eMERGE Network: PI Group Meeting Minutes

April 2019 ESP Conference Call

Monday, April 29th, 2019 at 2:00 p.m. EST (1:00 PM CST; 11:00 a.m. PST)

ESP: Howard McLeod, Kim Doheny, Lisa Parker, Stan Huff, Eta Berner, Vandana Shashi; **Baylor:** Richard Gibbs, Mullai Murugan; **BCH:** Ingrid Holm; **CCHMC**: John Harley, Bahram Namjou, Cindy Prows; **CHOP:** John Connolly, Hakon Hakonarson, Patrick Sleiman; **Columbia:** Chunhua Weng, Aileen Espinal, Stephanie Tang, Alex Fedotov, George Hripcsak; **Geisinger:** Marc Williams, Nephi Walton **Harvard:** Beth Karlson, Scott Weiss; **John Hopkins University**: Casey Overby Taylor, **KPW/UW:** Gail Jarvik, David Crosslin (CC), Eric Larson; **Marshfield:** Murray Brilliant, Scott Hebbring, Aniwaa Obeng**; Meharry:** Rajbir Singh, Samuel Adunyah; **Mayo:** Iftikhar Kullo, Richard Sharp; **Mt. Sinai:** Aniwaa Obeng **Northwestern:** Maureen Smith; **Partners/Broad:** Hana Zouk, Sandy Aronson; **VUMC:** Sarah Bland, Josh Denny, Wei-Qi Wei; **NHGRI:** Jyoti Dayal Gupta; Ken Wiley, Sheethal Jose, Robb Rowley, Teri Manolio; **CC:** Josh Peterson, Melissa Basford, Jodell Jackson, Kayla Howell, Laura Allison Woods, Michelle Stone, Brittany City

Absent: Rex Chisholm, Funmi Olopade

NOTES:

- **Welcome, Opening Remarks, General Updates |** *Robb Rowley & Howard McLeod*
  - The NHGRI would like to thank everyone for joining the ESP conference call including the ESP members, and the CC for organizing the packet prior to the call. The packet of preparatory materials provided to the ESP before the call was helpful to the ESP for updates on the Network.
- **Network Introductions |** Josh Peterson
  - eMERGE has sequenced 25,380 eMERGEseq participants. Non indication-based results have a ~4% positive rate and indication-based testing has a positive rate of ~2.2%.
  - Four sites have completed ROR, and several other sites are completing their RoR
  - The eMERGEseq Freeze V1 is to be released publicly on dbGaP by the end of this week.
  - Five Lessons Learned panels have been convened at steering committee meetings; three panels are scheduled between June 2019 and January 2020. There are also 11 lessons learned manuscripts that have been either published (four) or in development (seven).
  - There have been over 1280 external downloads from eMERGE dbGaP submissions, and 755 eMERGE Network and site-specific projects have been published as of March 2019.
  - Regarding how eMERGE can help inform the All of Us program, the VUMC site returns all results (negative, PGx, P/LP) directly to providers first through the EHR, then disclosing results to participants directly in order to simulate real world situations where genetic counselors may not be available.
  - Six eMERGE sites are returning negative results. Baseline and follow-up surveys are being administered to elicit participant understanding. Mayo & Northwestern are conducting interviews on a subset of participants to further investigate the impact of negative results.
  - The ESP made a recommendation to strive for consistency across outcomes collection forms, and the eMERGE Outcomes Workgroup has worked to centralize and harmonize

