Summary of ESP Call: April 2021

April 29th, 2021

11:00am-2:00pm ET (10:00 am- 2:00 pm CT, 8:00 am-12:00 pm PT)

Meeting Recording

Table of contents

Action Items

- The condition leads need to determine the specific models for integration of risk factors into the GIRA report for each condition and provide the variable logic, recommendation text, and details to the network prior to the summer sIRB amendment. (GIRA subgroup)
- Sites need to determine if and how the GIRA report will be entered into their EHR, including how to ensure physicians and participants can access and understand the GIRA. (EHRI workgroup)
- The Network will determine how to handle PRS scores that do not perform equally across all ancestries. (Steering committee & PRS workgroup)
- The Network should consider applying for external funding to continue the ELSI research, as there is a great opportunity to examine ELSI related issues through the return of results process. (ELSI subgroup)
- The Network should consider writing a team science paper on how to effectively resolve issues in a large network. (CC)
- The EHRI workgroup should consider writing a paper that references how sites will integrate the GIRA. (EHRI workgroup)

- **Opening Remarks | Robb Rowley (NIH/NHGRI) & Teri Manolio (NIH/NHGRI); Katrina Goddard (KPCHR)**
  - The Network has made a lot of progress in a short amount of time.
  - The ESP suggests for the network to write a publication regarding team science since the network has been able to resolve issues in an effective way.
- **ESP welcome and goals | Rex Chisholm (SC Chair, NU)**
  - Invitae has joined the Network as an affiliate and will be working on Tier 1 genes and possible monogenic contributors that the Network decides to focus on.
  - The question that the Network plans to address: How does a Genome Informed Risk Assessment (GIRA) impact the clinical actions taken by providers to manage risk, and the propensity of patient-participants to develop disease.
    - The goal is to recruit from an unbiased general population between the ages of 3-75, emphasizing underserved populations that are able to consent in English/Spanish.
    - The conditions that the Network decides to focus on will have recommended clinical actions that can be measured in a 1-2 period.
    - Participants will receive a return of results once during the study.
      - This report (GIRA) will include a summary, specific recommendations, a polygenic risk score report, a monogenic risk score report from Invitae, and a family health history report from MeTree.
  - The sIRB documents are prepared and currently under review by the Network. The sIRB is expected to be submitted in early May, 2021.
  - The final prioritization of the remaining trans-ancestry PRS scores is expected by May, 2021.
    - Abdominal Aortic Aneurysm, Asthma, Breast Cancer, Atrial fibrillation, Chronic Kidney Disease, Colorectal cancer, Coronary heart disease, Hypocholesterolemia, Obesity/BMI, Prostate cancer, Type 1 Diabetes, and Type 2 Diabetes are currently under consideration as the clinical components of the prospective cohort.
  - The CC will coordinate and integrate data from all sites, the Broad, and Invitae into the R^4 portal.
    - The goal is to have this in place during Q2/Q3 of 2021.
  - The GIRA workgroup has a draft of the GIRA report.
  - The Network has a well-developed process for decision-making:
    - A workgroup will make a recommendation on a topic that they have been working on.
    - This recommendation will go to a group of Co-Chairs from all of the working groups. The Co-Chairs will review the recommendation, and see if it conflicts with others recommendations from other workgroups.
    - The recommendation will then go to the leadership group for discussion.
    - Lastly, the recommendation will go to the PIs/SC for final decision/approval.
  - The main issues that are outstanding for the Network is the monogenic gene and polygenic model selection, and balancing comprehensive risk assessment and resources available to return results.
  - The Network is also faced with how to tie risk to actionability across different conditions and age ranges.
  - Recruitment is expected early summer/late Fall 2021.
  - GIRA Challenges and pending decisions:
    - **Action Item:** The condition leads need to determine the specific models for integration of risk factors into the GIRA report for each condition and provide the variable logic, recommendation text, and details to the network prior to the summer sIRB amendment.
    - **Action Item:** Sites need to determine if and how the GIRA report will be entered into their EHR, including how to ensure physicians and participants can access and understand the GIRA.
- **PRS updates and decisions | Eimear Kenny (Mt Sinai) & Patrick Sleiman (CHOP)**

