**Summary of External Scientific Panel/Steering Committee Meeting: September 2022**

September 28-29, Zoom & In-Person

**eMERGE Day 1: Wednesday, September 28th, 2021**

1. **NHGRI program official report | Robb Rowley (NIH/NHGRI)**
	1. Robb Rowley welcomed the group and congratulated everyone on accomplishments thus far.
	2. There were several announcements regarding new members who are joining NHGRI: Jahnavi Naurla (Scientific Program Analyst), Lt. Commander Iman Martin (Extramural Program Director), Renee Rider (Extramural Program Director), Dr. Julius Militante, and Dr. Veronica Abraham (NIH-ACMG Fellows).
	3. An update was made regarding updates to the NIH Data Management and Sharing Policy.
		1. This policy will have details on prospective genomic data and details on what metadata should be collected and shared.
		2. The policy will be effective January 25, 2023. There will be a policy requirement for submission of data management and sharing plans. NHGRI is preparing for implementation of this policy.
	4. 2 new directors were announced: Dr. Monica Bertagnolli (National Cancer Institute Director) and Renee Wegryzn (ARPA-H Director).
	5. Several funding announcements were made. These were also sent in an email.
		1. Multi-Omics for Health and Disease (Due date: November 19, 2022)
		2. Genomics Workforce Diversity (Due date: Ongoing)
		3. Promote Workforce Diversity (Due date: February 22, 2023)
		4. Supporting Talented Early Career Researchers in Genomics (Due date: February 28, 2023)
	6. Q & A
		1. Question: Are there going to be center requirements related to eMERGE in regards to the NIH Data Management and Sharing Policy?
			1. Answer: NHGRI is still assessing how this will impact the group and will follow up. There are already requirements in place for eMERGE regarding data sharing.
		2. Question: Is there anything preventing someone who already had a diversity supplement to apply for some of the announced funding opportunities?
			1. Answer: No there is not.
2. **Announcements, opening remarks | Rex Chisholm (SC Chair, Northwestern)**
	1. The goals for this program are to discuss roadblocks and potential solutions that have been encountered.
	2. Rex highlighted several breakout sessions that will be focused on issues affecting the workgroups.
	3. An update was made regarding great progress on GIRA testing. The assembly of GIRA pdf will be starting soon to ensure patients are getting accurate information.
	4. An update was made regarding enrollment progress. Recruitment is now at 3,330 total enrolled (15% of target).
3. **Panel: Outcomes presentation**
	1. Overall analysis
		1. Dave Veenstra introduced the Outcomes panel. The study has 25,000 participants, with high risk participants receiving their results in person. It is estimated to have 25% high risk participants.
		2. The outcomes study will measure the different actions in the study design following a high risk PRS result.
		3. It is difficult to determine if an individual participant’s actions were due to the PRS result.
		4. eMERGE will use a comparator group to compare to the averages of the high risk PRS group.
		5. The outcomes group has proposed to use participants just below the high risk PRS threshold in the study as a comparator group. While confounding is always a concern, these individuals are likely similar to the participants in the high risk PRS category. There was concern from the network about identifying individuals just below the threshold, this analysis would have to be conducted in a de-identified manner.
		6. The study outcomes can be ascertained from the EHR or participant survey.
			1. The participant survey will be used to gain information that would not be present in the EHR, such as lifestyle changes and assessing participant understanding.
			2. The clinician survey will also be used to learn clinician actions.
		7. The network will also look at condition specific analyses in addition to condition wide analyses.
		8. Condition leads have identified the key interventions that should be considered for the outcomes. These include encounters, referrals, and lab orders.
		9. The network will no longer be using the language of ‘primary’ and ‘secondary’ outcomes in order to better align with the cohort study design.
		10. Instead, the network will examine frequencies and changes at certain time points following return of results. Six months will be used for most outcomes, and twelve months will be used for new diagnoses.
		11. The comparator group will be used to examine the differences in orders/referrals/encounters and differences in new diagnoses and treatments.
		12. Nita Limdi presented an example of phenotype specific analysis using CHD.
			1. The CHD outcomes consist of an imaging and lab order, and assessing for a new diagnosis and if the participant completed the orders.
			2. It is estimated for 98 participants (0.5%) to have high monogenic risk and 975 participants (top 5% PRS) to have a high PRS.
			3. Within the phenotype, there are two comparisons. High monogenic risk compared to high PRS, and high PRS compared to not high PRS.
			4. Assuming 20-30% adoption in the high risk group, and 10% adoption in the not high risk group, gives adequate power to identify statistically the differences in adoption of the recommendation.
			5. Each condition has identified the most impactful outcome. For CHD, this is initiation or intensification of lipid lowering medication.
			6. In CHD, the PCE and integrated score can be examined, to perform a risk reclassification.
		13. The reason to select participants who are just below the PRS threshold for the comparator group is because they are very similar to participants above the high risk PRS threshold.
		14. Selecting all participants for a comparator group would increase confounding.
			1. There were prior discussions regarding the ethical obligations of knowing which participants are just below the high risk PRS threshold and not informing or treating them.
			2. Participants never receive an actual score for PRS, just if they are high or not high.
			3. It is important to select a control group similar to the high risk PRS group.
			4. It was suggested to use recent clinical visits to control for exposure for care in the selection of the comparator group.
			5. It was proposed to perform propensity score matching to select a group from the not high PRS pool.
			6. The RDD is a very powerful approach. It could be beneficial to discuss this with biostatisticians.
			7. **ACTION ITEM:** The Outcomes group must discuss how to select controls. This involves including biostatisticians and determining how to select what criteria participants would have in the not high risk comparator group.
			8. Previous discussions resulted in the Broad not sending eMERGE the actual percentage PRS scores with the clinical reports. The percentages would be available in AnVIL.
	2. Participant-based outcomes
		1. Maya Sabatello presented on participant-based outcomes from the Post-RoR survey.
		2. The post results survey will be distributed to participants six months following return of results.
		3. The post-RoR survey includes 14 questions, with one open ended text question. It involves five key sections that aim to explore participant knowledge of the RoR and identify barriers.
		4. The survey is similar for both pediatric and adult participants.
		5. The first key section is the process and understanding of the GIRA report.
		6. The analysis plan across all key sections is an overall evaluation, comparison to the baseline survey, and comparison with the EHR results.
		7. The second key section is recommendations. This was developed with the care recommendations in mind.
			1. Both medical and lifestyle recommendation questions include ‘other’ with a text field to gain understanding of any other modifications the participant has done.