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outcomes forms. Abstraction guides are being developed on all forms;the following have been finalized:
    - Aortopathy (Mayo)
    - Breast Cancer - Women (Columbia)
    - Cardiomyopathy (Northwestern)
    - Colorectal Cancer and Polyposis (KPW/UW)
    - Familial Hypercholesterolemia-Adult (Mayo)
    - Familial Hypercholesterolemia-Pediatric (Geisinger)
    - OTC (Geisinger)
    - Tuberous Sclerosis (Geisinger)
    - 22Q (CHOP)
  - Sites are actively working to augment the work of the Network. Three sites have obtained independent funding sources for related work and KPW is preparing a grant using existing eMERGE tools to allow eMERGE data to be accessed by the public and other researchers.
    - VUMC leads a 'MeTree' supplement to develop an implementation strategy for the use of Family Health History (FHH) collection tool into the EHRs of diverse institutions and worked with Duke University, Geisinger & Northwestern.
    - BCH obtained a RO1 in 2018 to deploy a Healthcare Provider Survey, and disseminated surveys to nine eMERGE sites in order to capture healthcare provider's perceived utility of genetic tests and results.
    - Marshfield used internal resources to initiate the sequencing of approximately 2,000 recruited individuals on the eMERGEseq platform evaluating genetic risk factors for de-novo/predicted family histories for cancer or Familial Hypercholesterolemia (FH) and incorporate genetic results? into the EHR for standard of care.
- **Return of Results: Empirical Data & lessons learned |** Iftikhar Kullo & Ingrid Holm
  - The ROR Workgroup has several ongoing projects, including NT277, NT300, NT323, NT330, and NT332, as well as proposals that have recently been submitted, including NT322, and NT273.
  - The Workgroup has recently published manuscripts in *Genetics in Medicine*, *Journal of Personalized Medicine*, and *Mayo Clinic Proceedings*.
  - The sites differ greatly between the methods of return of result, and the group is utilizing these differences in order to determine the impact of these various methods.
  - Many sites are very close to completing the return of positive results, and two-thirds of the sites are returning negative results. Of the sites returning negative results, many are almost complete. All sites are expected to have this completed by the end of the summer.
  - The Health Care Provider Survey (HCP) is only sent to providers that received positive results. The group plans to send a second survey to providers with negative results.
  - The Network iscontributing to best practices for ROR through several methods. Across the eMERGE sites are a variety of 'who', 'what', and 'how' on cohort recruitment and methods manuscript concept sheets regarding return of results. Cohorts were selected differently: some were selected based on phenotype, adolescent versus pediatric cohorts, and participant choice versus no choice for return of secondary findings. Different results were returned across sites. For example, P/LP were returned at most sites, KPW/UW is the only site returning VUS, and Marshfield and VUMC are the only sites returning PGx.

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- ROR projects are hybrids between research and clinical work. They can be used for determining clinical utility, familial and societal impact, and how these results are perceived by patients and providers.
- Ongoing ROR studies in eMERGE can help address theknowledge gap in understanding the penetrance of the ACMG59. Clarification may be needed from the ACMG to the larger scientific population.
- The ESP recommended that sites develop a plan to optimize the response rate of patient surveys through EHR reminders, medical appointments, and other methods, in order to improve the quality of results.
    - The participant survey subgroups' Participant Survey Tracker allows for the ROR group to monitor progress of participant surveys. Sites also utilize multiple email reminders, follow-up calls, and in-person reminders, as well as paper mail. REDCap is used for automatic reminders.
- The ESP recommended that the ROR and Outcomes workgroups focus on understanding the misconceptions surrounding ROR on patient care, and identify sustainable solutions or strategies that can address these misconceptions.
    - Data from the ROR and Outcomes group were collected from semi-structured interviews, participant surveys, and analyzed specifically in MCS NT300 and NT322. These data can be analyzed during the remaining year of eMERGE to guide research on common misconceptions surrounding ROR on patient care.
- The ESP recommended that the ROR workgroup study physicians' responses to variant reclassifications.
    - The CSGs are working to quantify the cost and psychosocial implications of ROR and responses to variant reclassifications, as well as the mechanisms of disclosing new interpretations and how participants and providers respond to changes in variant interpretation. This is collected via interviews of health care providers who received notification of a reclassified variant to explore their response.

- *Questions from ESPs:*
    - How has the diversity between the sites ROR process actually affected the study of ROR?
        - The lack of continuity between sites approach to RoR creates hurdles and reduces overall generalizability, however this allows the Network to study many different approaches toROR (adults/children, PGX/ACMG, primary/secondary)..
    - Are you pursuing more qualitative interviews with providers and were there difficulties recruiting providers?
        - The RO1 HCP survey grant includes interviewing providers that have received results that arepositive and negative. Recruitment is based done off existing participant referral. The second wave may be easier because physicians have received results. There is a 25-30% response rate for interviews, which is an expected range. It is unknown at this time if there is systematic bias in the non-responders.
- **EHRI: Integration of the CDS into the EHR |** Sandy Aronson & Casey Overby Taylor
    - The EHRI Workgroup has several ongoing projects, including: NT301, NT272, NT328, and NT213, as well as ongoing projects in collaboration with other workgroups, including: NT265 (EHRI/Phenotyping/Genomics), NT310 (EHRI/Phenotyping/Genomics), NT289 (EHRI/Genomics), NT236 (EHRI/Genomics), NT237 (EHRI/Genomics), NT294

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(EHRI/Phenotyping), NT295 (EHRI/Phenotyping), NT309 (EHRI/Phenotyping), and NT270 (EHRI/ROR).