- The primary goal of the PRS workgroup is to evaluate the scientific validity and performance of polygenic risk scores and to develop validated PRS metrics for the selected conditions. Additionally, the group is supporting the implementation of CLIA PRS test and of PRS in GIRA.
- The workgroup will have access to phenotype and covariate data at the end of the month and the timeline for having finalized validated PRS performance is the end of May with some potential extension for some conditions.
- The group first performed literature reviews and developed validation strategies with a particular interest in trans ancestry approaches.
- A standardized set of metrics have been developed and a codebase is being implemented.
- Five of the seventeen conditions were moved to the 'research development track' meaning research on the conditions is continuing but they are not being considered for clinical implementation.
- All sites are being asked for standardized metrics per population group that include odds ratio per standard deviation, AUC with and without covariates, positive predictive value, and odds ratio per high PRS group.
    - Code will be shared by sites on a GitHub repository.
- The group encourages the development of trans ancestry scores and condition leads to develop a plan for how to handle race/ethnicity and genetic ancestry in the implementation pipeline.
- All condition leads are currently reporting on performance metrics during the PRS workgroup calls.
- In summary, deliverables include:
    - Validated PRS for 12 conditions by the end of May.
        - Realistically, validation will need to continue for some conditions past May (additional data becoming available in diverse groups).
    - Support of PRS research development track.
    - Working with the Genotyping workgroup to transfer and implement PRS.
        - Some additional decisions, like the absolute value of scores and score robustness, will need to be worked out with the Genotyping workgroup.
    - Working with the CARE group to develop GIRA.
        - Each condition lead will be providing text that will go into the GIRA.
- Challenges the workgroup face include lack of data in non European populations, figuring out how to run validation on AnVIL, and developing and implementing approaches to adapt European ancestry PRS to other populations.
- Pending decisions include the group continuing in year 2 and how to handle trans ethnic versus single or multi ethnic scores.
    - **Action Item:** The Network will determine how to handle PRS scores that do not perform equally across all ancestries.
    - The ESP agrees that the PRS workgroup should continue on in year 2.
- The PRS workgroup has a subgroup focused on multi ancestry PRS methods.
- Selecting percentile thresholds is a balance between setting the bar too low or too high in addition to deciding the cutoff for being high risk for a condition.
    - Sites are comparing absolute risk levels using different factors.

- **ELSI contributions | Ingrid Holm (BCH) & Richard Sharp (Mayo)**
    - Ingrid Holm reviewed ELSI-related decisions made and updates since the last ESP meeting.
    - The workgroup has made a lot of progress since the last ESP meeting. The ongoing goal is to work together across sites to learn about the impact of PRS. They plan to summarize learning across the network and publish.
    - All ten sites have conducted interviews and/or focus groups. Ingrid reviewed the major findings from these interviews. A recurring concern was the misuse of research in healthcare and society within underrepresented minorities. These findings from interviews and focus groups will inform the recruitment and consent process.

- The ELSI sub-studies are called “year one” because the data collection is taking place in year one. The majority of the data analysis is still yet to be completed at almost all of the sites. During year two, the Network would establish several workgroups across several sites to do a deeper investigation in the focus groups and interview-based studies. By the end of year two, these studies would result in publications.
- The ELSI group is currently only funded for one year. The group should apply for outside funding to continue as there are many ELSI topics that can still be studied.
- The ESP feels that the ELSI group should focus more on the return and follow-up. The ELSI group must be able to articulate and distribute their methods and findings to the broader community. They also should plan a research program for the ELSI findings.
- There was concern from the ESP about participant’s education regarding genetic ancestry compared to self-reported ancestry, and how it would affect a PRS. The ELSI studies suggest the need for participant education to indicate the difference between the two concepts, and the significance for report interpretation.
- It must be made clear to the study participants what the researchers and the participants will learn in returning the GIRA to them, given that some PRS are not validated in all age ranges and in all ancestries. It should also be transparent on what eMERGE can and cannot provide along with the results.
- There is a high false positive rate in certain pediatric conditions. Pediatric condition leads are in the process of validating the PRS.