			2. This can be compared with the provider survey.
		8. The next key section is the translational efforts. This identifies any barriers the participant may have had in acting on the recommendations. This has built on prior ELSI work.
			1. This will be analyzed with demographic, health, and other data from the pre-screen and baseline survey.
		9. The fourth key section is psychosocial impacts. These questions are validated scales previously used in CSER and eMERGE 3. These will also be compared with the prescreening and baseline surveys.
		10. The final key section is on barriers to eMERGE participation. This includes access space and equipment, transportation, internet, and communication with clinicians.
			1. **ACTION ITEM:** The barrier to eMERGE participation questions from the Post-RoR survey can be contributed to the PhenX toolkit.
		11. Jennifer Pacheco presented on participant-based outcomes from the EHR.
		12. There are multiple types of EHR data needed for outcomes, including diagnoses, labs, and referrals and encounters.
		13. Many of these data are already on the eMERGE common variables OMOP queries.
		14. This is a good opportunity to update the shared common variables and queries list.
			1. Medications and labs could be added.
			2. Encounters could be added, however, CPT codes are not consistently used.
		15. The phenotyping group had proposed using eMERGE 1-3 subjects common variable dataset as a comparator group.
		16. Referrals and encounters are more difficult to obtain in the EHR.
			1. There are no common variables for referrals, which will be discussed in the Phenotyping breakout session.
			2. Sites have internal codes, and there are no standard specialist names. There are LOINC codes used but those are not used in the EHR.
			3. RegEx or NLP could be used to ascertain this information.
			4. Even within EPIC, there are different codes used for referrals across sites.
		17. Medications are not always accurately mapped to RxNorm, but in the past studies have included generic and brand names to overcome this.
			1. RegEx may need to be used to obtain doses if it is a short list of dosages.
			2. The group discussed whether it is important to differentiate between medications ordered and medications administered. Most sites do not fill in data for outpatient prescriptions.
		18. CAC scores and tumor grades are also difficult, and may need RegEx or NLP to ascertain.
		19. There were suggestions of performing a manual chart review on the estimated 624 high risk participants per site, not including the comparator group. This would replace the RegEx and NLP development.
		20. Most conditions wanted to learn if the referral was made, not the encounter.
		21. All conditions must be aware of the distinction between ordering and receiving in outcomes.
		22. The eMERGE 3 approach was a chart review in a REDCap database.
			1. This took a lot of work, and was not perfect.
			2. For various reasons, the study was unable to collect all the data.
			3. It could be an option to perform a very limited chart review in eMERGE 4.
			4. Chart review in e3 was limited to only participants with positive results.
			5. There was a proposal to use NLP to extract portions of the note, and assign likely statuses to patients. A reviewer can quickly check the extracted portions to ensure the NLP made the correct assignments.
		23. The comparator group’s EHR data could be pulled at 6 months, and if using e1-3 could be pulled once this fall or winter to gauge the data.
		24. The study must also decide how often to extract the common variables and other outcome variables from the EHR. How many data freezes will there be and what is the timing?
		25. The analysis plan is to compare the post RoR EHR data with the EHR data before the RoR.
			1. **ACTION ITEM:** A question about the wearable device for Afib will be added to the post RoR survey.
			2. **ACTION ITEM:** The outcomes group should propose to the PI’s a schedule for data freezes and EHR pulls for outcomes analysis, while minimizing redundant work at the sites and CC (example: Data freeze at 5,000; 20,000; and 25,000 participants returned).
	3. Provider survey
		1. Ingrid Holm presented on the [Provider Survey](https://docs.google.com/document/d/1tSi2L9zjBJEnATuvH23pZiQft6wrLkcu/edit) on behalf of the co-chairs.
		2. The provider survey subgroup falls under the Outcomes workgroup.
		3. The survey has been worked on with the CDS subgroup, and has been presented to the co-chairs and PIs.
		4. Lessons learned from the eMERGE 3 HCP survey were used in developing this.
			1. In e3, most respondents did not feel confident explaining the results to the patient.
			2. The e3 HCP survey had a 31% response rate.
		5. Medical actions are being obtained from the EHR, and non medical recommended changes will be assessed through the participant surveys. The purpose of the provider survey is to not ask the provider about their actions.
		6. It is also important to consider the burden on providers, as they are not participants and there will be a relatively high number of high risk GIRAs.
		7. At most sites, providers will be receiving more than one high risk GIRA.
		8. The purpose of the provider survey includes ascertaining the provider's understanding of the GIRA and the impact the GIRA had on their workflow.
		9. In-depth qualitative interviews for the providers will be held toward the end of the study.
			1. This has been agreed upon by all sites.
		10. The primary aim of the provider survey is to learn if the providers perceive the GIRA report as useful for clinical care.
			1. The hypothesis is that PCPs who are more confident in their understanding of PRS results will be more likely to perceive the GIRA as valuable for their patients.
		11. The sub aims are to understand why some PCPs do not review the GIRA, and why some PCPs do not act on or meet with their patient about the GIRA.
			1. The hypothesis is that PCPs with low confidence in their genetic knowledge will limit follow-up testing.
		12. The invitation to take the REDCap survey will be sent electronically to the provider within two weeks of them receiving their first high risk GIRA.
			1. Each provider will only receive one survey, even if they have multiple patients with high risk GIRAs.
		13. It was suggested to only survey providers who have a high risk PRS GIRA as their first high risk GIRA.
			1. There likely would not be enough positive monogenic GIRAs to use as a comparison with the high risk PRS GIRAs with regard to provider analysis.
			2. **ACTION ITEM**: The provider group should clarify when the survey will be sent, specifically after a high risk PRS, not monogenic result.
			3. It would also be important to make sure all phenotypes are represented.
				1. This will be difficult, but sites can send additional surveys to address this.
		14. It was difficult for the subgroup to determine how many providers would be receiving GIRAs across all sites.
		15. The survey responses can be correlated with EHR activity, which includes the provider opening the GIRA.
		16. One of the confounding variables will be that sites may have to place the Invitae report into the EHR as soon as it is available in the Invitae portal, which could occur prior to the GIRA return.
			1. The monogenic results will be embedded in the GIRA.
			2. Providers will be alerted to the Invitae report in the EHR potentially prior to the GIRA being communicated to the participant.
			3. Other than pediatric providers, providers will be familiar with monogenic reports.
		17. The providers will be asked if they received the GIRA. if they have not, the site will be contacted to determine why not. If they have, they will be asked a set of questions.
			1. These questions will group the providers into two groups.
