eMERGE Network: Steering Committee Meeting Attendance

October 6-7, 2016 in Rockville, MD

Baylor	Christine Eng
Baylor	Richard Gibbs
Baylor	Magalie Leduc
Baylor	Kim Walker
BCH	Ingrid Holm
CHOP	John Connolly
CHOP	Hakon Hakonarson
CHOP	Margaret Harr
CHOP	Frank Mentch
CHOP	Renata Pellegrino da Silva
CHOP	Patrick Sleiman
CHOP	Lyam Vazquez
CCHMC	Beth Cobb
CCHMC	John Harley
CCHMC	Todd Lingren
CCHMC	Melanie Myers
CCHMC	Bahram Namjou
CCHMC	Cindy Prows
Columbia	Wendy Chung
Columbia	Ali Gharavi
Columbia	George Hripcsak
Columbia	Krzysztof Kiryluk
Columbia	Ning Shang
Columbia	Nicholas Tatonetti
Geisinger	Kenneth Borthwick
Geisinger	David Ledbetter
Geisinger/JHU	Casey Overby
Geisinger	Sarah Pendergrass
Geisinger	Janet Williams
Geisinger	Marc Williams
GHC/UW/CC	David Crosslin
GHC/UW	Parimala Devi
GHC/UW	Adam Gordon
GHC/UW	Gail Jarvik
GHC/UW	Eric Larson
GHC/UW	Kathleen Leppig
Harvard	Vivian Gainer
Harvard	Elizabeth Karlson
Harvard	Rachel Knevel
Harvard	Shawn Murphy
Harvard	Lynn Pais
Harvard	Jordan Smoller
Harvard	Scott Weiss
Marshfield	Murray Brilliant
Mayo	Mariza Andrade
Mayo	Iftikhar Kullo
Mayo	Janet Olson
Mayo	Maya Safarova
Meharry	Samuel Adunyah
Meharry	Sid Pratap
Mt. Sinai	Aniwaa Owusu Obeng
Northwestern	Rex Chisholm
Northwestern	Geoff Hayes
Northwestern	Jennifer Pacheco
Northwestern	Luke Rasmussen
Northwestern	Laura Rasmussen-Torvik
Northwestern	Megan Roy-Puckelwartz
Northwestern	Maureen Smith
Northwestern	Justin Starren
Partners	Sandy Aronson
Partners/Broad	Birgit Funke
Partners/Broad	Maegan Harden
Partners/Broad	Niall Lennon
Partners/Broad	Lisa Mahanta
Vanderbilt	Lisa Bastarache
Vanderbilt/CC	Sarah Bland
Vanderbilt	Robert Carroll
Vanderbilt	Ellen Clayton
Vanderbilt	Josh Denny
Vanderbilt	Todd Edwards
Vanderbilt/CC	Bradley Malin
Vanderbilt	Jonathan Mosley
Vanderbilt	Josh Peterson
Vanderbilt	Dan Roden
Vanderbilt	Georgia Wiesner
NIH/NHGRI	Cecilia Dupecher
NIH/NHGRI	Sheena Faherty
NIH/NHGRI	Jyoti Gupta
NIH/NHGRI	Sheethal Jose
NIH/NHGRI	Rongling Li
NIH/NHGRI	Teri Manolio
NIH/NHGRI	Ken Wiley
CC	Melissa Basford
CC	Paul Harris
CC	Kayla Howell
CC	Jodell Jackson

Network Invitees

DNAnexus	Darren Ames
GeneInsight/Sunquest	Larry Babb

External Scientific Panel

Duke	Vandana Shashi
InterMountain Healthcare	Stanley Huff
JHU	Kimberly Doheny
UAB	Eta Berner
UNC. Chapel Hill	Gerardo Heiss
U.Pittsburgh	Lisa Parker

eMERGE Network: Summary of the eMERGE Steering Committee

October 6-7, 2016 in Rockville, MD

The first year two, Phase III eMERGE Steering Committee and ESP Meeting was held on October 6th and 7th, 2016 in Rockville, MD. In order to ensure that the Network continues on a productive note as we begin our second year, please find highlights from the Meeting below.

Presentation slides are available here (login required).

Day 1: Full-Day Session

Welcome, Opening Remarks, General Updates – *Rongling Li*

- Supplement Request Update
  - Network Supplements: The Geocoding and Impact of Return of Genomic Results on Health Care Providers supplements have been funded.
  - Site Specific Supplements: The Cascade Screening for Severe Hypercholesterolemia (Mayo) and Family network approach to assess the trickle-down effect of genetic testing (GHC/UW) supplements have been funded.
- Overall Program update:
  - The group reviewed expected race/ethnicity distribution of the data, program timeline, and dbGaP submission details.
- Goals for the meeting:
  - Update on genomic sequencing status and dataflow
  - Propose approaches of fully using the eMERGE resources
  - Share results of ongoing scientific projects
  - Report of workgroups activities, timelines, and results/products
  - Respond to the ESP recommendations
- Prospective New Affiliate Member: Meharry Medical College
  - 500 samples from Meharry with African American ancestry and early stage cancer phenotype will be sequenced by Baylor. The recruitment and sequencing timelines are being developed.

ACTION ITEM: Members are encouraged to investigate other funding mechanisms for supplements that were not funded.
ACTION ITEM: The Phenotyping Workgroup will develop an overall timeline for completion of all 42 eMERGE phenotypes.

