

eMERGE Network: ESP Conference Call Minutes

Monday, April 17th, 2017 at 3:00 p.m. EST (2:00 p.m. CST; 12:00 p.m. PST)

ATTENDEES:

Baylor: Richard Gibbs, Magalie Leduc; **CCHMC:** John Harley; **CHOP:** Hakon Hakonarson, John Connolly; **Columbia:** Chunhua Weng, Alexander Fedotov; **Geisinger:** Marylyn Ritchie, Marc Williams; **Harvard:** Beth Karlson, Scott Weiss; **KPW/UW:** Gail Jarvik, David Crosslin (CC), Eric Larson, Aaron Scrol; **Marshfield:** Peggy Peissig, Anne Nikolai; **Mayo:** Iftikhar Kullo; **Northwestern:** Rex Chisholm, Maureen Smith; **Partners/Broad:** Niall Lennon, Hana Zouk; **VUMC:** Josh Denny, Sarah Bland; **NHGRI:** Teri Manolio, Rongling Li, Ken Wiley, Sheethal Jose, Jyoti Gupta; **CC:** Josh Peterson, Jodell Jackson, Melissa Basford, Kayla Howell; **BCH:** Ingrid Holm; **ESP:** Howard Mcleod (Chair, Moffitt Cancer Center), Kim Doheny (Johns Hopkins University), Eta Berner (University of Alabama - Birmingham), Gerardo Heiss (University of North Carolina), Stanley Huff (Intermountain Healthcare), Vandana Shashi (Duke University);

ESP RECOMMENDATIONS:

1. The ESP recommended that the Network work together to capture the variability among the different sites and report these differences to the scientific community.
2. There are large datasets generated by eMERGE that are not being returned to the patients and the ESP would like to know how the Network is planning to use those datasets.
3. The ESP recommended that the Network should conduct surveys or studies comparing patients who receive or intend to receive positive, inconclusive, and negative results.
4. The ESP wanted to know how the eMERGE Network is addressing changes in variant classification overtime.
5. The ESP would like to hear more about the phenotyping and EHR integration efforts within eMERGE at the next meeting.

NOTES from ESP-PI Session:

- **Welcome, Opening Remarks, General Updates**
 - Rongling Li welcomed the PIs and ESP, and thanked them for their efforts.
 - The ESP noted that the pre-meeting materials were very helpful for describing the progress of the Network.
- **Network Intro: Summary & Response for ESP Recommendations from Oct. 2016**
 - Rex Chisholm reviewed the ESP's October 2016 recommendations and presented the Network's responses. Highlights included an emphasis on return of results and ELSI, harmonization and synchronization of sequencing center efforts, and EMR system implementation.
 - The ESP asked clarifying questions regarding response to their first recommendation, "ensure consistency in the return of results (ROR) across the Network"
 - Clinical Annotation Workgroup and ROR/ELSI Workgroup are studying and actively engaged in understanding methods for enabling consistency.
 - Clinical Annotation Workgroup is preparing a manuscript concerning discrepancies in annotation between our CSGs and ACMG recommendations.
 - ROR/ELSI Workgroup is preparing a manuscript examining the differences of ROR at each site and lessons learned from these data.
 - Each site has designed a unique Participant survey but there is a standard subset of questions across the Network that will allow for cross site analysis. Health Care Provider survey is a Network project and will be disseminated across all sites. The HCP survey is given after providers receive

the results and then there will be a follow up survey to the provider six months later. HCP survey is sent to all providers that have received a positive result for a patient.

- ESP suggested that the Return Of Results workflows at each site be collated and disseminated more broadly in order to be most scientifically useful.

- **Sequencing and Genomics Data Update**

- Note: The sequencing centers are reporting results in a consistent format between the two facilities. The Clinical Annotation & CSG Workgroups broke down reporting into:
 - Indication-based returnable results
 - Non-indication-based returnable results
 - Non-indication-based site specific returnable results
- Partners/Broad Overview: 434 clinical reports have been issued, 3579 sequences have been completed. They have received samples from all of their sites. UW, Geisinger & CCHMC have received sequencing data and Harvard will be sequenced shortly. By working closely with all of their sites, they have not encountered any serious issues that could not be resolved quickly.
 - Showed results for UW wherein they have reviewed 1103/1221 samples, mostly from a colorectal phenotype.
- Baylor Overview: 1129 reports have been issued, 6464 have been sequenced
 - 1682 patients have been reviewed both from Northwestern and Mayo. Found 4.5% indication based results and only 2.7% in the non-indication based results. These are similar findings as seen at Partners/Broad.
- David Crosslin (CC) discussed the progress of:
 - PGRNseq: Released to the network and updated to 9010 individuals.
 - eMERGE I-III reimputed data: will be released in the next two weeks. Note: There were issues with strand flipping and corrupt files.
 - eMERGE-Seq data: Will be downloaded off DNAnexus in the next few weeks.

