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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT368 |
| **Submission Date** | 11/25/2019 |
| **Project Title** | Automated knowledge alerts and variant reclassifications in eMERGE Phase III |
| **Tentative Lead Investigator** *(first author)* | Hana Zouk |
| **Tentative Senior Author** *(last author)* | Heidi Rehm |
| **All Other Authors**  | All appropriate staff from LMM, relevant representatives from sites below. |
| **Sites Participating** | LMM, UW/KP; Geisinger, CCHMC, Harvard |
| **Background / Significance** | The variant interpretation knowledge base is dynamic and thus variant classifications can change as new cases are identified and additional population data becomes available. This poses challenges to the clinical laboratory as resources are often limited to reassess all identified variants as well as challenges to communicate changes in knowledge to referring physicians. Here we present streamlined approaches to support variant reclassification as well as automated strategies to deliver updates to physicians.  |
| **Outline of Project** | * We implemented strategies to support both the re-evaluation of reported variants as well as non-reported VUSs in a manner that balances workload and yield for identifying new evidence.
1. Variant reclassification of reported variants
* Sending alerts in real-time to sites via the GeneInsight report platform when the variant has been re-classified based on evidence arising from routine clinical testing experience.
* Using ClinVar (2 star and above status) to identify VUS assertions in ClinVar that were discrepant with our reported LP classifications.
* Using ClinGen recommendations for interpreting the loss of function PVS1 ACMG/AMP variant criterion which came out in late 2018 as eMERGE reporting was wrapping up.
1. Non-reported variant reclassification (VUS and below)
* Identifying variants that were classified as VUS in eMERGE (and therefore did not report) but have since classified as LP/P based on updated evidence.
* Using ClinVar (2 star and above status) to identify LP/P assertions in ClinVar that were discrepant with current VUS (or below) classifications
* Using ClinGen recommendations for interpreting the loss of function PVS1 ACMG/AMP variant criterion which came out in late 2018 as eMERGE reporting was wrapping up.
* Use these processes above to assess the effort and workload that is needed for this type of undertaking. This in turn would help drive recommendations on the scope and extent of reanalysis endeavors for similar projects.

\*\*\* Please note that the Baylor CSG is also developing a concept sheet for a manuscript that describes the infrastructure they built for eMERGE and will also incorporate their re-analysis strategies and results. As the content for these two manuscripts develops we may end up merging re-analysis into one manuscript. \*\*\* |
| **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 |
| **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)* * n/a
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| **Desired Genetic Data** | [ ] eMERGE I-III Merged set (HRC imputed, GWAS)[ ] eMERGE PGx/PGRNseq data set [x] eMERGEseq data set (Phase III) ***Note: As a sequencing center, we already have this***[ ] 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** | N/A-TBD |
| **Ethical Considerations** | NONE |
| **Target Journal** | Genetics in Medicine |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | **Data generation** - Done**Data review/QC:** In Progress (ETA Jan 2020)First draft: March 2020Final draft: April 2020Submission: May 2020 |

**\*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