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| **eMERGE Network: Manuscript Concept Sheet** |
| **Reference Number** *(to be assigned by CC)* | NT323 |
| **Submission Date** | 1/29/2019 |
| **Project Title** | The Reckoning: What We Found After Return of Results for 25,000 eMERGE3 participants |
| **Tentative Lead Investigator** *(first author)* | Leppig, Kathleen (KPWA/UW) |
| **Tentative Senior Author** *(last author)* | Wiesner, Georgia (Vanderbilt) |
| **All Other Authors**  | ROR workgroup members from each site Rahm, Alanna |
| **Sites Participating** | All eMERGE sites |
| **Background / Significance** |  The eMERGE (Electronic Medical Records and Genomics) Network is a national consortium of 11 sites) supported by the NHGRI that combines DNA biorepositories with electronic health record (EHR) systems for large-scale, high-throughput genetic research. In eMERGE 3, up to 25,000 patients, some with selected phenotypes or ethnic backgrounds, will have been sequenced for approximately 100 genes and SNP’s, that are known to cause human disease. Returning the genetic results (ROR) to the patients is the essential and overarching goal for the entire project, and has required the development of a “clinical pipeline” at each institution.  This pipeline was described in the manuscript by Wiesner, et al., “Returning results in the genomic era: Initial experiences of the eMERGE network”. This study used the Consolidated Framework for implementation Research (CFIR) implementation science method to identify similarities and differences between eMERGE sites in planned RoR [Damshroder, 2007 and Orlando, 2017]. For the return of results process, three essential components were identified including disclosing the results to each of the participants, informing the health care provider (HCP) of their patient’s results, and incorporating the results in the electronic health record (EHR). This study also found variability in the RoR process with multiple disclosure and notification methods used by the sites.  This manuscript proposal will continue our implementation science analysis of the RoR pipelines developed at each eMERGE site. We will evaluate the performance of the initial RoR process, identify and categorize any deviations from the initial plans. We will describe the clinical or operational situation that prompted the deviation from the defined process. We will identify adaptations to the planned ROR process over time at each site, reasons predicating the adaptation, and outcomes of the adaptation. |
| **Outline of Project** | 1. Survey all eMERGE sites for current plans or “pipeline” for disclosure (see data elements below) using the RE-AIM assessment of reach, effectiveness, adoption, implementation, and maintenance [Weisner, et al.]. This implementation science method is particularly useful when assessing the effectiveness of an intervention after implementation. The IS framework is relevant for eMERGE 3 because it is agnostic to type of disease, population, or institution. Further, IS projects are focused on experiments that are conducted in the “real world”, rather than in a tightly controlled manner (Damschroder 2009 PMID 19664226; Orlando 2017 PMID 28914267 ). See Table for metrics associated with each domain. 2. At the end of ROR, describe experience with the ROR process and adaptations made over time. We will also measure the factors prompting the adaptation and the outcome of the adaption . |
| **Desired Data - Common Variables\*** *(Available from the CC)* | [x] 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)* 1) \*Site2) \*How many participants who completed genetic testing received genomic results for each site, taking into to consideration not every site planned to provide variants of unknown significance (VUS) or normal results3) What were the circumstances that prevented participants from receiving their results4) Were there any barriers for identifying a HCP for a participant who would be informed of the genomic results?5) Were any problems identified to integrate eMERGE results into the EHR6) What were the strengths and weaknesses of each site’s proposed pipeline. 7) How did each site adapt to deviations to their pipeline8) Define adaptations to the pipeline, for each of the essential RoR components9) What were the lessons learned from developing and implementing and adapting the RoR process (or what was the real-world experience of this process)1. Flow diagram for ROR and integration with EHR 2. Process adaptation table.3. Elements for collection at completion at RoR |
| **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** | Summary statisticsDescription of RE-AIM elements of reach, effectiveness, adoption, implementation, and maintenance (See Table) Process adaptation analysis for the three components of the RoR processCharacterize variabilities for each component of the ROR process for each site |
| **Ethical Considerations** | Each eMERGE site has developed and approved IRB for this study |
| **Target Journal** | AJHG |
| **Milestones***(This section should include the key dates for completion of project, including approval, project duration, draft completion, and submission.)* | Data collection completed by June 1, 2019Manuscript draft by August 1, 2019Submission by November 1, 2019 |