Announcements, Opening Remarks – *Rex Chisholm*

- The workgroup co-chairs and leadership team will meet at 5:15 pm to discuss the Workgroups and Network processes.

The eMERGE sequencing panel: CSG updates on performance, content curation and sequencing progress – *Richard Gibbs (BCM), Niall Lennon (Partners/Broad), Birgit Funke (Partners/Broad), and Larry Babb (GeneInsight/Sunquest)*

- Sequencing has begun at both centers and they are now in the data generation/variant calling/annotation filtration stage of the pipeline. The panel is unique in that it includes discovery genes and SNVs in a clinical reporting setting.
- Sequencing Timeline:
  - Both sequencing centers are committed to finishing sequencing by the end of year 3 (April 2018). Reporting

will be complete as outlined in the pipeline documentation.
    - The exact sequencing timeline is an evolving document. Sequencing centers will communicate with sites directly to coordinate sample shipment, sequencing start dates, and any timeline changes that may arise.
    - Sequencing centers will create a Network-wide progress dashboard that will be updated monthly (provided through DNAnexus). Investigators will be able to query data through this tool.
- Current reagent status: Partners/Broad version 2 of the assay captures the underperforming areas from version 1. All variants that remain uncovered (for both sequencing centers) have been identified as not clinically significant.
- Next Steps:
    - Develop near real-time synchronization of variant curation.
    - Complete the addition of CNV calls to reports.
    - Complete DNANexus data schema and tools (Baylor).
- Sequencing centers have collaborated to create a de-identified case repository, GeneInsight, that is now live and ready to be populated with data from the sequencing centers' clinical reports. Partners/Broad knowledgebase data for the genes/variants on the eMERGE-Seq panel is already available. An SFTP site has been developed for Partners/Broad contributing sites to receive identified clinical reports. Baylor contributing sites will receive their identified clinical reports from DNAnexus.
- How sites incorporate, interpret, and further report lab clinical reports will be captured in a manuscript led by the Clinical Annotation workgroup. Labs are limited as they do not have complete phenotype and clinical data. The group discussed the role of clinical experts in returning results and the possibility of setting up a list of experts for eMERGE phenotypes for which ClinGen does not already have a framework.

Prevalence and Clinical Implications of Genetic Variants Associated with Familial Hypercholesterolemia in a Large Clinical Population – *Marc Williams (Geisinger)*

- Geisinger investigators concluded, per preliminary internal review of MyCode™ data, that familial hypercholesterolemia (FH) is underdiagnosed and undertreated. In order to close the care-gap, a Geisinger pharmacy fellow is looking at an innovative patient-centered, multidisciplinary approach for the delivery of genomic sequencing results and pharmacist-led lipid management to patients with FH. The FH Care Team for patient and family members is comprised of a pharmacist, PCP, clinical genomics, cardiology, OB/GYN and dietician. The FH Clinic Flow was reviewed is as follows: identification of pathogenic variant, pre-visit contact to return result, initial visit with genetic counselor or PCP for baseline assessment, risk stratification and determination of treatment goals, regular follow-up care, and specialty care as needed. Geisinger investigators are assessing process metrics and intermediate outcomes in pursuit of reducing the incidence of cardiovascular disease events.
- A PRIMUS algorithm was used to impute pedigrees with Geisinger MyCode™ data. Researchers found that there is much relatedness within their MyCode™ community health initiative, particularly at the second and third generation level. With this algorithm, researchers were able to identify an *LDLR* mutation (exon 13-17 duplication) in FH cases, and subsequent correlation to ischemic heart disease (IHD). It was noted that *LDLR* elevation in the case study pedigree was modest – not typical for someone with FH, but clearly associated with IHD. In addition, Geisinger researchers identified potential modifying effect of *PCSK9* variant in the "n" of the aforementioned pedigree. Investigators inferred that If you carry both variants, you might have an intermediate phenotype and basis for *PCSK9* inhibitor treatment.
- In conclusion, it was suggested that investigators may want to consider potentially returning results for protective alleles in clinical practice.

Variability in Assigning Pathogenicity to Incidental Findings: Insights from *LDLR* Sequence Linked to the Electronic Health Record in 1013 Individuals – *Maya Safarova (Mayo)*

- The aims of this pilot project were:
    - To assess discordance in assigning variant pathogenicity between databases/submitters and expert

reviewers
    - Describe a framework to assign pathogenicity to incidental findings from *LDLR* sequencing.
- Mayo investigators leveraged data available from the eMERGE PGx project. A detailed overview was provided of variant selection (resulting in 25 LDLR variants), clinical characteristic criteria (n=124), reviewer criteria, prediction tools used and phenotyping criteria.
- Conclusions from the pilot study:
    - Out of 178 variants, 25 putatively disruptive low-frequency and rare variants in the LDLR sequences of 1013 biobank participants
    - In ClinVar, 26% of LDLR variants were reported to have discordant interpretation at the level of clinical actionability
    - Among two independent interpreters (laboratorian and cardiologist), the discordance rate was 40% (five-tier classification)
    - Based on independent review, two LDLR variants were deemed likely pathogenic, clinically actionable and returnable (disease prevalence of 1:507; 0.20%).
- The group acknowledged limitations to their pilot study: 1) Missing data: family members' information, knowledge of additional genetic and environmental factors, and assays for LDL receptor functional activity; 2) Limited sample size and number of interpreters; 3) Test data contain restricted number of variables; 4) Limited ethnic diversity – approximately 90% Caucasian.
- Next steps were identified:
    - Conduct a network-wide comparison of variant classification of FH-causing genes (*LDLR, APOB, PCSK9*) in 25,000 individuals
    - Compare laboratory expertise vs clinical expertise
    - Integrate phenotypic elements such as LDL-C levels and implement FH phenotyping eAlgorithm
    - For VUS's, utilize an *LDLR* functional assay (ongoing work at Mayo)
- Preliminary data is being worked on via a quantitative approach: a standardized approach built on cumulative estimation of strength of each predefined criterion in the contact of specific genes and syndromes to yield more consistency in variant classification.

