**Summary of Steering Committee Meeting: February 2022**

February 2-3, Hybrid (Zoom & In-Person)

[**eMERGE Day 1: Wednesday,** February 2nd, 2022](#kix.t5jofxj6oo59)

* 9:00-9:15 AM [Opening Remarks | Robb Rowley (NIH/NHGRI)](#rta5dxg4yapo)
* 9:15-9:30 AM [Announcements, opening remarks | Rex Chisholm (SC Chair, Northwestern)](#7xjuvpwkusu7)
* 9:30-10:10 AM [Assessing provider uptake & utilization | Ingrid Holm (BCH) & Jim Comino (UAB)](#g2nlshqtwvvn)
* 10:10-10:30 AM Scientific Presentation: [Identifying Persistent Respiratory Sequelae for COVID-19 Patients in the Electronic Health Record | Zachary Strasser (MGB)](#kix.s6sf9mbcekkt)
* 10:50-11:10 AM Scientific Presentation: [The Value of Population Screening for CDC Tier 1 Genomic Conditions | Greg Guzauskas (UW)](#7fxlmrvh0mjl)
* [Workgroup breakout session one](#kix.bgtubp59mf33)
  + 11:10-12:10 PM [PRS & Clinical Ops](#kix.wcaeeauhl626)
  + 11:10-12:10 PM [Provider Uptake & Outcomes](#kix.firzc1gcqtdo)
* 12:50-1:35 PM [Network-Wide Outcomes & Analysis Planning | Noura Abul-Husn (Mt. Sinai) & Nita Limdi (UAB)](#kix.fxp2ypf3s8ld)
* [Workgroup breakout session two](#kix.bgtubp59mf33)
  + 1:35-2:55 PM [Comprehensive Risk Assessment & Return](#kix.n0xav72dmddo)
  + 1:35-2:35 PM [Phenotyping](#kix.1zta04nm4jtt)
* [Workgroup breakout session three](#kix.bgtubp59mf33)
  + 2:55-3:55 PM [EHRI](#kix.yf8asgaaz84j)
  + 2:55-3:55 PM [R2/sIRB/ELSI](#kix.slcr5s9o6f4)
* 3:55-4:25 PM [Care & GIRA progress | Gail Jarvik (UW), Iftikhar Kullo (Mayo), & Cindy Prows (CCHMC)](#2mvc3yu4aefj)
* 4:25-4:30 PM [Closing remarks | Rex Chisholm (SC Chair, Northwestern)](#kix.cazn6jal4dhv)

[**eMERGE Day 2: Thursday,** February 3rd, 2022](#kix.jdkhurb9mh65)

* 9:05-9:20 AM [Invitae Custom Panel Update | Eden Haverfield & Tara Schmidlen (Invitae)](#tgq88x303iod)
* 9:20-9:45 AM [RA Training Update | Digna Velez-Edwards (VUMC), Ingrid Holm (BCH), & Wendy Chung (Columbia)](#chq0y7q5iu9n)
* 9:45-10:15 AM [R4 & End-to-End Testing Overview | Josh Peterson (CC) & Jodell Jackson (CC)](#reb1jpzhzmlq)
* 10:15-10:40 AM [Phenotyping Workgroup Update | Chunhua Weng (Columbia) & Wei-Qi Wei (VUMC)](#vzfsxf5rwvxh)
* 10:55-11:15 AM Scientific Presentation: [Developing and Validating a Genome Informed Risk Assessment Tool for Coronary Heart Disease | Mohammad Saadatagah (Mayo)](#vqgzzgvmhp6q)
* 11:15 AM-11:40 AM [PRS & Clinical Ops Workgroup Update](#tsnbs4ps81cs)
* 11:40-12:05 PM [EHRI Workgroup Update | Luke Rasmussen (NU) & Robert Freimuth (Mayo)](#ssb5ngxkupd1)
* 12:05-12:15 PM [Closing Remarks | Rex Chisholm (SC Chair, Northwestern)](#3i8wch688f9)

[Action Items](#kix.m4nlqta1yqbf)