			2. Group one are PCPs who received the GIRA but did not review the report. Group two are PCPs who received the GIRA and did review the report.
			3. The questions assess understanding of PRS.
		18. Ingrid reviewed the workflow for sending provider surveys to the PCPs.
			1. Sites determine if the high risk GIRA is the first high risk GIRA the provider has received, making them eligible to complete the survey.
			2. Sites will email the survey link to the provider.
			3. Sites must keep a log of which providers have been sent surveys.
		19. Selection bias could be involved as providers who had time to respond to the survey are more likely to have the time to review the GIRA.
			1. The network will be able to go into the EHR and determine which providers opened the GIRA.
		20. This process will be added in an amendment to the sIRB protocol.
			1. Once the provider completes the survey, they are a participant.
		21. The provider survey will likely be sent out prior to the provider meeting with the participant. The questions are worded to ask about what the provider plans to or did discuss with the participant.
			1. The decision was made to send the survey earlier to ensure providers remember the GIRA.
		22. The CC will not be taking an active approach in this process. The survey link will be generated in line with the participants R4 record.
			1. There will not be an alert system once the survey is completed, and the CC will not incorporate any tracking. The CC has not scoped out any work for this.
			2. The survey will be tied to the data line for each participant.
		23. Now that the survey has been finalized, the sites must develop a workflow. It is important to document each different workflow across the sites.
		24. **ACTION ITEM:** If there is feedback on the content of the provider survey, it must be brought to the Provider survey subgroup, and then to the Outcomes workgroup, before being presented to the PIs.
		25. There is a spreadsheet that sites were asked to complete with the expected number of providers and expected number of providers per GIRA.
		26. The in-depth interviews can include discussions on the not high-risk GIRAs.
	4. Q&A (01:49)
		1. Questions regarding social determinants of health can potentially be extracted from the EHR in a standardized way. The survey does include some questions around social standing.
			1. This may be worth looking into, but implementation would likely be very variable between EPIC sites. With this being the case, the questionnaire could match what is seen in Epic which is considered a standardized way of extracting that data.
			2. **ACTION ITEM:** Sites need to determine how social determinants of health are captured in their individual EHRs and Maya Sabatello’s group can help harmonize the information and the survey.
4. **Science Presentation: A Framework for Integrating Polygenic Risk Scores into the Electronic Health Record |Hana Bangash (Mayo)**
	1. Hana Bangash presented on their group’s framework to facilitate GIRA integration into the EHR.
		1. The goal of the framework is to take the GIRA report, integrate it into the EHR, and link to clinical decision support with an aim of guiding clinicians in interpreting and applying results to patient care.
		2. Details of the framework were described and included several domains: developing detailed workflows, identifying relevant institutional resources and applying for approvals, building new tools and developing new PRS education materials for clinicians.
	2. The first part of the framework focuses on PRS data ingest and storage.
		1. The team tried to use institutional solutions but limitations led to a requirement for a new genomic order in the EHR. This new order took 3 months to build. The features of the order include unique features such as the ability to upload scanned documents to the EHR, use smart phrases to send results in-basket and send portal messages to patients.
		2. To view results, patients can see results in the patient portal app by clicking test results to see the scanned report.
		3. Providers can see details in chart review, results review and document review.
	3. The next part of the framework focuses on working with IT to write GIRA data into Epic.
		1. A custom data parser is used to write the GIRA structured data to smart data elements. This process uses several pre-existing APIs. The workflow of the PRS data storage was described. After the coordinator downloads the pdf and csv file to a binder, a parser identifies the patient, searches the csv file and writes structured data into an Epic registry that is used to populate smart phrases into the clinical decision support message.
	4. The clinical decision support workflow was described.
		1. Narrative summary, scanned pdf and best practice header including intranet education were built into the clinical decision support system.
			1. The narrative summary contains a summary of the positive genetic results.
			2. The pdf copy of the GIRA is attached to the message.
			3. A best practice header alerts clinicians to the presence of abnormal results.
			4. An intranet education website was built so physicians would not have to copy and paste the link to an external website.
		2. A Web-based CDS built behind the firewall and includes similar educational resources to the eMERGE education resources.
		3. Additional emphasis was placed on increasing awareness of the study among clinicians through newsletter, sharepoint sites, conferences, and grand rounds.
	5. Because Mountain Park Health Center has limited resources and a different EHR system, adaptations were needed to facilitate results ingest and clinical decision support.
		1. A coordinator attaches results to various ECW orders for the various reports.
		2. Providers are notified through the Jellybean notification system. No structured data is stored.
		3. Patients are called by a coordinator and informed of their results.
		4. A PDF was created with clinical recommendations for GIRA findings and is available on the sharepoint and emailed to the providers. Mayo is also working on making the intranet education website available to mountain park clinicians as well as an expert hotline.
	6. Hana described successes the site has had in implementing the framework.
		1. The new custom data parses and genomic order were great successes allowing streamlining of the return of result workflow.
		2. The website with GIRA recommendations is now live with education materials.
		3. The workflows for return of results have been streamlined and adjusted for Mountain Park.
	7. Challenges were described.
		1. There was a significant investment in designing and implementing new technologies and tools.
		2. Multiple committee approvals were needed, in particular for the BPA alerts.
		3. There is a lack of automation in certain steps of return of results.
		4. The overarching challenge is to harmonize the workflows and keep timelines aligned.
	8. Q & A
		1. Can this workflow be generalized? Are there technical or regulatory barriers?
			1. Mayo will share technical workflow so other sites can implement them, especially if they use EPIC. For regulatory requirements, each site will have its own process.
		2. Can you elaborate on approvals and hurdles for approving this workflow?
			1. The new order required input from EPIC research for special approvals. Being able to use BPA header and a clinical support header required its own approval.
		3. Are we going to lose our comparators if it's easy at some sites and difficult at other sites?
			1. The major aspects of the content and who gets notified is comparable but there are going to be technical differences in what sites can do.
		4. Are there restrictions due to EPIC in regards to what custom EHR code can be shared?
			1. We are working to organize what we can share and get approvals from EPIC.
5. **Workout breakout session one**

