eMERGE Network: ESP Conference Call Minutes

Monday, April 30th, 2018 at 2:00 p.m. EST (1:00 p.m. CST; 11:00 a.m. PST)

ATTENDEES:

Baylor: Richard Gibbs, Eric Venner; **CCHMC:** John Harley, Cindy Prows; **CHOP:** Hakon Hakonarson, Patrick Sleiman, **Columbia:** Chunhua Weng, George Hripcsak, Ali Gharavi, Alexander Fedotov; **Geisinger:** Marc Williams, Jess Goehringer, Casey Overby (JHU); **Harvard:** Scott Weiss, Sandy Aronson; **KPW/UW:** Gail Jarvik, David Crosslin (CC), Eric Larson, Aaron Scrol; **Marshfield:** Murray Brilliant, Peggy Peissig; **Mayo:** Iftikhar Kullo; **Meharry:** Sam Adunyah, **Northwestern:** Rex Chisholm, Maureen Smith, Megan Puckelwartz; **Partners/Broad:** Heidi Rehm, 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, Brittany City; **BCH:** Ingrid Holm; **ESP:** Howard Mcleod (Chair, Moffitt Cancer Center), Kim Doheny (Johns Hopkins University), Eta Berner (University of Alabama - Birmingham), Stanley Huff (Intermountain Healthcare), Vandana Shashi (Duke University);

ESP RECOMMENDATIONS:

1. The RoR workgroup should publish either a manuscript or a report to the genomics community to create awareness of the initial RoR findings.
2. The Network should explore collaborations with the UDN on topics related to variant classification and VUS.
3. The Network should address some of the reasons for the delay between receiving clinical reports from sequencing centers and returning these results to the patients by the next ESP meeting.
4. The investigators should create an outline of their plans for the next 1.5 years of eMERGE and the goals they wish to achieve by the end of the 5th year.

NOTES from ESP-PI Session:

- **Welcome, Opening Remarks, General Updates**
  - Howard McLeod and Teri Manolio welcomed and thanked the Network for their service and work.
- **Network Intro: Summary & Response for ESP Recommendations from Oct. 2016**
  - Version 1 of the eMERGEseq dataset (n=15,745) has been released to the Network for analysis. The CC is coordinating with dbGaP to upload this data and make it widely available.
  - 23,000 eMERGEseq samples have been sequenced and over 13,000 clinical reports have been issued. Return of positive and negative results has commenced across the Network. Outcomes forms have also been deployed for subsequent data collection.
  - The Network continues to have substantial citations of publications with approximately 24,500 cumulative citations - a 23% increase since October 2017. 665 projects are either published or in-development. Many projects in Phase III are in development as sites were awaiting data to be released from the eMERGEseq dataset.
  - There has been over 1200 external downloads of the eMERGE data on dbGaP to date, however, once downloaded, many groups re-use the eMERGE data over time.

- The Network has recently initiated paneled discussions during Steering Committee meetings in order to discuss and collate lessons learned across eMERGE's disciplines of focus. Winter 2018 focused on Return of Results; Summer 2018 will focus on Phenotyping; Fall 2018 will focus on EHR Integration; Winter 2019 will focus on Outcomes; Spring 2019 will focus on Genomics and aspects of genomics medicine.
- Select responses to the ESP recommendations were presented. Please note that the full recommendation responses can be found in the ESP Packet and Background Materials.
    - Barriers and complications related to computable phenotyping include the complexity of the phenotypes. Through active project management the group has been able to organize and streamline development. The Network is also in the process of converting to the Observational Health Data Sciences Informatics (ODHSI) Observational Medical Outcomes Partnership (OMOP) common data model which will help streamline implementation.
    - The ROR workgroup uses surveys to address the use of genetic data, to gather participant and provider reactions and to understand initial and reclassified clinical results.
    - Columbia is piloting a project on Clinical Decision Support for eight ACMG genes. Outcomes and Phenotyping discussed piloting automated phenotype approaches to collect outcomes data after return of result. NT272, *Design and testing of clinical decision support system for 59 ACMG genes included in the eMERGEseq panel*.
    - The CSGs produced a manuscript detailing best practices and will be submitting to Genome Medicine imminently. NT244, *Harmonizing the sequencing and interpretation approach for the eMERGE III return of results program*.

- **Return of Results Panel: Lessons learned across the Network**
    - Progress to Date
        - The ROR/ELSI Workgroup has compiled and published "Ethical Considerations Related to Return of Results from Genomic Medicine Projects: The eMERGE Network (Phase III) Experience" Fossey et al, J Person Med, 2018.
        - The group examined the Institutional Review Board (IRB) process at nine academic institutions in the electronic Medical Records and Genomics (eMERGE) Network, for proposed electronic health record-based genomic medicine studies, to identify common questions and concerns. Based on a their analysis, the group generated a list of general recommendations, as well as specific IRB recommendations.
    - ROR Processes in eMERGE
        - The ROR/ELSI Workgroup, led by Georgia Wiesner and Kathy Leppig, worked to define the return of results processes across sites. Georgia and Kathy discovered that the majority of sites are returning results to participants by a genetic counselor and later upload to the EHR. However, a subset of sites first input the result into the EHR, notify the participant that there is a result, and then return the result through the PCP.
            - Results are integrated into the EHR both through scanning of the PDF as well as integration of the XML document.
    - ROR of Positive and Negative Results
        - Nearly all sites have begun returning both negative and positive results.
        - There is variation among sites on what result is returned and how:
            - Geisinger, Harvard & CHOP will not return negative results to participants.