- **Return of Results/ELSI Workgroup Update**

- Ingrid Holm and Iftikhar Kullo reviewed workgroup accomplishments, harmonizing activities & network-wide collaborations, and future efforts.
- Accomplishments included: catalogued approaches to ROR at each site; obtained supplemental funding to develop and pilot a survey of healthcare providers who are receiving genomic information as part of eMERGE III; presenting the CERC survey paper “Public attitudes toward consent and data sharing in biobank research: a large multi-site experimental survey in the US” at AJHG 2017; and developing manuscripts 1) summarizing how IRBs at the various eMERGE sites reviewed each site’s proposed return of results and 2) interview of HCPs to inform the HCP survey.
- Harmonizing activities and network-wide collaborations included: monthly workgroup calls; developing subgroups to focus on legal considerations, healthcare provider survey, and participant survey; collaborating with the outcomes workgroup on the familial implications of returning results subgroup; participating on the Outcomes Workgroup and Clinical Annotation Workgroup calls to further collaborative efforts including data collection; developing a disclosure of return of results project to detail each site’s plan for ROR in order to summarize ROR pipelines and assess similarities/differences; participating on a joint project with the Clinical Annotation Workgroup and CSGs to investigate incidental and secondary findings from the first 10,000 eMERGE-Seq participants.
- Future efforts include: developing data collection tools to study the ELSI impact of ROR, implementing the HCP survey across all eMERGE sites in order to facilitate the subgroup’s end goal of developing a set of generalizable recommendations for returning genomic sequencing results; developing a REDCap database for the participant survey to collect data across all sites; generating a best practice informed consent document for genome sequencing projects that involve ROR;

explore best practices for contacting family members and methods to increase efficiency of cascade screening; coordinate more joint projects with the Clinical Annotation and Outcomes workgroups; study the positive and negative results on patients

- **Discussion and Suggestions from ESP**

- No additional questions or concerns were raised as many issues were brought up during the presentations themselves.
- Good Network-related activities occurring throughout the eMERGE.

NOTES from ESP-NHGRI Executive Session:

The External Scientific Panel (ESP) met with members of NHGRI staff in Executive Session after the ESP teleconference held on April 17, 2017.

- The ESP recognized that the Network has made significant progress and the ESP packages that the CC prepared were informative.
- The ESP felt that the collaboration among the different working groups is evident in the presentations. The ESP members were impressed by the high number of Network-related projects instead of site-specific studies.
- The ESP recommended the Network work together to capture not only the lessons learned across the network sites but also the variability among the different sites, and produce a report describing these differences as it will benefit the broader scientific community.
- The ESP recognized that eMERGE sites are returning all negative results and a small percentage of positive results. However, there are large datasets generated by eMERGE that are not being returned to the patients and the ESP would like to know how the Network is planning to use those datasets.
- The ESP recommended that the Network conduct surveys or studies comparing patients who receive positive, inconclusive, and negative results. The ESP emphasized that there are limited studies on patients who have received or intended to receive inconclusive results, and studies on these patients would create awareness about the perspectives of both the patient and provider when dealing with inconclusive results. Adding these patients can also increase the sample size for certain phenotypes as the number of positive results is very small.
- The ESP wanted to know more about how the eMERGE Network is addressing the changes in variant classification over time. Since variant classifications do change, it may benefit the scientific community to understand how these changes occur and how the results are updated to the patients.
- The ESP members discussed that the presentations lacked information on the efforts related to Electronic Health Record (EHR) Integration and Phenotyping using the EHR. They would like to hear more about the phenotyping and EHR integration efforts within eMERGE at the next meeting.
- The NHGRI staff informed the ESP members on the beginning of consideration for a possible eMERGE phase IV. The Network has already started brainstorming ideas for a potential next phase and NHGRI is planning to hold a workshop to discuss the future of eMERGE in the fall.