**Notes can be found in the workgroup google docs, linked below for reference.**

* 1. **Provider Uptake & Outcomes**
	2. **PRS & Clinical Operations**

**Action Items:**

* Leah Kottyan will be reaching out to the group about similar efforts at different sites regarding PRS in the clinical implementation pipeline to connect individuals for discovery opportunities.
	+ People who already have a disease for which a PRS was developed can be identified and be used to analyze environmental components.
1. **Scientific Presentation: Lessons learned from the FOREST project: Implementing a family history collection tool into the EHR | Georgia Wiesner (VUMC)**
	1. The presentation covers family history in clinic, implementation science, the FOREST study, initial metrics and lessons learned
		1. Family Health History (FHH)
			1. Having a family history of a first degree relative increases the rate for that individual twofold
			2. Family history is a really good risk predictor
			3. It’s hard to obtain in the clinic -- why, and what are we going to do about it?
			4. There are a lot of barriers to FHH collection.
				1. Patient education, accuracy, cultural differences
				2. Provider knowledge, awareness, complexity, guidelines, time.
				3. Health system inadequacies in data collection and actional information,
			5. The current FHH process is the patient gives their information to the provider, who asks themselves relevant questions before submitting for data processing, which then goes into a healthcare plan and the medical record.
			6. Different ways to gather family history information and put it in a more usable format that is more readily available across the system. The bulk of the work could be performed by computer systems that perform analysis, collecting and collating and putting guidelines together for the clinician.
		2. The FOREST project is thinking about implementation with the family history and cancer risk study.
			1. Part of the NCI moonshot grants of studies designed to look at and identify people at hereditary cancer risk and be able to provide coordinated care.
			2. The design is one of implementation science.
			3. This study has unique aspects such as deploying this in two academic medical centers that are highly different from each other.
			4. The implementation science approach consists of:
				1. Pre-implementation (assess all stakeholders, characterizes stakeholders, and evaluates factors that affect implementation),
				2. Implementation (align choice of strategies to the results of assessments, varying strategies, multiple strategies, close monitoring during initial period and adapting implementation to overcome challenges as they arise
				3. Post-implementation (measure outcomes such as provider adoption, patient reach, effectiveness, fidelity, adaption for unique populations, and persistent barriers)
			5. FOREST is using MeTree, a standalone computer based program that’s patient facing. It’s designed to facilitate use of guidelines. For cancer, it enables risk stratification.
			6. FOREST Aims:
				1. Deploy a care delivery model that will facilitate systematic risk assessment for hereditary cancers in diverse clinical environments.
				2. Improve access to genetic healthcare providers who provide counseling, testing and follow up management for participants at risk for hereditary cancer syndromes.
				3. Explore the feasibility of a care delivery model to improve family engagement with cascade testing after genetic testing.
			7. The implementation process has not been easy. It required identifying stakeholders, a security review of MeTree and HealthIT, committee reviews, and engagement with research and patient community.
		3. Lessons Learned -- Automating FOREST
			1. Outcomes
				1. Focus groups -- very supportive, sensitive to confidentiality of information, MMC group less supportive of integrating reports into EHR, wanted their PCP to have report.
				2. Study chosen by VUMC HealthIT as beta testing site to link EPIC with patient recruitment and study management.
				3. Successful MeTree EHR link with specified and approved demographic elements.
				4. Successful implementation of e-consent.
				5. Meharry Medical Center recruitment to begin soon.
		4. FOREST metrics for identification of high cancer risk
			1. 11,645 invited via portal
			2. 2,096 (18%) interested
			3. 875 consented (41%)
			4. 522 MeTree initiated (60%)
			5. 268 (51%) MeTree completed
			6. n=86 (32%) high risk
		5. Summary
			1. A scalable and automated system to identify individuals at high risk for inherited cancer was deployed.
			2. Integration between MeTree and VUMC EPIC has been completed.
			3. There has been a strong interest in participation in this study.
			4. 32% of MeTree completed at “high cancer risk”
			5. Ongoing:
				1. Deployment at Meharry Medical Center
				2. Participant and provider surveys
2. **Workout breakout session two**
	1. **R2/sIRB/ELSI**