**eMERGE Day 1: Wednesday, February 2nd, 2022**

1. **Opening Remarks | Robb Rowley (NHGRI)**
   1. The NHGRI is impressed of what the Network was able to accomplish virtually in a one-year time period.
   2. Clesson Turner has left the ESP and has joined the NHGRI. Brandon Lee from the Baylor College of Medicine has joined the eMERGE ESP.
   3. The NHGRI has established the TiDHE (Training, Diversity, and Health Equality) Office to help champion a diverse genomic workforce.
   4. NIH Repayment program is available to help MD’s, PhD’s, and genetic counselors repay their student loans in an effort to keep health professionals in research careers.
   5. The NIH is looking to develop genomic research skills for undergraduates enrolled in minority-serving institutions or Institutional Development Award (IDeA)-eligible institutions. The application due dates are July 01, 2022, and July 01, 2023.
   6. The NIH is also offering the “Masters for Medical Students in Genomics” funding opportunity. This opportunity serves to help medical schools develop a genomics-based curriculum for masters programs for medical students. The application due dates are January 25, 2023, and January 25, 2024.
   7. The NIH’s “Advancing Genomic Medicine Research” funding opportunity aims to stimulate innovation and advance understanding of when, where, and how to implement genomic information and technologies in clinical care. The application due dates are August 1, 2022, and March 13, 2023.
   8. The NIH’s “BIoethics Supplements from NIH Office of Director” funding opportunity aims to address bioethical issues in scope to inform policy and develop ethics capacity. Please contact Rene Sterling or Dave Kaufman if you have any questions about this opportunity. The application due date is March 17, 2022.
2. **Announcements, opening remarks | Rex Chisholm (SC Chair, Northwestern)**
   1. SC Meeting Goals and Reminders: The Network hopes to finalize the GIRA format, plan for the Invitae panel, discuss plans for provider surveys and feedback, outline primary outcomes analyses and plans for sub analyses, and identify barriers for recruitment and strategize solutions.
   2. The sIRB amendment was approved in November 2021. The R4 recruitment portal has been tested by all sites and is in the final stages. The portal is expected to launch on February 14, 2022.
   3. Data Use Agreements (DUA) between the sites and the Coordinating Center (CC) have been fully executed at 3 institutions. Duke (MeTree) contracts have been released to sites; 2 being fully executed. Invitae contract templates are expecting to be released shortly. Sites must have a MeTree and Invitae DUA in place for those services to be utilized; however, this does not prevent sites from beginning recruitment.
   4. Sites can begin recruitment once the R4 portal has officially launched, their DUA with Vanderbilt have been executed, and when the IRB amendment is finalized.
   5. Network challenges over the next 6 months are: the development and testing of GIRA generation software, executing remaining contract/DUAs for partner organizations, determining methods and approvals necessary for data integration of reports for sites, and E2E testing for initial recruitment of participants.
   6. Some sites had concerns regarding timing of data and release to participants and EHRs in regards to the 21st Century Cures Act. This was addressed between the Network and the ESP, and it was agreed that the R4 portal acts as a staging area for the data prior to any return of reports to sites, EHRs, or participants. R4 data storage does not conflict with the 21st Century Cures act. The recommendation from the ELSI workgroup is to hold genetic samples until as close as possible to the GIRA return. The goal is to avoid time gaps between the signed Invitae report and GIRA return.
   7. Sites can use the existing API in REDCap to pull R4 reports. Structured data will be captured from Invitae, MeTree, and Broad. The intact structure message and the PDF/PNG of the pedigree will be captured in a REDCap variable. Some of the messages needed for downstream GIRA generation will be parsed out of the data variables . The parse variables are going to populate a partner-specific instrument, so those specific data elements can also be pulled.
   8. The Network milestones for the next 6 months are to finalize contracts and begin recruitment; complete GIRA software testing; finalize PRS ancestry adjustments; to begin the data flow between external partners, R4 , and sites; and to complete next IRB amendment to finalize/return GIRA materials.
      1. An ESP teleconference is scheduled on April 14th at 1pm EST.
3. **Assessing provider uptake & utilization | Ingrid Holm (BCH) & Jim Cimino (UAB)** 
   1. Ingrid Holm and Jim Cimino are co-chairs of the Provider Survey Subgroup, which falls under the Provider Uptake & Outcomes workgroup. The group must consider the medical actions already gained from the EHR and the participant surveys, and the burden on providers, when designing the provider survey. In eMERGE III, the provider survey response rate was 35%.
   2. There will be a relatively high number of returned GIRAs. Most providers would receive more than one high risk report.
   3. If the survey is the best format to assess these outcomes, the suggested content includes the PRS/GIRA understanding, if they find the GIRA clinically valuable, and the perceived impact of the GIRA on their patients.
   4. There are logistical issues associated with provider surveys:
      1. How will sites connect the participant to the provider? The CDS subgroup will be examining how sites are notifying providers that results are available. This would connect to the surveys. Provider surveys can only be in R4 if they are linked to the participant.
      2. How to handle providers with multiple patients with a GIRA? There could be one survey per participant, and some providers would get multiple surveys. There could be one survey per provider, but it is unknown when that survey would be sent (first GIRA returned, or at the end of the study). There could be one survey per provider for the first positive GIRA, and then an end-of-study survey.