PMI Network Update – *Josh Denny (Vanderbilt)*

- President Obama announced the PMI Cohort Program on January 20, 2015. The PMI Working Group Report met March-September 2015, with awards announced in February 2016 and July 2016.
    - PMI Cohort Program Pilot OTA (**Vanderbilt**/Verily/Michigan/**Broad**)
    - Communications OTA (Wondros)
    - Data and Research Support Center (**Vanderbilt**/Verily/**Broad**/**Columbia**/UM/UT Houston/**Northwestern**)
    - Biobank (**Mayo**)
    - Participant Technologies Center (PTC- Scripps, Vibrent, Sage + others)
    - HPOs (Regional Medical Centers; Community Health Centers; Veterans Affairs Medical Centers)
        - Regional Medical Centers: California Precision Medicine Consortium; Columbia University Medical Center; Geisinger Health System; Illinois Precision Medicine Consortium; New England Precision Medicine Consortium; Trans-American Consortium for the Health Care Systems Research Network; University of Arizona-Tucson; University of Pittsburgh at Pittsburgh
        - Health Center Pilot Sites: Cherokee Health Systems, Knoxville, TN; Community Health Center, Inc, Middletown, CT; Eau Claire Cooperative Health Center, Columbia, SC; HRHCare, Peekskill, NY; Jackson-Hinds Comprehensive Health Center, Jackson, MS; San Ysidro Health Center, San Tsidro, CA
- Josh provided a status report of the PMI Network. He reviewed the PMI Cohort Program timeline and awards to date, highlighted important elements of the PMI Working Group Report (September 17, 2015) and discussed the "expression of interest" web portal and Patient Provided Information (PPI) development. Josh notes that PMI is

initially targeting ages 18+, but the goal is to eventually include children. Thus far, the program has recruited ~5,000 people around the US to assist in designing and testing features of the program.

- Expression of Interest (EOL) Web Portal: Built an "expression of interest" web portal as a gateway for testing to determine types of questions to ask. The group conducted community engagement studios that targeted 16 priority populations in an effort to optimize diversity and inclusivity.
    - Concerns: Trust, security, how data would be used
    - Return of value varies greatly (not one-size fits all)
- Participant Provided Information (PPI) Development: First versions of survey will be finalized soon (English/Spanish). Question domains selected for PMI cohort enrollment that will be included in the PPI modules at launch: sociodemographic data, personal habits, family health history, personal medical history, medications.
    - Healthcare access and utilization, diet, physical activity, sleep, anthropometry, occupational history, oral health, and pain will be completed through this year.
- The program is building a variety of tools to support web-based GWAS for simple and common analyses.
    - Individual level data – require process of requesting access and going through an IRB. Access policies are still in development.
    - Computation environments can take this data and export to a manipulatable environment.

EHRI Infobutton Subgroup: DocUBuild Platform – *Luke Rasmussen (Northwestern)*

- The EHRI Workgroup's Infobutton subgroup is currently developing the DocUBuild Platform, an authoring platform that promotes sharing and reuse of content. The purpose of DocUBuild is to support unique institutional needs by: 1) making content accessible via multiple modes of delivery; and 2) making content discoverable and targeted in an infobutton context.
- The consortium is invited to provide feedback, specifically what is practical and pragmatic at your institutions and within your workflows.
- DocUBuild is temporarily located at: http://bit.ly/docubuild_tmp
    - Login email: demo@emerge.com
    - Login password: emerge
- Next steps: planning some evaluations and publications in this area
    - Infobutton context elements in existing information resources (led by ClinGen)
    - Utility of prospective vs retrospective context annotation
    - Usability of a tool to annotate infobutton context
    - The DocUBuild Platform

ACTION ITEM: Review the **DocUBuild Platform**, and provide feedback to **Luke Rasmussen** regarding what is practical and pragmatic at your respective institutions and within your workflow. Login email: demo@emerge.com; Login password: emerge

Estimate of disease heritability using 4.7 million familial relationships inferred from electronic health records – *Nicholas Tatonetti (Columbia)*

- Emergency contact data is a more reliable indicator of risk of disease than self-reported demographics and problem lists, which is can be noisy and missing in EHR data.
- Relationships can be inferred by matching emergency contacts to other patients in the medical system's EHR. Roughly 3.1 Million relationships were provided/inferred in Columbia's EHR using this method. The method yielded approximately 1.5 million relationship defined in Cornell's EHR, indicating the generalizability of the method. The method has been validated against genetic data.
- Heritability studies conducted with this more accurate relationship and clinical phenotypes will have uncontrolled ascertainment bias that will be highly variable. This can be controlled by repeated subsampling. Heritability using this method of relationship inference is sensitive to noise and robust to missing data. An overall study found

significant heritability for 328 traits.

