to date have been limited by investigating common variants, studying cohorts from the general population, and treating skin cancer diagnosis as a binary outcome. Half of all transplant patient who develop a metastatic skin cancer will have 10 or more skin cancers, indicating that the total count is clinically important. Previous GWAS and GRS studies of skin cancers have observed only modest effect sizes. By examining rare variants among a high-risk population, we are likely to identify genetic or pharmacogenomic risk factors for developing multiple skin cancers that could be more broadly generalizable.  We have already published our cohort definition (organ transplant recipients) and have validated our outcome definition (total number of skin cancers per patient). We will examine the role of rare genetic variants as measured in the eMERGE exome chip dataset, as well as maintenance immunosuppressant medications as they relate to the total number of skin cancers per patient over time. | |
| **Outline of Project** | 1. Describe the patient cohort, basic analyses to confirm known associations 2. Measure skin cancer risk by immunosuppressant 3. Measure skin cancer risk by rare genetic variants 4. Test GxE interactions for skin cancer risk | |
| **Desired Data - Common Variables\***  *(Available from the CC)* | xDemographics  xICD9/10 codes  xCPT codes   * Phecodes * BMI | * Common Variable Labs   xCommon Variable Meds   * Other: Case/Control status on Phase I and Phase II phenotypes |
| **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** | * 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?** | * Yes, if so please list   X No | |
| **Planned Statistical Analyses** | Gene-based analyses likely using SKAT-O, multiple logistic regression for medications | |
| **Ethical Considerations** | Ethical considerations around the return of genomic research results in organ transplant recipients who could potentially be identifiable by the large number of skin cancers in several patients. | |
| **Available Funding or Resources** | Skin Cancer Foundation (Wheless) $50,000 | |
| **Target Journal** | American Journal of Transplant, Journal of Investigative Dermatology | |
| **Milestones**  *(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | Project approval by January 1,2021  Data collection phase completed by April 2021  First draft of Manuscript 1 by June 2021  Initial submission of Manuscript 1 by July 2021 | |

**\*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