        - Variability across sites in terms of who handles and returns the result (specialist, genetic counselor, or PCP) and process of returning result (phone, in person or mail).
        - Some sites allow participants to decide what type of result to receive and the method of receiving the result.
    - These differences and variability will inform provider processes and affect participant acceptance and utilization of results.
- How can eMERGE contribute to best practices for return of results?
    - Based on a review of return of results across eMERGE sites, the group discovered there is a broad spectrum of ROR:
        - Some cohorts are unselected, while other cohorts are selected for a particular trait
        - One site is selecting participants based on genotype
        - Choice vs no choice for return of secondary findings
        - Negative results returned at some sites, while not returned at others
        - Variation in timing of placement of results in EHR across sites
        - Randomization vs observational study design
        - Pediatric vs adult
    - Moreover, there is a range of what is being returned across sites:
        - Pathogenic/Likely Pathogenic at most sites
        - Primary vs secondary pathogenic and likely pathogenic
        - Variants of unknown significance by KPW/UW
        - PGx variants by select sites
        - Selected SNPS
        - No carrier status
    - Finally, sites are encountering a range of different scenarios after return of a results, including:
        - Approaches to returning results when participants are deceased
        - Patients who refuse to engage with genetic counseling
        - Different agenda than dictated by results: “Why doesn’t this explain the cancer in my family?”
        - Results revealing new disease
        - Impact of results at different ages and implications for genomic screening.
    - The Network can leverage this documented variability in process and experience in order to inform the ROR process for genomic medicine, and develop recommendations as an outcome of eMERGE Phase III Return of Results/ELSI.
- Ongoing and Proposed New Projects
    - Ongoing projects include: eMERGE ROR Process Description; Participant Surveys; HealthCare Provider (HCP) Surveys; Familial Implications of ROR.
    - Proposed new projects include: Optimizing single IRB review for genomic research; Deliberate ignorance of genomic results; Preferences for research updates among eMERGE biobank participants (collaboration with EHRI Workgroup)
    - The group has also developed novel tools to assist with return and disclosure of updates
        - Web-based tools for secondary findings (Harvard, Geisinger) and interpretation of variants (KPW/UW, Mayo)

        - Ongoing collaboration with eMERGE workgroups (EHRI, Clinical Annotation, and Outcomes) and CSER
    - **ESP Comments**:
        - ESP suggests examining opportunities across NHGRI collaborations to share studies, specifically the Undiagnosed Disease Network (UDN). There is potential for collaboration as they work heavily with variants of unknown significance.
        - Are all the participants that are receiving negative results being surveyed as well?
            - Some sites are conducting qualitative interviews of participants receiving negative results. The auxiliary R01 Healthcare Provider (HCP) grant provides funding towards interviews of providers receiving negative results.
        - Clarification of how the pace of the RO1 (HCP) affects the dissemination to the community.
            - The RO1 has begun, and will overlap with eMERGE for the next several years, and then will provide the opportunity to continue to compile the data even after the eMERGE grant ends.
            - The ROR group cautioned to not withhold data for the end of the RO1 grant but rather continually publish best practices and lessons learned as they are generated in a timely manner.
        - Reviewing literature on research concerning the return of infectious disease findings post blood donation draws may help inform incidental findings return in eMERGE.
        - Central to eMERGE work are issues of penetrance and pathogenicity and the relationship to phenotypic expression.
        - There are potentially interesting ethical issues related to duty to warn and how these implications affect not only the individual but also the family.
        - Dealing with aspects related to 'genetic' information as opposed to other types of information that would have further implications beyond the participants is a topic of consideration and discussed heavily in the ACMG secondary findings recommendations.
- **Year 5 Extension**
    - Due to an array of delays including, custom panel creation, harmonizing and sequencing of samples across two CSGs, full execution of return of clinical reports/results to all sites, as well as suboptimal funding for the amount of work requested in this phase, the sites will not have adequate time to return results and capture outcomes by end of year IV. Nor will the workgroups be able to execute all that they have been tasked with. Based on expert recommendations from the eMERGE & Beyond: The Future of Electronic Medical Records and Genomics workshop, a one year extension would allow the Network to generate more meaningful results.
    - The eMERGE PIs have submitted applications for extension to the NHGRI, which will then be submitted for review during the May 2018 Council. If approved, a one-year extension of the eMERGE III Return of Results Program would begin June 1, 2019 and conclude April 1, 2020.
    - Please note, this indicates that the ESP would be asked to continue to advise the Network for an additional year.
- **Discussion and Suggestions from ESP**
    - Is the ROR/ELSI Workgroup investigating participant's change in behavior as a result of ROR?
        - Questions related to behavioral changes, as well as discerning lifestyle changes, are included on the Participant Survey. Additionally, actions taken post-return of result are being investigated by the Outcomes Workgroup as viewed in the EHR. Finally, ROR is also

asking HCPs via the HCP Survey if they had provided any referrals or recommendations to the participants as well.

