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| **eMERGE Network: ESP Conference Call Minutes**Thursday, February 25, 2016 | 3:30pm EST (2:30pm CST; 12:30pm PST) |
| **Attendees:** **BCH:** Ingrid Holm; **CCHMC:** John Harley; **CHOP:** John Connolly, Hakon Hakonarson; **Columbia:** Alexander Fedotov, Ali Gharavi,George Hripcsak, Chunhua Weng; **Geisinger:** Marc Williams; **GHC/UW:** David Crosslin, Aaron Scrol; **Harvard:** Elizabeth Karlson,Shawn Murphy, Scott Weiss; **Marshfield:** Murray Brilliant; **Mayo:** Iftikhar Kullo, Stephen Thibodeau; **Mt. Sinai: Northwestern:** Rex Chisholm; **Vanderbilt:** Dan Roden; **Baylor:** Richard Gibbs; **Partners/Broad:** Birgit Funke, Stacey Gabriel, Niall Lennon,Heidi Rehm, **NHGRI:** Rongling Li, Teri Manolio, Ken Wiley,Jyoti Gupta, Kira Wong; **CC:** Paul Harris, Melissa Basford, Kayla Howell, Brianne Brucker Derveloy; **ESP:** Howard McLeod (Moffit Cancer Center), Eta Berner (University of Alabama – Birmingham), Kimberly Doheny (Johns Hopkins University), Gerardo Heiss (University of North Carolina), Stan Huff (InterMountain Healthcare), Lisa Parker (University of Pittsburgh), Vandana Shashi (Duke University) |
| **Welcome, Opening Remarks, General Updates – *Rongling Li & Howard McLeod*** |
| * Rongling welcomed the ESP members, and highlighted addition of two new eMERGE III ESP members: Kim Doheny (Johns Hopkins University) and Vandana Shashi (Duke University).
* Howard thanked the coordinating center for creation of the ESP conference documents, and expressed his excitement at the kickoff eMERGE III.
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| **Network Introduction – *Rex Chisholm*** |
| * In Phase III, the Network incorporated sequencing and a focus on return of results to participants.
	+ The Network will have ~87,000 GWAS samples available to conduct common variant analysis.
	+ The Network developed an eMERGE III sequencing panel, consisting of 109 genes (ACMG56 and 53 submitted by sites) and ~1500 SNPs.
	+ This phase of eMERGE will focus on “detailed, deep sequencing” in order to discover novel, rare and new variants, as well as further develop the knowledgebase on previously identified variants.
* In Phase III, The Network has implemented the following organizational changes:
	+ Sites: Columbia and Harvard were added. Mt Sinai and Marshfield are Network partners emeritus.
	+ Sequencing Centers: Sequencing this phase will be performed by Partners/Broad and Baylor.
	+ Workgroups: Clinical Annotation and Outcomes workgroups have been assembled. CERC and PGx workgroups have been absorbed into relevant Phase III workgroups. The Pediatrics workgroup has been discontinued, with the understanding that the work is represented in the newly formed workgroups and if pediatric specific opportunities should arise, they could be addressed based on the project. The CERC Survey workgroup continues and is wrapping up their Phase II work.
* The Network clarified that the 25,000 subjects selected for sequencing on the panel may be new subjects or part of the original cohort. The decision to enrich with Phase III phenotypes of interest is site-dependent, with mixed recruitment strategies.
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| **DNA Sequence & Analysis Pipeline – *Richard Gibbs & Niall Lennon*** |
| * Currently, the CSGs are validating sample preparation and sequencing processes, and expect to begin sequencing by May 2016. Technical conclusions indicate that both reagents are very high quality, and minor pipeline differences are being scrutinized.
* Differences in the reagents used by the CSGs were discussed. Partners/Broad is using the Illumina product, and Baylor is using the NimbleGen product. Both have similar performance in tests to date.
* ESP questioned if controls were being shared or sourced. Controls are indeed either shared or sourced, based upon practical issues such as the amount of DNA available and where it comes from.