- The group discussed a clinician's responsibility to inform a patient's relatives about heritable conditions that may put the relative at risk of harm, vs HIPPA privacy requirements.
- The group discussed how to account for environment and therapeutic effect in heritability studies (ex: by matching case/controls).

Adolescent and Parent Choices about Return of Genomics Research Results: Development of Tools to Facilitate Decision Making – *Melanie Myers (CCHMC)*

- CCHMC conducted focus groups to fill the knowledge gap around adolescent perspective on return of genetic results in two phases:
    - Design and evaluate supplemental messaging for return of genomic research results from the eMERGE-Seq panel. Participants were presented with a mock eMERGE report, an online video, and paper copies of existing materials from My46.
    - Develop and refine preference models facilitate both parent's and adolescent's choices about return of results. The current version of the tool allows choices based on preventability, treatability, and age of onset with two exclusion criteria (adult onset conditions with no actionability in childhood, and carrier status).
- Lessons learned:
    - Supplemental information is needed before testing, not just when results are available.
    - Interpretation of positive/negative results varied with context.
- All groups strongly agreed that adolescent participation should depend on age, maturity level, and personality of the individual. Adolescents wanted a third party (their pediatrician) present to moderate decision making.

Evidence of hybrid vigor in a human population from PheWAS – *Todd Edwards (Vanderbilt)*

- Vanderbilt biobank and Tennessee State/US Census evidence suggests recent and ongoing admixture in US population race/ethnicity with an increase in heterozygosity.
- Increased heterozygosity is associated with an overall decreased burden of disease, specifically protection from reproductive disease (ex: menstrual disorders).
- Increased heterozygosity is also associated with increased risk for autoimmune and fibroproliferative disease (chronic asthma exacerbation).

Facilitating Investigator-Initiated Grant Applications in Genomic Medicine – *Teri Manolio (NIH/NHGRI)*

- As the Genomic Medicine field matures, the opportunity for Investigator-Initiated (as opposed to Institute-Initiated) research increases.
- Currently, the NHGRI receives few Investigator-Initiated applications in the Genomic Medicine field. The group discussed the known reasons for this (concern that NHGRI is not willing to fund, no clear home for peer review) and provided additional insight (acceptance rate of discovery vs implementation projects, partnerships with other Institutes needed). Teri shared feedback from the study sections on why Genomic Medicine applications tend to review poorly (too vague, not innovative).
- The group discussed targeting NHGRI study sections other than SEIR (DIRH, HSOD), how to work with CSR (use the language of the study section you are targeting in your application's specific aims, interact with CSR when then call you to discuss your project), and open Investigator-Initiated funding opportunities. Investigators are encouraged to apply for funding if they have ideas.

Day 2: External Scientific Panel Session

Opening Remarks – *Teri Manolio (NIH/NHGRI) & Rongling Li (NIH/NHGRI)*

- Welcome and thank you to the ESP for their expertise and contributions to the Network.

Comments from ESP Interim Chair – *Eta Berner (UAB)*

- Eta Introduced ESP members Geraldo Heiss (UNC), Stan Huff (Intermountain Healthcare), Lisa Parker (U Pittsburg), and Kim Doheny (Johns Hopkins).
- ESP will ask clarifying questions after each presentation if needed and hold in-depth comments and recommendations for the end of the day.

eMERGE Network Overview: Priorities and Goals; Review of Progress of Prior ESP Recommendations & Best Practices Topics – *Rex Chisholm (SC Chair, Northwestern)*

- Rex reviewed the Network specific aims, publication status, and responded to the recommendations made by the ESP in February of 2016: Network wide project being developed to study social and ethical issues, all variants are being provided to sites for their review.

The eMERGE sequencing panel: CSG updates on performance, content curation and sequencing progress – *Richard Gibbs (BCM), Birgit Funke (Partners/Broad) and Sandy Aronson (Partners/Harvard)*

- The CSGs provided an overview of the pipeline, the sequencing panel, the capture design, and the timeline. They also provided current progress and initial results, and outlined next steps.
- Sandy provided an update on the flow and integration of data between the two CSGs. eMERGE Network efforts show that it is possible for two discreet labs to have clinical data flow into a single shared repository (GeneInsight Knowledgebase), with the data harmonized and useable (able to be queried).
- The group discussed and clarified what data would be on which platform. Sites will have access to both raw genetic data and clinical interpretation results. VCF files will be available via DNANexus for all contributing sites. Structured results will be available as XML files via DNANexus (for Baylor sites) and Partners sFTP site (for LMM/Broad sites), and Query & Download (XLS) files will be available via GeneInsight (for LMM/Broad sites). De-identified data will be available via DNANexus (XML) and via GeneInsight (XLS) for all sites. "De-identified" in the context of the case repository is data stripped of PHI such as name, and date of birth.
- Richard clarified the status and function of the Dashboard on DNAnexus and how it will be used in the eMERGE Network to track progress and run simple queries.

ACTION ITEM: CSGs will work to develop near real-time synchronization of variant curation.
ACTION ITEM: CSGs will complete the addition of CNV calls to reports.
ACTION ITEM: Baylor will complete the DNANexus dashboard and tool development.