**Action Items:**

* Sarah Jones will work with the IRB to clarify the circumstances for handling participants who age into the 18+ category who may still require a legal guardian.
	1. **EHRI**
1. **Science Presentation: Diagnostic yield from combined cardiomyopathy and arrhythmia genetic testing | Beth McNally (Northwestern)**
	1. **Background**
		1. Genetic testing for heritable cardiomyopathies and arrhythmias is now recommended internationally by cardiology professional societies to establish a genetic etiology, guide by clinical management, and identify at-risk family members. The goal is to assess the yield and the management implications of using a combined cardiomyopathy and arrhythmia panel, known as “The Big Panel”, which tests more genes instead of fewer genes. This is important because there has been a push to test fewer genes, in part driven by variants of uncertain significance.
	2. **About Invitae Sponsored Testing Program**
		1. The aims are to ensure equity of access to genetic testing, reduce the time it takes to reach diagnosis, and streamlining access to treatments or clinical trials.
		2. Invitae had two commercial partners that paid for genetic testing. There were about 1200 different providers referring patients over a one-year period of time.
		3. One option you could do from having sponsored testing is to ask: was paying for the test one of the barriers?
		4. The testing program produced a really nice outcome dataset.
	3. **Methods**
		1. Patients were referred through a sponsored testing program by 1,203 clinicians between July 2019 - July 2020.
		2. Eligibility criteria:
			1. Suspected or known diagnosis of a familial cardiomyopathy or arrhythmia.
			2. Family history of familial cardiomyopathy or arrhythmia.
			3. Personal or family history of unexplained sudden cardiac death.
		3. Just under 5,000 programs full gene sequencing was done, with variant analysis up to 150 genes, which is their combined panel.
		4. They reviewed de-identified data, all approved by the IRB.
	4. **Diagnostic Yield of Combined Panel**
		1. 4,800 subjects, positive or molecular, resulting in just under 20%.
		2. Variant of uncertain significance found in 51% and a negative result in 28.9%.
		3. If a clinician indicated there was a high index of suspicion, those individuals were more likely to have a positive result -- 25.7% versus 9%. So, it turns out clinicians are reasonably good at predicting high index of suspicion.
	5. **Age Range Found in Cohort**
		1. The mean age was about 40, range 0-93 years old. There was a good number of individuals over the age of 60.
		2. Ancestry did skew towards white Caucasian participants at just under 60%, Black African American participants were just under 12%, and Hispanic was at 7.8. Other categories added up to another 8%.
	6. **Positive Genetic Results Were Found Across the Age Span**
		1. Ranges from 22.1% in the youngest group, but 16.3% in that 60+ group, indicating that we have genetic diseases across the life span.
		2. People in the middle ages of the life span are more likely to have that genetic diagnosis of hypertrophic cardiomyopathy.
		3. Dilated cardiomyopathy is evenly distributed across the lifespan, as many in the younger group as in the older group. So, that’s a disease that we really have to think more about getting everybody genetically tested.
	7. **Condition-specific Gene Panels**
		1. If we had just used condition specific panels, what would we have missed? We would miss a fair number of testing.
	8. **Pathogenic and Likely Pathogenic Variants by Gene**
		1. The genes implicated are very skewed. This dataset had a lot of hypertrophic cardiomyopathy patients.
	9. **Missed Diagnoses Prevented by Broad Combined Panels**
		1. 10.9% of positive results would be missed by a disease-specific panel.
		2. Majority of those were people across cardiomyopathy subtypes.
		3. Importantly, we had a lot of people with hypertrophic cardiomyopathy, and you really do need to order a broad panel of genes for those individuals.
		4. If you order a larger panel you are much more likely to get a more positive result, and that is pretty much across the spectrum.
		5. A lot of these results have clinical indications of how it’s going to change care, and that affected about 66% of the participants in the results.
	10. **Impact on Families**
		1. Among 954 patients with positive results, 32.2% had family members referred for genetic testing.
		2. 958 family members of positiver probands were tested (~3 per positive original patient).
		3. 402 family members who actually had a positive result.
	11. **Conclusion**
		1. Combined cardiomyopathy and arrhythmia genetic testing identified clinically-relevant variants for 1 in 5 suspected cardiorhythm patients.
		2. 26% of patients with high index of suspicion had positive results, yet even 9% of low index patients were also positive.
		3. Over two-thirds of positive findings may impact patient care.
2. **Workout breakout session three**
	1. **Comprehensive Risk Assessment & Return**
	2. **Phenotyping**

**Action Items:**

* A Google document will be created to survey sites on how referral information is collected at each site.