- Coordination between Outcomes and development of instruments between ROR
    - The ROR and Outcomes group works closely including providing timing and implementation of surveys. Many members overlap between the two workgroup. Participants are also being asked many similar questions that will solidify the findings from the EHR in the Outcomes surveys.
- To inform group working on ROR, Outcomes, and ELSI research, it would be beneficial to produce a publication documenting process of development of study investigating a participant's behavioral change via the Participant Survey, HCP Survey and Outcomes Forms.
- A major aim in eMERGE is to allow for machine readable information and the Network is taking steps to support that. This will consist of going from EHR integration PDF to XML result. The PDF result currently serves as a backup, leading up to the machine readable XML which will allow for parsing and triggering of clinical decision support thus streamlining the whole result utilization process.
- Disseminate the key barriers, successes, and lessons the EHRI workgroup has learned from their work.
    - Fall Steering Committee/ESP meeting will feature an EHRI panel discussing these topics and will schedule to occur on ESP day.
    - Rex notes that sites have worked closely with the CSGs to develop and iterate upon the XML file formats in order to accommodate site-specific needs per their IRBs and EHR systems.
- The Network should provide future updates on status on the OMOP conversion and challenges associated with the process.
    - The OMOP group has developed a phased approach to implementing the OMOP-CDM across all sites. In Phase I, sites converted their eMERGE cohorts to OMOP v5.2 (complete). In Phase II, sites will implement Columbia's OMOP version of the Network's Type 2 Diabetes phenotype, which was selected as it had previously been run across all sites except Harvard.
    - Sites are tasked with documenting their experiences to compare implementation of the T2D OMOP phenotype query against the original run of the query. Sites will then select one or two additional eMERGE phenotypes to run on OMOP in order to further validate the common data model and ability to easily transfer code for phenotypic queries. Sites will also work on testing the various tools that sit on top of the CDM. The intent is to draft a paper detailing these efforts.
- Updates on educational efforts and training.
    - ClinGen action sheets and ACMG recommendations are a launching point for education.
    - Action sheets were created for actionable secondary findings which are in the process of being developed. They were used to provide information to non-geneticists for these conditions. These action sheets are essentially the first step of clinical decision support artifact.
    - Geisinger and Columbia are incorporating action sheets. This effort will help address these education issues and the groups aim to have examples of these artifacts shortly. They then

plan to disseminate these elements in front of end users to determine how the information is being utilized.

Continue to next page to review the ESP Executive Session Minutes.

eMERGE Network: ESP Executive Session Minutes

Monday, April 30th, 2018 at 3:00 p.m. EST (2:00 p.m. CST; 12:00 p.m. PST)

ATTENDEES:

External Scientific Panel: Eta Berner (University of Alabama, Birmingham), Kim Doheny (Johns Hopkins University), Gerardo Heiss (University of North Carolina)*, Stanley Huff (Intermountain Healthcare), Howard McLeod (Chair, Moffitt Cancer Center), Vandana Shashi (Duke University), Lisa Parker (University of Pittsburgh); **NHGRI**: Jyoti Gupta, Sheethal Jose, Rongling Li, Teri Manolio, Ken Wiley;

**Absent at the meeting, but reviewed the ESP packet and provided recommendations.*

NOTES:

The External Scientific Panel (ESP) met with members of NHGRI staff in Executive Session after the ESP teleconference held on April 30, 2018. The ESP members appreciated the materials provided and felt eMERGE was making good progress. They were impressed with the Return of Results (RoR) workgroup presentation and believes that it has the potential to have a major impact on the field of genomic medicine. They recommended that the RoR workgroup publish either a manuscript or a report to the genomics community to create awareness of the initial findings that will come out of the projects presented by the RoR workgroup during the call. The ESP stated that the lessons learned from RoR, along with the Electronic Health Record (EHR) Integration and Outcomes research, will be valuable contribution to the genomic medicine community from eMERGE Phase III.

The ESP felt that eMERGE has the potential to establish various cross-NHGRI collaborations. One such collaboration could be with the Undiagnosed Disease Network (UDN) program on topics related to variant classification. Since the UDN receives a high number of variants of unknown significance (VUS), they may benefit from results generated from the eMERGE Network.

They noticed that most sites experienced delays between the time they receive their clinical reports from the sequencing centers and the time the sites begin returning these results to the patients. They recommended that the Network should address some of the reasons for this delay by the next ESP meeting. They also recommended that the investigators create an outline of their plans for the next 1.5 years of eMERGE and the goals they wish to achieve by the end of the 5th year.

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