- **Protocol updates and decisions | Digna Velez-Edwards (VUMC) & Wendy Chung (Columbia)**
  - Final target population and Inclusion/exclusion criteria
    - The goal of recruiting participants is to recruit from the general population and also to not focus on any one type of disease.
    - The age range decided on for participation is 3-75 years.
    - Study materials will be in both English and Spanish languages.
    - Inclusions
      - Able to consent in English or Spanish.
      - Able to provide HCP
      - Intent to stay in area
      - Willing to accept GIRA scores
    - Exclusions
      - Inability to provide consent
      - Bone marrow transplant
      - eMERGE staff and investigators
      - Unable to provide an HCP to receive results
      - Not a patient at a parent institution in eMERGE
  - How are participants identified
    - Participant recruitment can be customized by site as long as the agreed upon inclusion/exclusion criteria are met.
    - Harmonized recruitment materials and consent documents are being created by the CC.
      - Site specific information (contact information, site name/logo) will be customized per site but messaging will be consistent.
  - Recruitment timeline
    - Recruitment
      - Prescreening can be completed electronically with the option to have study staff assist if necessary.
    - Enrollment
      - Participants will submit their consent and complete a baseline survey.

            - Participants will also have the option to submit blood or saliva samples at this visit or up to 3 months after enrolling.
        - 3 months
            - Participants will be compensated with an approximate $20 gift card each when enrollment is complete and after the Pre-ROR survey is complete.
            - The participant will be encouraged to start their MeTree family history information collection.
        - 6 months to 12 months
            - The current plan is to have the GIRA returned around 6 months after sample collection, but there is allowance for extra time at the beginning of this study.
        - 12 months
            - A post-RoR survey with another compensation opportunity will be provided at this time point.
    - Decisions made since last ESP call
        - Age range for inclusion will be 3-75 years.
        - Invitae will provide monogenic testing and results with only pathogenic/likely pathogenic results being returned.
            - Participants can opt in to the Invitae patient portal to receive VUS reclassification information.
        - All reports (monogenic, PRS, GIRA, and MeTree) will be returned at one time.
        - Participants will receive “not at high risk” results by mail/email/patient portal.
        - Study staff (coordinator, genetic counselor, study nurse, or study physician) will return “at high risk” results to participants.
    - Decisions remaining
        - Final list of monogenic genes for sequencing
            - The Network is currently considering Tier 1 alone or Tier 1 plus TP53, PTEN, PALB2, STK11, LMNA.
        - Which prediction models to use that will work on the R^4 portal.
        - Thresholds for what PRS risk level to return.
        - The most appropriate way to represent risk to participants on the GIRA.
        - Including a control group of participants not at high risk to return results to similarly as at high risk participants.
    - The reports that will be placed into the EHR will be made by sites separately.
        - CLIA laboratory reports (PRS and monogenic) will be placed in the EHRs.
        - Not all sites will be able to include the entire integrated GIRA.
    - The rationale and reasoning for a comparator group to receive results similar to the at risk participants was discussed.
        - High-risk participants will receive their results in person and not at high risk would not.
        - Ambiguous recommendations for actions will be difficult to measure if participants took up those recommendations or not.
        - In order to measure the effectiveness of the in person return, a subset of participants receiving results in the same manner is needed.
        - The intent is to have a single return of results visit and will not be by each phenotype.
        - The 'internal' control option of using in person but looking at the 'not high risk' should be considered.
        - Adding in the randomized return does let you analyze some elements more specifically.
    - Concern on how recommended actions are implemented was discussed.
        - Ambiguity in some of the guidelines do not provide firm direction on what a participant needs to do.
        - The current plan is to give all at high risk participants the same information with standardized methods.
        - There is placeholder language in GIRA for the monogenic results that recommends seeing a genetic counselor.

        - It is anticipated that less than 1% of participants will have a high monogenic risk result.
        - Clinical recommendations will be customized from each phenotype lead.