CERC Survey Project Update & Discussion – *Ingrid Holm (BCH) & Maureen Smith (Northwestern)*

- During Phase II, the eMERGE Network conducted a survey designed to help policymakers understand how underrepresented populations thought about biobank research (including: benefits, concerns, information needs and wiliness to participate). The hope is that the findings will be of value to those involved in biobank governance

and the development of educational materials for individuals considering taking part in biobank research.

- Results:
    - The study found little evidence that type of consent and data use affected willingness to participate in a biobank.
    - The group identifies demographic characteristics and attitudes that may help target efforts to increase wiliness to participate in biobank research.
    - Only 75% of parents willing to participate in a biobank would agree to let their child participate
    - Parents perceived fewer benefits and greater concerns for their child participating in biobank research compared to themselves.
- Next steps are to determine demographic, SES, trust and privacy issues that explain differences in parent/child willingness to participate.

Clinical Annotation Workgroup Report –*Gail Jarvik (GHC/UW)*

- Workgroup accomplishments include applying the ClinGen approach to Gene-Disease validity to develop a consensus list of genes and variants that will be returned Network-wide. A manuscript describing this process and the outcome (the variants to be returned), is in development. The group also harmonized interpretation discrepancies of previously reported variants in the eMERGE-Seq panel.
- Next steps:
    - Review the update to the updated ACMG 56 gene list to be released this winter.
    - Compile a list of Network experts on the genes/SNVs on the eMERGE-Seq panel for rapid feedback as the group considers lower penetrance/impact variants (focusing on molecular experts and care experts).
    - Develop an additional (incidental/secondary) findings manuscript.
    - Review lower penetrant risk variants. This includes defining "low penetrant" and deciding if they should be returned.
    - Ancillary study of CNVs.

ACTION ITEM: The Clinical Annotation Workgroup will develop a list of experts to support variant interpretation.
ACTION ITEM: The Clinical Annotation Workgroup will work with CSER to plan the joint meeting scheduled for February 2017.

Genomics Workgroup Report – *Megan Roy-Puckelwartz (Northwestern), Patrick Sleiman (CHOP), & David Crosslin (GHC/UW/CC)*

- The group discussed the aims of the Geocoding supplement (to enrich phenotypic data from the EHR with environmental variables to enable gene-environment interaction analysis (including SES, and food desert data). The group discussed expertise available and working with the Phenotyping Workgroup.
- Workgroup accomplishments include development of an analysis pipeline, identifying tools needed in DNAnexus, completing an in-person DNAnexus training, and outlining SPHINX updates.
- The CC is imputing and merging pre-e3 data, developing a coordinated phenotyping dataset, and recalling/annotating the PGRNSeq data.
- A subgroup has been created, focusing on the imputation and sequence alignment of the HLA region. The goal of the subgroup is to generate highly accurate HLA calls and link this to phenotype data.

ACTION ITEM: CC will make all documentation around imputed/merged dataset available to the Network.
ACTION ITEM: CC will make a coordinated phenotyping dataset available to the Network.
ACTION ITEM: CC will complete Q/C and make all documentation around the PGRNSeq data available to the Network.

Phenotyping Workgroup Report-Out – *Josh Denny (Vanderbilt) & George Hripcsak (Columbia)*

- Workgroup accomplishments to date include:
    - The first four prioritized Phase I and II Phenotypes have been (re)implemented. The group will continue to pursue (re)implementation of the remaining phenotypes. Lead authors of Phase I and II phenotype manuscripts will be provided a status summary.
    - Development/implementation of Phase III phenotypes is in progress and expected to be complete by February of 2018.
    - The Network definition of "Consistent Care" is mature. Next steps include defining and validating the definition clinically and adding it to PheKB.
- Next Steps/Discussions:
    - Phase III Phenotype development/Validation: Does the number of case/controls need to be increased? Does training/test environment need to be noted?
    - The group expressed concern over the large list of covariates in some Phase I and II phenotype data dictionaries.
    - Volunteers are converting their data model to OMOP. The group will discuss the possibility of cross-platform work.
    - Determine possible phenotypes for HLA studies.

ACTION ITEM: The Phenotyping Workgroup will continue to (re)implement the remaining Phase I and II Phenotypes.
ACTION ITEM: CC will reach out to lead authors of Phase I and II manuscripts with a status summary.
ACTION ITEM: The Phenotyping Workgroup will work to complete development/implementation of Phase III phenotypes by February 2018.
ACTION ITEM: The Phenotyping Workgroup will clinically define and validate the Consistent Care definition and add it to PheKB.

eMERGE PGx Project Update & Discussion – *Laura Rasmussen-Torvik (Northwestern)*

- Laura provided the group an overview of the aims of the workgroup, described the role and function of the group in Phase III, and gave an update on the accomplishments and progress of group project.
    - Four manuscripts have been published to date, two more are currently in review.
    - The CC remapped and recalled the PGRNSeq dataset.
    - Five projects are ongoing, with an additional 7 PGx phenotype project in progress (several other e-III phenotypes have indicated they will use PGRNseq data in addition to GWAS and e3 sequencing data).
- Next steps
    - Haplotype level analysis
    - Develop a schema to prioritize PGx Phenotypes among the rest of the e-III phenotypes
    - How to/should the group work to capture PGx outcomes outside the EHR.