**\*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

 **Documenting adaptations (needed for each site):**

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|  | **When did the adaptation happen for RoR?**  |
|  | Disclosure to Patients  | Informing Health Care Provider  | Integration into the Electronic Health Record  |
| Intervention  |   |   |  |
| Implementation strategy  |  |  |  |
| Setting  |    |    |  |
| Other  |  |  |   |

**SUGGESTED ELEMENTS FOR COLLECTION AT RETURN OF RESULTS COMPLETION**

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| ***Criteria*** | **Criteria Definition** | **Participant RoR** | **HCP RoR** | **EHR Integration** |
| ***Reach*** | number (%) and representativeness of the eligible intervention population | Number of participants sequenced/siteNumber (%) planned to be returned | Number of participants sequenced/siteNumber (%) planned to be returned by type of participant result | Number of participants sequenced/siteNumber (%) planned to be returned by type of participant result |
| ***Effectiveness*** | number (%) of participants identified by intervention | Number (%) participants received results Number (%) by type of variant (P/LP; VUS; No variant, PGX)  | Number (%) HCP received results Number (%) HCP received > 1 result Number (%) by type of variant (P/LP; VUS; No variant, PGX) | Number (%) EHR record with uploaded results Number (%) by type of variant (P/LP; VUS; No variant, PGX) |
| ***Adoption*** | number (%) and representativeness of the participating intervention sites | Number (%) of planned returned (expect 100%) by site  | Number (%) of planned disclosure (expect 100%) by site) | Number (%) of planned upload (expect 100% for positive) |
| ***Implementation*** | extent of intervention delivery as intended (integrity) and frequency of use (exposure) | Site timeline for returnNumber (%) of planned returns by initial RoR processNumber (%) of deviations to planned returnTypes of deviations to planned returnsNumber (%) Type of delivery by specialist (ie GC, etc) | Site timeline for returnNumber (%) of planned returns by initial RoR processNumber (%) of deviations to planned returnTypes of deviations to planned returnsNumber (%) Type of delivery by method (ie letter, call from GC, etc) | Site timeline for returnNumber (%) of planned EHR uploads by initial RoR processNumber (%) of deviations to planned EHR uploadNumber (%) and type of deviations to planned upload. |
| ***Maintenance*** | long-term (>6 months) impact | Analysis of Timeline; adjustments for deviations | Analysis of Timeline; adjustments for deviations | Analysis of Timeline; adjustments for deviations |

**References**

Damschroder LJ, [Aron DC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Aron%20DC%5BAuthor%5D&cauthor=true&cauthor_uid=19664226), [Keith RE](https://www.ncbi.nlm.nih.gov/pubmed/?term=Keith%20RE%5BAuthor%5D&cauthor=true&cauthor_uid=19664226), [Kirsh SR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kirsh%20SR%5BAuthor%5D&cauthor=true&cauthor_uid=19664226), [Alexander JA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Alexander%20JA%5BAuthor%5D&cauthor=true&cauthor_uid=19664226), [Lowery JC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lowery%20JC%5BAuthor%5D&cauthor=true&cauthor_uid=19664226)**.** Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci Vol 4:50, 2009

[Orlando LA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Orlando%20LA%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Sperber NR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Sperber%20NR%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Voils C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Voils%20C%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Nichols M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Nichols%20M%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Myers RA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Myers%20RA%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Wu RR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wu%20RR%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Rakhra-Burris T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rakhra-Burris%20T%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Levy KD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Levy%20KD%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Levy M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Levy%20M%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Pollin TI](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pollin%20TI%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Guan Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Guan%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Horowitz CR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Horowitz%20CR%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Ramos M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ramos%20M%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Kimmel SE](https://www.ncbi.nlm.nih.gov/pubmed/?term=Kimmel%20SE%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [McDonough CW](https://www.ncbi.nlm.nih.gov/pubmed/?term=McDonough%20CW%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Madden EB](https://www.ncbi.nlm.nih.gov/pubmed/?term=Madden%20EB%5BAuthor%5D&cauthor=true&cauthor_uid=28914267), [Damschroder LJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Damschroder%20LJ%5BAuthor%5D&cauthor=true&cauthor_uid=28914267) Developing a common framework for evaluating the implementation of genomic medicine interventions in clinical care: the IGNITE Network's Common Measures Working Group. Genet Med 20:655-663, 2017

Weisner et al., Returning results in the genomic era: initial experiences of the eMERGE network. (manuscript in preparation)