- **Input & feedback from the ESP**
    - The ESP approved the reclassification plan with Invitae and encouraged the network to implement it.
    - The ELSI group is doing worthwhile work and is encouraged to continue to find ways to incorporate feedback and continue to address more ELSI questions that come up as the project continues.
    - The Network must be transparent with participants about some PRS not being validated for certain groups.
        - This is a great opportunity within the Network's research to address this limitation.
        - Collecting and analyzing data on how participants understand and respond to the information given to them is important.
        - It is also important to continue funding the ELSI subgroup and projects longer than the first year.
        - **Action Item:** The Network should consider applying for external funding to continue the ELSI research, as there is a great opportunity to examine ELSI related issues through the return of results process.
    - The Network has a great opportunity to push research forward and should not shy away from addressing these complex issues that are so important to the field.
    - The Network risks missing out on advancing certain elements of research by focusing on only the validated/pathways that are current (or almost there) clinical practice.
    - The distinction between genetic ancestry and self-reported race and ethnicity and how providers and participants is important for the Network to better understand.
        - NIH is projecting that race and ethnicity will not be used in studies in the future.
    - The network needs to clearly define the questions they are interested in answering for the remaining barriers, such as:
        - For example, deciding on what the network can say about the data they gather by returning to all ancestries (or age groups).
        - Identifying where the Network can make the biggest impact given the study design/plan is also a barrier needing to be addressed.
    - **Action Item:** The Network should consider writing a team science paper on how to effectively resolve issues in a large network.
    - **Action Item:** The EHRI workgroup should consider writing a paper that references how sites will integrate the GIRA.
    - The ESP panel noted the inconsistencies with sites GIRA storage policies.
        - Understanding if the barriers are EHR-specific or state/local policies is important and needs to be investigated.
        - Northwestern has a mechanism within their EHR that allows for research results to be seen through the EHR but not stored within the EHR.
    - Pros and cons of returning to a randomized subset of 'not high risk' participants need to be weighed.
        - Some pros include a more robust data set for analysis.
        - Cons include an increased workload for research staff and if returns can be provided to an increased number of participants.
        - Returning results by mail or patient portal to the not high risk is much more similar to clinical practice.
    - The ESP encourages the Network to think of age as a continuous variable instead of dichotomously so the pediatric participants are not in a separate study than the adult participants.
        - There are some issues identified with the pediatric group compared to the adult group that makes it difficult to group them together, such as:
            - Surveys being completed by the parent and not the child

        - Results being returned to the adult and not the child
    - A question of eMERGE being better served to use the pediatric data as foundational work was discussed.
    - Getting community providers excited about this project regarding adults will be much easier than with the pediatric population based on the state of the current science.
    - There are several potential interesting ELSI issues that can be investigated on returning PRS to children.
  - A single protocol for the Network, while thinking through how to address the ethical issues that appear, is ideal.

- **Official ESP Recommendations**

Meeting Summary

eMERGE Network- External Scientific Panel and Steering Committee

Executive Session- 04/29/2021

ESP	**Katrina Goddard (Kaiser Permanente) – Chair** **Kimberly Doheny (Johns Hopkins University)** **Stanley Huff (Intermountain Healthcare)** **Janina Jeff (Illumina)** **Lisa Parker (University of Pittsburgh)** **Clesson Turner (Uniformed Services University of the Health Sciences)** **John Witte (University of California San Francisco)**	NHGRI	**Dave Kaufman** **Teri Manolio** **Robb Rowley** **Baergen Schultz** **Rene Sterling** **Ken Wiley**

The External Scientific Panel (ESP) met with NHGRI program staff members during the executive session of the eMERGE ESP and Steering Committee (SC) Virtual Meeting held on April 29, 2021. The ESP members recognized the significant strides that the Network has made since the December 2020 ESP/SC meeting, reflected in the Network materials. The ESP appreciates that the Network still has many hard decisions to make and urged the Network to continue to define and address the unanswered questions. The ESP believes that the Network has a unique opportunity, in a research setting, to address some of the questions that clinicians are facing early on in the implementation of polygenic risk scores (PRS)/Genome Informed Risk Assessments (GIRA) and should challenge itself to take on these questions knowing that singular or perfect solutions do not exist.

The ESP pointed out that the eMERGE Network has always had a group of broadly distributed institutions, each contributing different expertise. The unique challenges that a heterogeneous Network will face are offset by the substantial benefit that a multi-site, multi-disciplinary approach brings to the challenges of implementing GIRA in the larger healthcare systems. Making these challenges—and the process undertaken to address them—transparent to a larger audience may enable other researchers, institutional leaders, and clinicians to benefit from this network's experience. As one example, the Network could publish the reasons that sites did not all agree to insert the GIRA into the electronic medical record (EMR) as a guide for other healthcare systems considering inserting genomic results into the EMR.

<u>Polygenic Risk Scores (PRS) Validation and Evaluation Considerations</u>

The ESP was impressed with the PRS Validation and Evaluation workgroup's efforts to date. The ESP thought that the workgroup should continue past year one to help the Genotyping and CARE workgroups integrate the PRS into the GIRA.