EHR Integration Workgroup Report – *Sandy Aronson (Partners/Harvard) & Casey Overby (Geisinger/JHU)*

- The co-chairs provided update on work-to-date: 1) facilitating establishment of the network infrastructure for clinical genomic report delivery; 2) an upcoming network-wide paper (description of first stage of establishing a multi-lab-multi-site network infrastructure for structured delivery of results); 3) establishing a process to capture factors influencing implementation; 4) current and planned projects.
- The workgroup focused on the transfer of clinical reports in a robust manner. Co-chairs approached their workgroup goal by gathering requirements, determining the network topology and setting file formats. Note: SFTP and XML are manageable by all sites, and real-time data access is not a requirement.
- The workgroup discussed milestones the to be captured throughout this project, both network and site-specific. The

workgroup will also conduct a retrospective review of barriers as compared with collected anticipated barriers collected.

- Next Steps:
    - The eMERGE EHRI WG contributed to defining requirements for common eMERGE network infrastructure
        - EHRI community input on requirements for sites to receive lab report content
        - Implement next steps for approved network-wide paper concept sheet – NT184: Establishing Electronic Genetic Report Flow Within the eMERGE Network to Enable Genomic Clinical Decision Support
    - Facilitate next phase of network buildout
    - Establishing a process to capture factors influencing implementation
        - Site-contacts to prepare milestones and projected timelines
    - Research focus – upcoming concept sheets
        - Longitudinal study of barriers to implementation
        - IT capabilities and mechanisms for decision support delivery & reporting
    - Planned interactions and collaborations with liaison groups with the knowledge that there are multiple delivery mechanisms that should be considered.
        - ROR WG – categories of results & decision support delivery mechanisms
        - Outcomes WG – reporting process and intermediate outcome metrics
        - EHRI WG - IT capabilities and mechanisms for decision support delivery & reporting
        - Includes Infobuttons
        - Shared responsibility in some areas (e.g., user response to CDS

ACTION ITEM: EHRI Workgroup sites will prepare milestones and projected timelines to establish a process to capture factors influencing implementation.
ACTION ITEM: EHRI Workgroup will liaison with ROR/ELSI and Outcomes Workgroups.
ACTION ITEM: EHRI Workgroup will continue progress on barriers concept sheet and develop a concept sheet for IT capabilities and mechanisms for decision support delivery and reporting.

RoR/ELSI Workgroup Report – *Ingrid Holm (BCH) & Iftikhar Kullo (Mayo)*

- Collected data from all sites on return of results projects and plans at each site, as well as outcome measures – Completed
- Project to study the ELSI impact of ROR on health care providers (HCP) across the eMERGE sites
    - Applied for a supplement through eMERGE and received an award funded by the ELSI branch. Pilot study across the eMERGE sites, and subgroup of ROR/ELSI workgroup.
    - The goals of the pilot project are to develop and test a survey of HCP that can be implemented across the eMERGE Network with future funding.
    - In discussion for applying for additional NIH funding to facilitate goals of the overall study: To assess the impact of disclosure of unsolicited genetic results on provider perceptions of appropriate clinical management, including both HCPs' perceptions of clinical benefit/utility, and their perception of their responsibilities in relationship to the role of other HCPs
- Project to study the ELSI impact of ROR on patients across the eMERGE sites: Develop data collection tools to implement across sites
    - How to harmonize baseline and post-disclosure participant surveys to understand the impact of return of genomic information to participants: subgroup of ROR/ELSI. Baselines were previously developed, making harmonization difficult. Domains in baseline: disclosure. Domains in post-disclosure: privacy, intent to share with family members, decisional regret, and impact of genetic results.
- Patient Motivations Project – patient motivations for seeking elective genetic counseling in the context of clinical

genomic sequencing.
    - Richard Sharp (Mayo) is leading this project at Mayo. Discussing how to transform this into a network-wide project.
- Process of Disclosure Project – returning genomic results to eMERGE III participants, the process of disclosure
    - Georgia Wiesner (Vanderbilt) is leading this project. Goal is to develop a core set of processes that will be employed the eMERGE sites in returning results.
- IRB Perspectives Project – gather experiences at sites with IRB interactions around return of unsolicited genetic results
    - Robyn Fossey and Iftikhar Kullo at Mayo will lead this project. Goal: to learn about the alternative IRB perspectives, concerns and insights, which will be informative to investigators/IRBs outside of eMERGE.
    - As a reminder, discussions regarding how results are being returned at each site:
        - Positive results
            - Automated deposit in HER
            - Letter ("bland" vs "informative")
            - Face to face with a genetic counselor (ex: Mayo)
            - Primary care provider, specialist
            - Participant choice
        - Negative results
            - Letter (ex: Mao, but with disclaimers)
            - Placement in patient portal
- Familial Implications of ROR - family communication supplement designed to understand how to contact family members
    - Janet Williams at Geisinger leads this project, which is a collaboration with the Outcomes Workgroup.
    - Joint meetings with the Outcomes WG to coordinate efforts across the WG
- Joint publication with Clinical Annotations group – eMERGE process and criteria for actionability of variants for return – Formulating concept sheet

ACTION ITEM: ROR/ELSI Workgroup will finalize and deploy data harmonized post-disclosure survey across sites.
ACTION ITEM: ROR/ELSI Workgroup will develop a concept sheet for developing a core set of disclosure processes that will be employed across eMERGE sites in returning results.