- eMERGE is the first and only Network that can transmit structured data lab results to a variety of providers and sites. This is accomplished with a custom XML format. However, reporting standards are needed, especially as most clinical sites (9/10) use non-structured data format. GI XML served this purpose, but the investigators wanted a standard that could grow beyond eMERGE to be a national standard.
- Fast Healthcare Interoperability Resources (FHIR) is the newest (next) generation standards framework created by HL7. FHIR aims to simplify implementation without sacrificing information integrity. It leverages existing logical and theoretical models to provide a consistent, easy to implement, and rigorous mechanism for exchanging data between healthcare applications (see here).
- FHIR standards could improve computation, as well foster theintegration and interoperability of genomic testing data. FHIR combines features of HL7s v2, HL7 v3, and CDA product lines while leveraging the latest web standards and applying a focus on implementability.
- Mullai Murugan (Baylor) spoke to the creation of a national-based HL7 FHIR specification for utilization, and Nephi Walton (Geisinger) has worked on sending results directly into the EHR without the ancillary genetic system.
- A pilot subgroup could be formed, but currently, the issues are being logged using HL7 FHIR's ZULIP process. Targeted meetings are setup to resolve the issues. The investigators have met with the CSGs to demonstrate the current and planned work and to gain recommendations on how to have efficient collaboration.
- There are a few challenges, including that the clinical genomics workgroup.timeline is codependent with HL7 It can take time to develop resolutions, even though there is a need for quick decisions on critical path issues/changes. To ensure forward progress the group has to establish its own standards. As the investigators continue through development and mapping, they track questions, issues, and discrepancies that can be adjudicated at a later time with the FHIR workgroup.
- Geisinger uses the genomic indicator function in EPIC to create a genetic phenotypes. Genomic indicators serve as the disease or metabolizer status providing a a point of reference for CDS Genomic indicators are used to establish clinical decision support, health maintenance schedules, and development of care paths.
- Investigators built and integrated genomic indicators for CDC tier one conditions,several PGx variants, and integrated the decision support into the test environment.
- The vision is for labs to use FHIR resources to integrate genomic information into the EHR and use VAR format to drive genomic indicator for infobuttons and patient's CDS. Investigators recognize that there is still significant work to be done to integrate the genomic data into the EHR.
- Lessons learned includes that there continues to be need work with definitions and standards surrounding genomic indicators and phenotypes. It remains unknown ifgenetic indicators can be passed from the laboratory to the EHR. The investigators recognize the importance to include the laboratory in the process of establishing standards. The investigators plan to develop information resources on genetic conditions for patient/physician information.
- In addition to other EHRI work, the EHRI Workgroup is writing a manuscript that summarizes the October 2018 Steering Committee meeting lessons learned panel.

- *Questions from the ESP?*

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- How is the current work shared?
    - The current specifications for the FHIR standards are still in draft mode, so is not quite ready for dissemination. However they continue to work with the FHIR workgroup to helphelp inform and refine the national standards for genetic testing results.
    - For AoU, the plan is to create a FHIR standard; the lessons learned from the the GC group will be a great resource.
    - Genomic Indicators are still in a developmental state with labs and EMR vendors not currently adopting the standard. It will be critical to demonstrate to vendors that this is useful to facilitate the adoption of the FHIR standard. The group is currently working with EPIC. If EPIC adopts the standards it may help shift the utilization.
    - Investigators also upload relevant code and applications it to GitHub, which is a publicly used site to help disseminate the tools needed to implement the FHIR standard.
- eMERGE is uniquely positioned to research the penetrance of P/LP in ACMG 59. Has this been considered?
    - The Clinical Annotation Workgroup is going to examine this, and the Outcomes forms are assessing penetrance at baseline and six-months post return.
    - For the cohorts selected for a particular trait it would be excluded, however the other variants will be examined to determine if relevant traits are present.

- **Discussion and suggestions from the ESP**
    - The ESP appreciated the significant progress the EHRI workgroup has made towards establishing a FHIR standard for sharing genetic testing results., there is a lot of commonality in the challenges surrounding FHIR standards.
    - The ESP is impressed with the significant amount of hard work and they encouraged the Network to continue the effort.