While the ESP encouraged the development of trans-ancestry scores, they acknowledged that the validity of PRS will still vary across groups recruited into eMERGE. This variation requires the Network to address how they will explain the opportunities and limitations of GIRA to patient-participants from different racial/ethnic backgrounds and their providers. The Network will need to clarify the limitations of each PRS and the GIRA in which it is integrated, and this clarification may need to be individually tailored. Also, the Network should communicate clearly to patient-participants during recruitment that the limitations of the study may vary across individuals, as well as to health care providers as part of the return of results. eMERGE provides an opportunity to understand the potential value of these tools in a clinical setting for patients of different racial/ethnic backgrounds and patients with different levels of access to care.

Ethical, Legal, and Social Implications (ELSI) Considerations

The ESP emphasized the importance of the site-specific ethical, legal, and social implications (ELSI) research projects to the design, implementation, and evaluation of this phase of eMERGE, and appreciated how early findings have helped inform the research framing and approach. Contributions to appropriate recruitment and retention strategies were also noted. The ESP encouraged the Network to continue incorporating feedback from the site-specific ELSI projects. They also noted the potential value of extending the role of ELSI investigators across the duration of the study as ELSI questions will continue to arise as the Network moves from study design to implementation. The Network's formative efforts on PRS implementation afford a unique and timely opportunity to continue answering and addressing PRS-related ELSI questions, paving the way for broader implementation. For example, the Network could consider evaluating clinician and patient-participant perspectives on the distinction between socially-constructed race/ethnicity and genetically-determined ancestry and how this may affect understanding of PRS results. While the ESP highlighted that continuing the ELSI component of eMERGE is worthwhile and important, the ESP recognizes that the site-specific ELSI projects were only funded for one year. The ESP encouraged eMERGE investigators to consider other funding sources to continue the ELSI work, as was done in eMERGE III.

Additionally, the ESP appreciated that the ELSI subgroup is thinking about how to address changes in monogenic gene variant classification after the eMERGE study ends and encourages the Network to move forward with implementing a reclassification plan.

Protocol Considerations

The ESP had several comments in response to pending protocol decisions. A critical decision recognized by the ESP was the need for the Network to finalize the comparison group(s) to be used in the outcome analyses. This will facilitate several downstream decisions (e.g., survey questions, outcome measures). The ESP acknowledged the challenges when there are concerns with a condition for scientific, ethical, or other reasons. The issue is particularly noteworthy for the age range of return but not limited to this consideration. The Network should address these remaining issues, finalize a list of conditions, and move forward to establish language for the return of results that describes the limitations of the GIRA for each unique condition and population.

Recommendations

The ESP remains excited about the past progress and future work that the eMERGE Network will tackle to help determine the roles of PRS and GIRA in clinical care. The Network's ability to identify, clearly define, and thoughtfully address the difficult decisions in a timely manner will help ensure the success of this phase of eMERGE.

ESP Recommendations for the Network:

1. The EHRI workgroup could consider submitting a manuscript describing the factors that contribute to each sites' ability to integrate the GIRA into the EMR.

2. The PRS Validation and Evaluation workgroup should continue past year one to support the genotyping implementation including the transfer and integration of PRS into the GIRA.

3. The Network should give additional thought to how they will educate patient-participants and providers about the variable validity and utility of returned results since some PRS will not be validated in all populations recruited into eMERGE.

4. The Network should consider evaluating clinician and patient-participant understanding between socially-constructed race/ethnicity and genetically-determined ancestry and how this may affect understanding of PRS results. This evaluation will impact how returned results are perceived, understood, and used by clinicians and patients. These results will have important implications for the broader scientific and clinical community now and in the future.

5. The Network should resolve whether trans-ancestry, single, or multi-ethnic PRS scores are integrated into the GIRA. The Network will continue to benefit from including the Broad Institute in discussions on the best approach, especially regarding whether a PRS result will be reported at all for individuals whose genetic ancestry does not fall within a validated PRS score. Early clarification of the limitations (or not) of the CLIA reporting process could simplify downstream planning.

6. The Network should continue incorporating feedback from the site-specific ELSI projects throughout the study.

7. eMERGE investigators are encouraged to consider other funding sources to continue the ELSI work for this phase of eMERGE.

8. The Network should move forward with implementing the proposed reclassification plan for monogenic gene variants.

9. The Network should finalize which comparison groups are most critical for advancing our understanding of patient-participant outcomes and ensuring adequate statistical power for corresponding analyses. Consider finalizing the decision soon since the decision has significant impact on finalizing outcomes.