**eMERGE Day 2: Thursday, September 29th, 2022**

1. **eMERGE Network overview: Priorities, goals, progress and ESP recommendations | Rex Chisholm (SC Chair, Northwestern)**
	1. The goals of the ESP Meeting are to recognize the significant progress that's been made, discuss GIRA testing plans, give an update on timeline and to summarize pending decisions and roadblocks.
	2. Accomplishments since April 2022 were highlighted:
		1. There are 3,330 participants enrolled with 45% identifying as non-white. 11% of the paritcipants are pediatric, and 66% are female.
		2. A provider survey has been developed to assess outcomes and to understand how implementation is progressing.
		3. Participant Broad samples and MeTree data are flowing to and from R4. A contingency survey was developed to supplement history for participants who are unable to complete MeTree.
		4. GIRA infrastructure has been finalized for the majority of conditions. GIRA PDF testing is coming soon and should happen in October.
		5. Numerous papers are planned to be submitted this year related to PRS validation, clinical implementation, and lessons learned from eMERGE.
	3. Goals for the next 6 months were outlined.
		1. GIRA software testing and launch is targeted for August-October, 2022. We are in good shape to get the software launched in November.
		2. The EHRI group is working on developing plans for how to integrate GIRA into EHRs by December 2022
		3. In January 2023, return of results and outcomes surveys will be deployed.
	4. Several study challenges were discussed
		1. Reduction of full in-kind support from Invitae was a challenge. Additional funding sources are under investigation.
		2. Medical care cost coverage will be heavily dependent on each site. These discussions are ongoing and will require operationalizing plans and IRB approval.
		3. There are concerns about the development and implementation of workflows related to GIRA return. Additional discussions are ongoing.
		4. The timing of data freeze and interim analysis has not been finalized at this time.
	5. Q & A
		1. Question: Was it resolved about the comparator group being those below high risk or whether it will be everybody?
			1. Answer: We will compare high risk to not high risk. There will be additional discussions whether there will be changes to this outcome.
2. **Comments from the ESP Chair | Dan Rader (University of Pennsylvania**
	1. Dan shared his praise for how hard everyone has been working and recognized the great progress. He shared his congratulations on terrific work.
3. **Provider Uptake & Outcomes Update | Nita Limdi (UAB) & Dave Veenstra (University of Washington)**
	1. Nita Limdi and Dave Veenstra reviewed the overall study design, which estimates 25% of the participants receiving a high PRS score. Participants with a high risk PRS will have the GIRA returned in person.
	2. The group created a new framework to examine the study outcomes that focuses on prespecified versus exploratory/post-hoc analysis, instead of primary/secondary outcomes.
	3. The Outcomes group has discussed clustering outcomes across phenotypes, for example pediatric, adult cardiometabolic, and adult cancer in their first paper.
	4. Since this is a cohort study, the findings will be examined at different timepoints following the return of results. The data points will be collected via participant surveys and EHR.
	5. There will be a comparator group consisting of participants who do not have a high PRS.
	6. The approaches will allow the study to examine unobserved confounders. These are still being finalized.
	7. The Outcomes and Phenotyping workgroups have been working together to determine how to collect outcomes data from the EHR.
	8. The Outcomes workgroup is in the process of clearly defining outcomes for each cluster of phenotypes.
	9. The study outcomes will be the frequency of actions taken or diagnoses made, instead of if an action or diagnosis was made.
	10. The Network is proposing to conduct an initial analysis after 5,000 participants have been enrolled. This will assist in gauging the feasibility of sites returning not high risk GIRAs to participants in person.
		1. This will allow the network to select appropriate comparator/control participants in a diverse distribution reflective of the high risk GIRA participants.
	11. The ESP agrees with the study moving away from primary and secondary outcomes. They also agree with defining pre-specified outcomes.
	12. The ad-hoc and exploratory outcomes are in addition to the prespecified outcomes. The adhoc and exploratory outcomes refer to clinical outcomes that are recognized by examining the data.
	13. The ESP is interested in hearing if the network is planning to use the interim analysis for purposes other than defining the comparator group. For example, an overall process analysis for streamlining.
	14. The ESP encourages the Outcomes group to clearly define the number of participants.
	15. In person return also includes telehealth visits. It refers to a contact with the participant instead of the mailed letter GIRA return. The mode of contact return (in person, telehealth) will depend on the site.
4. **PRS & Clinical Operations | Leah Kottyan (CCHMC), Eimear Kenny (Mt. Sinai), & Niall Lennon (Broad)**
	1. In addition to the 10 conditions that went through CLIA validation, manuscripts have been prepared and submitted for multiple conditions. A flagship manuscript is in process which will follow the initial 23 conditions to the 10 that are being used in eMERGE IV.
	2. Future directions include enabling the discovery pathway PRS development, providing recommendations for future groups and PRS selection, and using eMERGE data to monitor effectiveness of ancestry adjustment and evaluate the percentage of participants in high risk groups.
	3. So far, the Broad has received 353 samples from 5 sites and about 200 of those are in process with 153 reports having been generated and delivered to R4. The average turnaround time has been 6 weeks which is expected to come down (the target has been 4-6 weeks).
	4. The number of samples with high risk per conditions and for more than one condition (assuming the conditions are uncorrelated) looks reasonable at this time.
		1. There was 1 individual with 3 high risk conditions (CHD, HCL, and T2D) which was expected in about 1 in every 700 so seeing it in the first 150 may have been concerning although the 3 conditions can be highly correlated.
	5. The Broad took the All of Us data and imputed it.
5. **R2/sIRB/ELSI | Digna Velez Edwards (VUMC), Ingrid Holm (BCH), & Wendy Chung (Columbia)**
	1. As of September 25, 2022, a total of 3,395 participants have enrolled.
	2. First return of results is planned to be in November of 2022.
	3. As of now, the last participant enrolled is projected to be in February of 2024.
		1. To reach this goal, the Network needs to enroll approximately 6 people/site/day.
	4. Current enrollment contains approximately 52% white and 48% minority persons and an almost 2:1 ratio of women to men.
	5. Future efforts for recruitment and retention include:
		1. Implementing the backup survey for family health history, increasing recruitment efforts across the Network, and initiating retention communications.
	6. Reconsenting minors that have their 18th birthday during the study will require a new part 2 consent form.
	7. Regarding retention, postcards have been developed and approved which will be mailed to participants prior to return of results.
	8. Strategies for provider education/support depends on site recruitment strategies.
		1. In-person service sessions with providers have been proposed.
		2. General PRS education to help providers understand the science and allow for personal determination of clinical utility is also proposed.
		3. Another strategy for provider education is to hold specific condition education sessions to learn about clinical areas being studied.
	9. The ELSI subgroup has several manuscripts in progress which cover a variety of topics, such as lessons learned from prior eMERGE phases, best practices regarding harmonizing education materials, and patient interest and concerns in underserved communities, and others.
	10. The ESP feels that the currently planned manuscripts are excellent concepts for publishing.
	11. The ESP is concerned about the medical care cost issue that has arisen for enrolled participants.
		1. The consents do not state that any tests will be covered by eMERGE.
		2. Some sites do have language that some costs **may** be covered, but does not explicitly say costs **will** be covered.
	12. In regard to those who turn 18 years in the study and possibly age out of their current healthcare system, data that had previously been generated can be used but no future data will be collected.