Executive Session Meeting Summary

eMERGE Network – ESP Teleconference

4/29/2019

ESP	**Howard McLeod (Moffitt) – Chair** **Eta Berner (UAB)** **Kimberly Doheny (JHU)** **Stanley Huff (IMH)** **Funmi Olopade (U Chicago)*** **Lisa Parker (U Pittsburgh)** **Vandana Shashi (Duke)**	**NHGRI**	**Jyoti Dayal** **Sheethal Jose** **Teri Manolio** **Robb Rowley** **Ken Wiley**

The External Scientific Panel (ESP) met with members of the NHGRI staff in Executive Session after the ESP teleconference held on April 29, 2019. The ESP members appreciated the Network's comprehensive responses to their comments and suggestions from the October 2018 ESP in-person meeting. They

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commended the extraordinary effort of coordinating such a large network. The workgroups have made a significant effort addressing the ESP's past meeting recommendations.

The ESP was impressed with the Return of Results (RoR)/Ethical Legal Social Implications (ELSI) workgroup's various studies that are currently in progress that address the practical ELSI issues related to clinical genomics. The ESP noted that the Network is on course to collect 6-month outcome data from returning the ACMG variants. However, they pointed out that the twelve month and longer follow-up is critical to maximize the study of penetrance. The ESP recommended that the Network review the current RoR schedule to identify any delays that will impact the collection of 12-month outcome data. The ESP recognized the Network's success in obtaining additional funding but recommended considering applying for additional grants or supplements to capture outcome data beyond the twelve months. The eMERGE expertise applied to this effort will significantly help the field of genomic medicine.

The ESP recognized that the 25-30% response rate to the healthcare provider (HCP) survey is a good response. They urged the Network to consider ways to obtain additional responses, especially to the pathogenic/likely pathogenic variant results. An approach that goes beyond e-mails and letters offers an opportunity to improve response rates and to increase awareness among providers of the eMERGE Network. Other programs have found that conducting town halls or educational sessions not only improves the number of responses but also increases patient referrals and provider engagement with the program. An example the ESP highlighted was an approach taken by the Undiagnosed Disease Network (UDN) to engage providers by speaking at departmental meetings. This increased referrals and survey response rates for the UDN. A similar approach could be considered for the eMERGE Network.

The ESP was impressed with the Electronic Health Records Integration (EHRI) workgroup's efforts and acknowledged that the Network's efforts extend beyond eMERGE. The Network has made significant progress with establishing standards for incorporating XML-based genetic testing results and clinical decision support systems (CDSS) into the EMR. This includes being a critical driver for establishing FHIR standards in genomic medicine. However, the extent of deployment of these standards among the Network is not clear. What are the lessons learned with deploying these in the EMR? How many sites have already installed genomic based CDSS? The ESP noted that the Network has a manuscript concept sheet (NT272) listed that addresses the impact of CDSS in clinical care and encouraged this effort to continue. The ESP appreciated that these tools and techniques are not unique to genomics, but the Network should continue to be the leader in helping healthcare systems integrate genomic information by researching standards and sharing their lessons learned. As such, the Network should continue and expand its work with other consortia and commercial entities that are focused on developing CDSS and use existing frameworks, instead of creating a different infrastructure specifically for genetic data.

Lastly, the ESP recognized that the Network finishes this phase of eMERGE in less than a year. They emphasized the importance of prioritizing the manuscript concept sheets of the lessons learned and network-wide efforts to ensure the outstanding work by eMERGE is shared among the greater scientific and healthcare community.

ESP Recommendations

To investigators:

1) The Network should research the discrepancy in RoR between the sites to ensure that the significant effort to date can capture 6-month and 12-month outcome data.
2) The Network members should consider applying for additional grants or supplements to analyze the data and study penetrance.

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3) Regarding the healthcare provider survey, the Network should attempt to connect with providers personally, such as conducting town halls or educational sessions to engage providers and create awareness of the eMERGE Network.
4) The EHRI workgroup should clarify what sites have integrated the XML-based genetic testing results and CDSS into the EMR. The workgroup should also work with other consortia and commercial entities that are focused on developing CDSS and use existing frameworks to help reduce effort and ensure adoption.
5) The Network should prioritize the publication of the lessons learned manuscripts before the end of the current phase of eMERGE.

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