Outcomes Workgroup Report– *Hakon Hakonarson (CHOP), Josh Peterson (Vanderbilt) & Marc Williams (Geisinger)*

- The workgroup has completed mapping the possible outcomes for returned genes and subsequently prioritized gene(s)-outcomes pairs the workgroup intends to study (added 22q with CHOP leading). It is now defining specific outcomes projects.
- Process, intermediate and clinical outcomes (not actively capturing clinical outcomes)
- Initially prioritizing the following gene-outcomes pairs:
    - Familial hypercholesterolemia (site lead: Mayo for adults & Geisinger for pediatrics)
    - Breast cancer (site lead: Columbia)
    - Polyps/Lynch Syndrome (site lead: UW)
    - HF/cardiomyopathy (site lead: Northwestern)
    - Arrhythmias (site lead: Vanderbilt)
- Outlined a process to reconcile and synchronize site outcomes assessments and provided a basic example for Familial hypercholesterolemia.
- Familial implications of ROR (Janet Williams at Geisinger)
    - Collect outcomes directly from proband around this cascade testing issue. The subgroup was formed with

representation from both the Outcomes and ROR workgroups, and meets on a monthly basis.

- Economics subgroup
  - Waiting for more info about outcomes collected
  - General approach: analysis of standardized costs attached to differences in healthcare utilization between Variant Positive (+) and Variant Negative (-) cohorts
  - Projected (outside scope of workgroup): analyze projected savings over time for when health outcomes are expected to change as a result of ROR
- Pediatrics subgroup:
  - Pediatric-specific outcomes for workgroup phenotypes
  - Focus on two phenotypes: asthma and TPMT
- Next steps:
  - Focus on completing protocols; develop standardized data collection forms; develop a workgroup manuscript around measuring outcomes for large sequenced panels.

ACTION ITEM: Outcomes Workgroup will complete protocols.
ACTION ITEM: Outcomes Workgroup will develop standardized data collection forms for prioritized gene-outcomes pairs.

External Scientific Panel: Executive Session

Attendance:

ESP: Stanley Huff (IMH); Kimberly Doheny (JHU); Eta Berner – Interim Chair (UAB); Gerardo Heiss (UNC); Lisa Parker (U Pittsburgh); Vandana Shashi (Duke)*; Howard McLeod (Mofitt)*; NHGRI: Jyoti Gupta; Sheethal Jose; Rongling Li; Teri Manolio; Ken Wiley;

- The External Scientific Panel (ESP) met with members of the NHGRI Program Staff in an Executive Session before and after the Steering Committee (SC) meeting on October 7, 2016. Since some ESP members attended the first day of the SC meeting held on October 6, 2016, Rongling provided a brief update on Day 1 of the meeting. The ESP gave a brief overview of their previous recommendations and what the Principal Investigators (PIs) have addressed in their reports to the ESP members.
- Overall, the ESP was extremely impressed with the Network activities and progress. The investigators' presentations clarified the ESP members' concerns on consistency of variant annotation, data pipeline and data sharing, and clinical data reporting. The ESP made some recommendations to improve the network research approaches according to the current progress.
- The ESP stressed that the Network should strive for consistency across sites wherever possible throughout its process of return of results (RoR). Particularly where consistency is not achieved, the Network should use the differences as a naturally occurring experiment and study the implications of the different practices. They suggested that the researchers should explore best practices among the different sites and work together to resolve any conflicts so as to ensure consistency in the RoR process.
- The ESP recommended that the Network sites create a timeline that details the period between receiving the clinical reports from the sequencing centers and returning results back to the patients. It was not clear in the presentations how long it would take before the reports are returned to the patients.
- The ESP stressed that it is critical to address the ELSI issues as well as the scientific issues that come up when PIs decide what results they will return to the patients. In addition, they should publish on challenges faced, issues unresolved, lessons learned, and best practices developed. They noted that decision-making on pathogenic and likely pathogenic variants to be reported back to patients seems to differ across sites but these differences and the reasons for them are not clear. The ESP recommended that PIs record their decision-making process on which

variants they choose to return to their patients, record the number of times PIs make changes in what was proposed to be returned, analyze these decisions systematically and then disseminate this analysis through publications. It may also be valuable to include ELSI investigators or those who have research experience/interest from a philosophy of science perspective as observers of these decision-making processes.

