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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT354 |
| **Submission Date** | 7/22/2019 |
| **Project Title** | Does clinical context expand the clinical implications of actionable genetic findings and high PRS scores? |
| **Tentative Lead Investigator** *(first author)* | Hila Rasouly  |
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| **All Other Authors**  | Jordan Nestor, Atlas Khan, Enrico Cocchi, Maddalena Marasa, Natalie Vena, Wendy Chung, George Hripcsak, Krzysztof Kiryluk, and any other eMERGE investigators |
| **Sites Participating** | Columbia, other interested sites & sequencing centers |
| **Background / Significance** | Pathogenic variants in ACMG 59 and other actionable genes have major implications for clinical management of disorders causally related to mutations in those genes (e.g. management of breast/ovarian cancer in *BRCA1* mutations). More recently, polygenic risk scores (PRS) have also been proposed to be similarly actionable for individuals in the top percentile of the distribution for some complex traits such as breast cancer or coronary heart disease. However, actionable genetic findings may also have management implications for co-morbidities that are causally unrelated to the mutation. In a recent exome sequencing study, we detected ACMG mutations in 1.3% of 3,315 patients with chronic kidney disease and in each of these cases, the ACMG findings had implications for kidney care (Groopman et al., NEM 2019). For example, the detection of a *BRCA1* mutations could influence the choice and intensity of immunosuppression in patients with glomerulonephritis or those with a renal transplant. Similarly, mutations predisposing cardiomyopathy or cardiac arrhythmias had implications dialysis prescription, or prescription of diuretics and other antihypertensive therapy. These considerations suggest that actionable mutations may have implications for management of many other clinical comorbidities. A better understanding the spectrum of clinical disorders impacted by actionable genetic findings would broaden our perspective on the clinical utility of actionable mutations, and would enable data interpretation and counseling based on individual context. The purpose of this project is to explore whether actionable genetic findings and high PRS scores have clinical implications for causally unrelated comorbidities and identify common mutation- comorbidity pairs that may require further study.  |
| **Outline of Project** | We hypothesize that detection of actionable genetic mutations (such as ACMG finding) or determination of a high polygenic risk score for a complex trait will have management implications for co-morbidities causally unrelated to the genetic findings. We propose to examine all available ICD9/10 diagnoses in participants with diagnostic mutations in ACMG and other actionable genes in eMERGE III. We will also review all available ICD9/10 diagnoses in individuals in the eMERGE GWAS imputed dataset with the highest PRS scores for 8 complex disorders (Coronary Artery Disease, Atrial Fibrillation, Inflammatory Bowel Disease, Type 2 Diabetes, Breast Cancer, BMI, Chronic Kidney Disease, Hypertension). These PRS’s will be calculated in approved concept sheet NT 350 We will next review all current relevant guidelines and literature and also solicit expert opinion from eMERGE investigators, to determine whether the actionable mutations/high PRS scores would have implications for management of co-existing causally unrelated clinical conditions.  |
| **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[ ] 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** | [x] eMERGE I-III Merged set (HRC imputed, GWAS)[ ] eMERGE PGx/PGRNseq data set [x] eMERGEseq data set (Phase III)[ ] eMERGE Whole Genome sequencing data set[ ] 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** | -Tabulate the co-morbidities causally unrelated to the actionable mutations/high PRS scores- Review all current relevant guidelines and literature and also solicit expert opinion, to determine whether the actionable mutations/high PRS would have implications for management of these other clinical conditions - Determine the proportion of cases where ACMG/actionable mutations//high PRS scores have potential clinical management implications for other co-morbidities- Determine the clinical disorders most impacted by actionable mutations/high PRS scores- What are differences in clinical implications between high PRS and actionable SNV findings?- Develop general frameworks for counseling and management based on commonly encountered mutation-comorbidity pairs |
| **Ethical Considerations** | No |
| **Target Journal** | AJHG, Genetics in Medicine, etc |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | * July 2019: Introduce concept sheet
* August-December 2019: collect sequence data and common data variables
* Jan 2020 to May 2020: data analysis and solicit expert opinion
* May 2020 write paper
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