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| **Clinical Annotation Workgroup – *Birgit Funke & Heidi Rehm*** |
| * The Clinical Annotation Workgroup was formed in response to the Network’s need to build a solid foundation for consistent interpretation of results from the eMERGE-seq panel across sites. The workgroup has developed a pipeline to assess the clinical validity of gene/disease associations and assign draft ClinGen classifications to the eMERGE-seq panel of 109 genes, ~900 site proposed SNPs and pharmacogenomic loci. Further work will include finalizing ClinGen classifications and coming to a consensus on which variants are clinically actionable and therefore, returnable (site-specific policies and procedures will impact returnability as well).
* Participant consent was discussed, with particular interest in those participants consented before the creation of the sequencing panel. A broad range of return of results options has been discussed with participants. Options presented are site dependent and cohort-specific, ranging from broad consent with the full expectation to return results if care is affected (Geisinger) to a tier system designed to engage patients and providers in the return of results process (VU).
* The Network’s plans for providing candidate gene information to patients and family members was discussed. Variant of unknown significance (VUS) results will not generally be returned to healthy patients, but GeneInsight does have a mechanism to update reports over the length of the study, so if a variant becomes implicated in disease it can be returned in the future. Further, raw data, including VUS data will be stored and available for analysis (ex: to study penetrance).
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| **Discussion and Suggestions from ESP** |
| * The ESP requested further information on the frequency of genetic testing data being returned to site EHRs, and if that was accomplished by a special pathway. The EHRI workgroup identified that a file-based transfer from GeneInsight is the optimal process for returning data to EHRs. The Network has identified local solutions, but not a generalizable solution to date.
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| **Executive Session** |
| * The ESP was pleased with the ESP packet and network presentations, and felt the investigators presented a good foundation for the future work that the Network will do. They felt that the presentations were aspirational due to the newness of eMERGE3, but the plans presented for future work were reasonable.
* The ESP expressed appreciation for how the eMERGE network had previously disseminated lessons learned from Ethical, Legal and Social Implications (ELSI) research to the scientific community and recommended that the network continue to study social and ethical issues, especially relating to the process of reporting clinically reportable variants (e.g. who is involved when decisions are made about returning results, etc). Therefore, other institutions and consortia can make use of the same practices and learn from any pitfalls. They expect to see publications on the process of gaining consistency in variant interpretation and clinical reportability.
* Regarding reporting of variants of all classes as described in the “ACMG Standards and Guidelines” to study sites (note: reporting variants of all classes to site investigators does not mean returning variants of all classes to patients’ EMRs. Sites will decide, based on their study objectives and IRB approval, which variants they will return to patients), some ESP members recommended reporting of all classes of variants to the study sites because: 1) it would increase possibilities for scientific enquiry; and 2) it would also allow the network to compare the ethical, legal, and social implications across sites of having a clinical report including information that they do not plan to report to patients. However, a few ESP members advocated the potential merits of permitting and studying different reporting practices, as well as the opportunity to study patient service seeking following reports and impact (including financial and service utilization) on institutions of different degrees of reporting.

NHGRI staff noted that reporting variants of all classes to sites likely has significant budgetary implications which the Institute will try to work through with the investigators.* The ESP expressed some concerns about having one sequencing center appearing to be leading the sequencing efforts based on the presentations given. The NHGRI staff reassured them that the two sequencing centers are working together well and communicating to harmonize data flow. One center is leading on clinical reporting using GeneInsight, which was the focus of the presentation to the ESP, and the other center is leading on sequencing data generation and management using DNANexus.
* The ESP members discussed the potential value of reinstating the pediatric working group, and ultimately felt that it was best to continue without one given that it has not been judged to be productive in the past.

**ESP Recommendations:**1. The ESP recommended that the network study the social and ethical issues involved in the process of making scientific decisions about variant annotation and reporting clinically reportable variants (e.g. who is involved when decisions are made about returning results, etc). This study could lead to a network publication.
2. The ESP recommended that both sequencing centers issue clinical reports for all variants to the sites, pending resolution of budgetary issues.
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| **eMERGE Network: Steering Committee/External Scientific Panel Meeting** October 6-7, 2016 | Bethesda, MD |
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