**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Reference Number** | NT244 |
| **Submission Date** | July 17, 2017 |
| **Project Title** | Harmonizing the Sequencing and Interpretation Approach for the eMERGE III Return of Results Program |
| **Authorship approach** | In addition to an overall author list, we will also detail author groupings that will have separate first and last authors for each major subtopic -See PMID:17095691 for an example of this approach  |
| **Tentative Lead Investigator (first author)** | Partners/Broad, BCM, CC representatives |
| **Tentative Senior Author (last author)** | BCM, Partners-Broad and CC PIs |
| **All other authors**  | Relevant staff from BCM, Partners-Broad, CC, NHGRI and sites  |
| **Sites Involved** | Partners-Broad, BCM, NHGRI, all sites |
| **Background / Significance** | One aim of eMERGE phase III is to sequence, interpret and return clinically relevant variants in 25,000 individuals using a NGS-based sequencing panel. The eMERGE III Seq panel was developed and validated by two CLIA laboratories and comprises the original 56 ACMG genes as well 53 genes and individual variants submitted for inclusion by participating sites. Comparable test performance and consistency in interpretation in reporting approaches are key to establishing equivalency across both centers. Here we describe the design and implementation of the eMERGE sequencing panel for eMERGE III. We aim to cover the entire process, in order to contextualize the many issues that have needed to be addressed in order to make a fully functional data flow. This high-level manuscript is expected to complement some of the more detailed efforts in specific areas.  |
| **Outline of Project** | * Process for choosing content for the eMERGE sequencing panel: ACMG56 and Site’s Top6 and SNPs
	+ Significant contributors: Gail Jarvik, Adam Gordon
* Analytical test design, validation, performance metric tracking
	+ Significant contributors: Niall Lennon, Birgit Funke, Donna Muzny, Kim Walker, Jianhong Hu
* CNV Detection
	+ Significant contributors:
* Clinical validity assessment for all genes and SNPs
	+ Significant contributors: Emily Kudalkar, Birgit Funke, Heidi Rehm, Gail Jarvik, Clinical Annotation WG, Magalie Leduc, Christine Eng
* Actionability assessment for all genes and SNPs
	+ Site-specific ROR plans
		- Mayo polygenic risk score
	+ Significant contributors: Adam Gordon, Gail Jarvik, Hana Zouk, Birgit Funke,Magalie Leduc, Clinical Annotation WG
* Pre-test launch and post-launch variant interpretation harmonization approaches across CSGs to ensure and maintain consistency in variant interpretation
	+ Significant contributors: Hana Zouk, Birgit Funke, Heidi Rehm, Clinical Annotation WG, Magalie Leduc, Eric Venner
* Approaches for return of PGx data to sites
	+ Significant contributors: Hana Zouk, Birgit Funke, Barb Klanderman, Magalie Leduc, Eric Venner, Donna Muzny, Richard Gibbs, Steve Scherer,
* Data Delivery -
	+ research; raw data
	+ clinical; EHR integration
	+ bridging research and clinical
	+ Significant contributors: Larry Babb, Sandy Aronson, EHR WG, Eric Venner, Richard Gibbs, Darren Ames, Mullai Murugan, William Salerno
* Discuss range of sequencing results being returned to patients including Indication-based returnable results, non-indication-based consensus returnable results, and non indication-based site-specific returnable results.
	+ Significant contributors: Hana Zouk, Heidi Rehm, Magalie Leduc, Christine Eng, Yaping Yang, Yunyun Jiang
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| **Desired****Variables** **(essential for analysis****indicated by \*)** | Analytical test validation parametersGene-disease strength of association for each panel geneSNV pathogenicitycalls for designed panelCSG interpretations for variants in genes |
| **Desired Data** | Data from variables listed above - all available from CSGs and Clinical Annotation WG |
| **Planned Statistical Analyses** | TBD |
| **Ethical considerations** | none |
| **Target Journal** | Science Translational Medicine (1st)AJHG (2nd)Genetics in Medicine (3rd) |
| **Milestones\*\*** | **Finalize publication strategy and delineation of author subgroup leads:**July 2017First draft: Fall 2017Submission: Winter 2018 |

**\*\*** This section should include: Timeline for completion of project, including approval, project duration, first and second draft of the paper and submission.