- The ESP had concerns on the reporting done by the sequencing centers (CSGs) and what is given back to their respective sites. They noted that inconsistency remains between the 2 CSGs on the types of reports (i.e. negative, positive, and inconclusive) being generated. NHGRI staff explained that there were budgetary constraints which prevented them from achieving full consistency between the CSGs. Baylor has an automated process for reporting while LMM has a largely manual process. However, LMM has agreed to provide specific variant categories such as variant of uncertain significance (VUS) and negative reports to some sites to achieve their scientific objectives. The ESP felt that it is necessary to assess the impact of the inconsistency between the 2 CSGs' reports on the Network goals and attempt to minimize differences across clinical sites based on the CSG to which they are assigned. This assessment can be of both ELSI and scientific significance.
- The ESP recommended that eMERGE PIs should work with the HL7 standards group through the HL7 Clinical Genetics Working Group (WG) teleconferences. They can have one person from the EHRI WG attend HL7 calls and provide input to the developers. The HL7 standard is getting a lot of support and is being adopted by several EHR vendors. This is a great opportunity for the researchers to simplify the phenotyping process for research. It will also benefit the standards group to understand the needs of the researchers.
- The ESP felt that the NHGRI Program Staff should make sure that the sites continue to collect outcomes data and study the impact on return of results for the PGx project. They asked whether, decades from now when more genetic variants are known for commonly used drugs, those new risks will be reported to relevant variant carriers among the PGx participants.
- The ESP suggested that the Network take the opportunity to describe and analyze the process of switching EMR systems and its impact on eMERGE research and implementation. Both Mayo and VU are switching from their homegrown EMR systems to Epic. It may benefit the network to hear about the sites' experience of switching EMR systems and what implications it may have. The ESP felt that the PIs should consider reporting that experience beyond the network, (e.g. publishing on how the challenges are addressed) for the benefit of others who will face similar decisions and implementation issues.
- The ESP recommended that the Network members work together to create more collaborative, network-wide products. For example, the phenotyping and EHRI WGs should work together and NHGRI staff should encourage them to do so.
- The ESP felt that investigators should consider the 'ancillary study' mechanism as a collaborative approach, which was successfully implemented by many NIH-supported studies, in order to broaden access by the scientific community to the national resource represented by the eMERGE Network.
- Lastly, the ESP encouraged the Network to actively disseminate lessons learned, best practices, experiences in conducting research, and results from the genomic discovery and clinical implementation research using EHR and biorepositories to the scientific community.

ESP Recommendations

To investigators:

- The Network should explore best practices among the different sites and work together to resolve any conflicts so as to ensure consistency in the process of return of results.
- The Network sites should create a timeline that details the period between receiving the clinical reports from the CSGs and returning results back to the patients.
- The Network should address the ELSI issues as well as the scientific issues that come up when PIs decide what

results they will return to the patients and they should publish on challenges faced, issues unresolved, lessons learned, and best practices developed.

- The Network PIs need to document their decision-making process regarding which variants they choose to return to their patients, record the number of times PIs make changes in what was proposed to be returned, analyze these decisions systematically and then disseminate this analysis through publications.
- The sites should assess the impact of the inconsistency between the 2 CSGs' reports on the Network goals and attempt to minimize differences across clinical sites based on the CSG to which they're assigned.
- The Network PIs should work with the HL7 standards group through the HL7 Clinical Genetics Working Group (WG) teleconferences.
- The Network should take the opportunity to describe and analyze the process of switching EMR systems and its impact on eMERGE research and implementation.
- The Network members should work together to create more collaborative, network-wide products.
- The investigators are encouraged to consider the 'ancillary study' mechanism as a collaborative approach in order to broaden access to the national resource represented by the eMERGE Network.
- The Network should actively disseminate lessons learned, best practices, experiences in conducting research, and results from the genomic discovery and clinical implementation research using EHR and biorepositories to the scientific community

To NHGRI:

- NHGRI Program Staff should make sure that the sites continue to collect outcomes and study the impact on return of results for the PGx project. NHGRI should ensure that any newly discovered risks are reported to variant carriers in the PGx participants.
- NHGRI Program Staff should encourage more collaborative projects among the eMERGE Network members.

Summary of Action Items

1. Members are encouraged to investigate other funding mechanisms for supplements that were not funded.
2. The Phenotyping Workgroup will develop an overall timeline for completion of all 42 eMERGE phenotypes.
3. Review the DocUBuild Platform, and provide feedback to Luke Rasmussen regarding what is practical and pragmatic at your respective institutions and within your workflow. Login email: demo@emerge.com; Login password: emerge
4. CSGs will work to develop near real-time synchronization of variant curation.
5. CSGs will complete the addition of CNV calls to reports.
6. Baylor will complete the DNANexus dashboard and tool development.
7. The Clinical Annotation Workgroup will develop a list of experts to support variant interpretation.
8. The Clinical Annotation Workgroup will work with CSER to plan the joint meeting scheduled for February 2017.
9. CC will make all documentation around imputed/merged dataset available to the Network.
10. CC will make a coordinated phenotyping dataset available to the Network.
11. CC will complete Q/C and make all documentation around the PGRNSeq data available to the Network.
12. The Phenotyping Workgroup will continue to (re)implement the remaining Phase I and II Phenotypes.
13. CC will reach out to lead authors of Phase I and II manuscripts with a status summary.
14. The Phenotyping Workgroup will work to complete development/implementation of Phase III phenotypes by February 2018.
15. The Phenotyping Workgroup will clinically define and validate the Consistent Care definition and add it to PheKB.

16. EHRI Workgroup sites will prepare milestones and projected timelines to establish a process to capture factors influencing implementation.
17. EHRI Workgroup will liaison with ROR/ELSI and Outcomes Workgroups.
18. EHRI Workgroup will continue progress on barriers concept sheet and develop a concept sheet for IT capabilities and mechanisms for decision support delivery and reporting.
19. ROR/ELSI Workgroup will finalize and deploy data harmonized post-disclosure survey across sites.
20. ROR/ELSI Workgroup will develop a concept sheet for developing a core set of disclosure processes that will be employed across eMERGE sites in returning results.
21. Outcomes Workgroup will complete protocols.
22. Outcomes Workgroup will develop standardized data collection forms for prioritized gene-outcomes pairs.

Next Meeting: February 1st and 2nd, 2017 in Bethesda, MD

emerge network
ELECTRONIC MEDICAL RECORDS & GENOMICS