	13. Updated calculations may be needed to estimate if people are at high risk or have multiple risks due to the current enrolled population of older, mostly female participants.
	14. Retention after return of results may need to be developed to remind participants about the study and that the person is enrolled.
	15. The current recruitment curve should show more inflection points upward as sites reevaluate recruitment methods and modify their approaches.
	16. Adjustments for site-specific recruitment targets may need to be addressed in a future date.
6. **Comprehensive Risk Assessment & Return (CARE) | Gail Jarvik (UW), Iftikhar Kullo (Mayo), & Cindy Prows (CCHMC)**
	1. The GIRA is close to being tested in the R4 Portal.
	2. A RoR education document has been developed for providers and a talking point sheet has been developed for study staff.
	3. An EHR encounter note template with Epic smart phrases is under development.
	4. The monogenic report and/or the Broad report may be placed in the EHR before the high risk GIRA in order to be compliant with the Cures Act.
	5. Bottlenecks to MeTree survey completion became apparent prior to the June SC meeting.
		1. Possible solutions to this issue have been discussed with the outcome being development of a rescue survey being developed and launched.
	6. MeTree completion rates show to be higher for sites that dedicate study staff to help participants complete MeTree compared to those that allow participant completion.
	7. The back-up survey for family health history is complete and pending PI approval.
	8. The back-up survey will be entered into the R4 Portal but data will not be integrated in the GIRA.
	9. Medical care costs subgroup was created to investigate and operationalize covering specified tests/procedures for high risk participants.
		1. The clinical care recommendations in the GIRA will be the tests/procedures potentially covered.
		2. Billing policies and procedures varied across the Network.
		3. Decisions have been made to cover tests only for high risk PRS, only evaluation screening, and for tests will be paid if recommended for a given demographic in the GIRA recommendations.
		4. Tests recommended to be covered can be found [here](https://docs.google.com/spreadsheets/d/1pTKsB02mR4BYTz_qxvUb3LlA6vfWMtr8/edit#gid=483832582).
		5. Three options have been identified for coverage:
			1. Use study funds to cover the recommended list for **all** participants regardless of socio-economic status.
			2. Option 1 plus economically disadvantaged participants may receive additional assistance from institutional programs.
			3. Sites will **not** use study funds to cover any recommended tests/procedures.
		6. Outstanding issues include:
			1. How to address MCC if some sites are required to cover tests for all participants?
			2. Will sites need to identify on a per participant basis which tests were paid for using research funds? ESP states yes during this discussion.
			3. Can each condition lead create a letter of medical necessity to assist getting tests covered by insurance?
	10. Communication to the participant regarding needing a test and the site covering might be included in the GIRA.
	11. Providers will be alerted when the GIRA is returned to the participant and may serve as a good opportunity to notify the provider that the cost of the test may be covered.
	12. A concern that is brought up multiple times is the possibility of influencing outcomes if tests are being paid for by study funds.
	13. The outcomes question becomes important to define in this case. If provider/participant behavior is the outcome, does paying for a screening test/procedure affect behavior post-RoR?
7. **EHRI & Clinical Decision Support (CDS)| Luke Rasmussen (NU) & Bob Freimuth (Mayo)**
	1. Current activities of the EHRI workgroup include workflows and shared infrastructure/solutions.
	2. Sandy Aronson (MGB) is leading a hazard assessment with both clinical and tech/ops stakeholders.
		1. A full evaluation of probability, impact, contingency, and mitigation are out of scope however.
	3. Cong Liu (Columbia) led a panel proposal for the 2023 AMIA Informatics Summit.
	4. Future activities are to identify and consider applicable existing standard specifications such as HL7 FHIR and dissemination of information learned by way of manuscripts, abstracts, and panels.
		1. New data structures could be utilized to disseminate data in eMERGE years 3-5.
	5. Discussions on general architecture and structures were very helpful in preliminary thoughts on how to implement data getting to the EHR.
	6. Practical implementation requires those involved in eMERGE and the day-to-day staff at sites that work in operations.
	7. The temporal relationship between uploading of the GIRA/CDS and participant notification are site-dependent.
	8. The workflows on the timing of how the discrete data and the PDFs are still being developed.
	9. HL7 v2 could be considered for data movement in place of using FHIR.
8. **Phenotyping| Chunhua Weng (Columbia) & Wei-Qi Wei (VUMC)**
	1. In the past few months, the phenotyping workgroup has been working with the GIRA workgroup to collect and review condition-specific requirements for EHR clinical variables data collection. Additionally, the workgroup has been collaborating with the outcomes workgroup to collect EHR variables.
	2. VUMC is implementing a metadata framework and Columbia completed a survey evaluation for phenotype metadata framework. The results were submitted to AMIA 2023 Joint Summits Conference.
		1. The metadata paper includes survey results from 24 participants who answered questions about the phenotyping metadata framework and how helpful the framework is in choosing a phenotype.
		2. There were no surprising findings. Most respondents find the metadata useful. Limitations included the tradeoff between expressiveness and tractability. If there are too many metadata elements out there, the data collection process can be very time consuming.
		3. A data dictionary for implementing the framework is currently being developed.
	3. The submission and revision of the NLP paper from eMERGE III has also been worked on continuously.
	4. The GIRA data extraction guideline document ([here](https://docs.google.com/document/d/1S2k9Oz7XeMTuHz2qlMvsuo6Ln9LROVYg/edit)) is to guide eMERGE sites in pulling clinical data elements from their electronic medical records for conditions that need additional information than what is included in the participant survey.
	5. Next steps for the phenotyping workgroup include harmonizing the extractions of referral and encounter data from Epic across the network and coordinating with the outcomes workgroup to plan for referral outcomes extractions from the EHR.
		1. The phenotyping workgroup is responsible for coordinating the outcomes data pulls from the EHR. Some things like referrals and missingness will be discussed and coordinating which subjects are needed to pull this data from like a control group or which eMERGE subjects, etc.
		2. Data freeze points also need to be determined and coordinated with the outcomes group.
		3. Defining dates for each encounter are also being discussed currently. Outcomes extractions use baselines of 6 and 12 months which are relative to each individual patient. Index dates for each participant need to be built to make sure this is consistently implemented across participants and sites.
		4. The importance of prevalence versus incidence of disease in the EHR, especially with older patients, should be stressed. There needs to be a robust control group and ideally randomize participants into groups based on whether or not someone received a return of results. If randomization cannot be completed, a control group can be used.
			1. Making sure an outcome is a true outcome on the GIRA reports is also important.
9. **Input/Feedback from the ESP, general discussion**
	1. The ESP is very impressed by the general progress that has been made.
	2. The ESP would like the network to make a decision on the size of interim analysis. They prefer the smaller proposed amount of 20%.
		1. It would be beneficial for the network to write a formal analysis plan of what will be learned in the interim analysis.
	3. The ESP could not come to a consensus regarding the medical care cost coverage. They recognize the challenges of balancing the impact on the study with the ethical obligations to the participants.
10. **Closing remarks | Rex Chisholm (SC Chair, Northwestern)**
	1. The eMERGE Network really appreciates the time taken from the ESP to advise all sites.
	2. Thank you to the CC for coordinating the meetings and arrangements.

