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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT405 |
| **Submission Date** | 10/01/2020 |
| **Project Title** | Considerations for return of polygenic risk scores to pediatric research participants in eMERGE4. |
| **Tentative Lead Investigator** *(first author)* | Sharice Wood (CCHMC) and Elizabeth Bhoj (CHOP) – co-first authors, contributing equally |
| **Tentative Senior Author** *(last author)* | Sara Van Driest (VUMC) |
| **All Other Authors**  | All interested members of the eMERGE4 (e4) Pediatric Subgroup of the sIRB Workgroup |
| **Sites Participating** | All sites represented by the e4 Pediatric Subgroup of the sIRB Workgroup: Coordinating Center, NHGRI, CHOP, Columbia, CCHMC, UW, VUMC, Mayo, Northwestern, Mt. Sinai (based on roster 9/22/2020) |
| **Background / Significance** | A major goal of e4 is to return calculated polygenic risk scores (PRS) within the context of a comprehensive risk assessment to a diverse cohort of research participants, including pediatric participants. PRS methods are relatively novel, and PRS have been predominantly developed for diseases affecting adults, using data from adults. Guidance for determining which PRS may be appropriate for return to pediatric research participants are lacking. Guidance is also lacking for returning PRS within the context of a comprehensive risk assessment that includes family history risk, clinical risk measures, and therapeutic recommendations to reduce risk.  |
| **Outline of Project** | The goal of this project is to develop a consensus statement of the considerations for evaluating PRS for return to pediatric research participants with examples of returnable and non-returnable phenotypes for various pediatric age groups. We will summarize and organize the discussions of the Pediatric Subgroup as we define the age ranges of actionability for each phenotype targeted PRS under consideration. We will report the criteria to be evaluated to determine whether a PRS (or phenotype targeted comprehensive risk assessment, which includes PRS, depending on the focus of the workgroup), is potentially returnable to pediatric participants. We will share expert deliberation regarding when to return a PRS or comprehensive risk that includes multiple combinations of high, “not high risk” as determined by PRS, family history and clinical factors. *The criteria to consider may include but are not limited to ethical, practical, and scientific considerations such as*: Validation of the PRS in pediatric patients OR reasonable expectation of concordance of adult and pediatric disease mechanism / pathogenesis.Actionability of a high comprehensive risk for the specific age group.Ability to measure the recommended action within e4.Anticipated risk of the recommended action for the participant and family.The phenotypes being considered by e4 provide concrete examples to be evaluated using the criteria we generate and discussed in the manuscript.Of note, we will start with the assumption that there is a published, validated PRS for each of the considered phenotypes. We will NOT evaluate the validity of specific PRS as a part of this manuscript effort, as that is beyond scope. Likewise, we will not define metrics of PRS validity, nor thresholds for defining “high risk” for PRS, family history, or clinical risk measures. |
| **Desired Data - Common Variables\*** *(Available from the CC)* | [ ]  Demographics [ ]  ICD9/10 codes[ ]  CPT codes[ ]  Phecodes[ ]  BMI | [ ]  Common Variable Labs[ ]  Common Variable Meds[ ]  Other: Case/Control status on Phase I [ ]  and Phase II phenotypes**None** |
| **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)* **None** – this is not a data analysis project |
| **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[ ]  eMERGE Exome chip data set[ ]  eMERGE Whole Exome sequencing data set[ ]  Other (not listed above): **None** |
| **Does project pertain to an existing eMERGE Phenotype?** | [ ]  Yes, if so please list [x]  No |
| **Planned Statistical Analyses** | **None**.  |
| **Ethical Considerations** | This manuscript will generate an ethical guideline for return of PRS information for pediatric participants in research studies such as e4, and may serve as a template for return to other participant populations (e.g. minorities, age groups in the adult age range, etc.). There are also commercial entities planning to return PRS data to parents of young children; while this manuscript will focus on return within the context of a research study, we may also provide insights for clinical and commercial efforts. |
| **Target Journal** | To be discussed by authors; potentially *Genetics in Medicine* vs a pediatric journal. |
| **Milestones** | September and October 2020 – Pediatric Subgroup MeetingsNovember and December 2020 – Generation of First Draft of Manuscript by Writing GroupJanuary 2021 – Circulation of Manuscript to All AuthorsFebruary 2021 – Manuscript Submission to Journal |

**\*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