**Action Items**

**Coordinating Center:**

* N/A

**Provider Uptake & Outcomes:**

* The Outcomes group must discuss how to select controls. This involves including biostatisticians and determining how to select what criteria participants would have in the not high risk comparator group.
* The barrier to eMERGE participation questions from the Post-RoR survey can be contributed to the PhenX toolkit.
* A question about the wearable device for Afib will be added to the post RoR survey.
* The outcomes group should propose to the PI’s a schedule for data freezes and EHR pulls for outcomes analysis, while minimizing redundant work at the sites and CC (example: Data freeze at 5,000; 20,000; and 25,000 participants returned).
* The provider group should clarify when the survey will be sent, specifically after a high risk PRS, not monogenic result.
* If there is feedback on the content of the provider survey, it must be brought to the Provider survey subgroup, and then to the Outcomes workgroup, before being presented to the PIs.
* Sites need to determine how social determinants of health are captured in their individual EHRs and Maya Sabatello’s group can help harmonize the information and the survey.

**Phenotyping:**

* A Google document will be created to survey sites on how referral information is collected at each site.

**PRS/Genotyping:**

* Leah Kottyan will be reaching out to the group about similar efforts at different sites regarding PRS in the clinical implementation pipeline to connect individuals for discovery opportunities.
	+ People who already have a disease for which a PRS was developed can be identified and be used to analyze environmental components.

**R2/ELSI/sIRB:**

* Sarah Jones will work with the IRB to clarify the circumstances for handling participants who age into the 18+ category who may still require a legal guardian.