         1. A suggestion was made to limit the survey to providers who had at least one or two GIRA returned. A model, typical high risk result could be used to ask the providers to react to. This would remove the focus on the participant interaction. Depending on the sample size, there may end up having a skewed response due to a wide variety of scenarios.
         2. A suggestion was made to survey providers at the end of the study to survey the overall impressions. This would require providers to recall a fair amount of information.
         3. A suggestion was made to have a minimum, really short survey.
         4. A suggestion was made to interview the primary care providers with a larger number of eMERGE participants, and interviewing lower volume primary care providers. Compensation could be provided for their time.
   5. The workgroup is suggesting provider interviews in addition to or to replace the surveys. This could be labor-intensive, but would receive more in-depth information. Providers can also be compensated, which lessens the burden. This could be combined with a survey, and at the end of the survey, invite providers to interview. A small number of interviews with the providers with the highest volume of returns would be beneficial, in addition to a survey. The focused interviews would be held at the end of the study.
   6. Survey domains can include how prepared clinicians feel they are to receive and act on GIRAs, perceived patient understanding, and how the GIRA affected their workflow. Did the providers perceive that they had primary responsibility for their patient to deal with the results? These can be assessed via Likert scales.
   7. A brief, targeted survey would collect valuable information. The survey must be extremely short and easy.
   8. The survey results could be used to identify providers to request interviews from.
   9. 10 out of 12 sites surveyed responded that they would be potentially interested in participating in interviews. The interviews would be uniform across sites, recorded, transcribed, and analyzed.
      1. A suggestion was made for if sites do not have the staffing to hold interviews, miniature focus groups could be held. Personalizing surveys would receive more buy-in from providers.
   10. The network is not planning to survey or interview providers associated with participants with not high risk GIRAs.
   11. The CDS workgroup will be discussing the workflow for alerting PCPs for not high risk results. The CDS workgroup received varied responses from the sites regarding providing clinical decision support for not high risk GIRAs.
   12. It may be easier to identify a domain of practitioners and survey them, with a subset of questions to ask if the practitioners saw a patient with a high risk GIRA. There may be different ways to target providers depending on how the participants were recruited. If there is interest in provider understanding of reports, it may be informative to survey providers who have received negative reports.
       1. The prescreening survey asks participants who their primary provider is.
   13. There is agreement that a combination of surveys of providers receiving high risk, and potentially not high risk GIRAs, as well as identifying providers from all sites for one-on-one interviews would be preferred.
4. **Scientific Presentation:** **Identifying Persistent Respiratory Sequelae for COVID-19 Patients in the Electronic Health Record | Zachary Strasser (MGB)** 
   1. Numbers vary widely for how many people continue to have persistent, recurrent, or new symptoms after recovering from COVID. The latest research shows anywhere between 30-70%. Some studies include: One with a cohort of 179 hospitalized patients in Italy with 43.4% having dyspnea at follow up. VA EHR data showing 73,435 COVID patients with increased incidence of respiratory diagnoses up to 6 months follow up compared to patients with influenza. EHR data evaluating 273,618 patients with COVID with 8% having a diagnosis of abnormal breathing between 90 and 180 days after COVID.
   2. Active research questions include accurately identifying patients who have worsened respiratory symptoms after COVID using the EHR, predicting who will develop the symptoms, and identifying if those symptoms are causing other issues for these individuals.
   3. There are challenges for identifying ongoing respiratory disease caused by COVID in the EHR including: The common challenges of EHR data with regard to inaccuracy of diagnostic codes, missingness, biases, documentation variability between physicians and different clinics, and healthcare utilization differences. The unique challenge is that this phenotype has a temporal nature. Diagnoses are being looked for after the time of COVID. ICD codes do give dates although do not give information on the onset of the problem. Another challenge is the evolving understanding of the COVID diagnosis. The phenotype casts a wide net to make sure no patients are missing.
   4. The validated model for incorporating temporal sequences for patient classification has been used in recent studies. All structured data elements are lined up in order for patients and temporal representation mining is done looking at each structural element and its relationship to the next structural element. For example, diagnosis 1 is followed by medication 1 and that sequence is its own specific feature/vector. This allows for millions of sequences for analysis.
   5. The next step includes doing a dimensionality reduction with a sparsity filer where extremely rare sequences are eliminated. A joint mutual information algorithm is also performed which takes all sequences that seem to be providing information in a correlated way and only uses sequences that are valuable.
   6. This type of classification with binary sequences often outperforms the models that rely on simple individual features. The sequences capture a relationship that a patient might experience if they are going through the healthcare system making the model effective for COVID patients who go on to develop respiratory symptoms.
   7. The proposed idea includes using the local EHR repository to extract all common structures data from COVID patients and come up with a rule to create a positive screen (patients that had COVID followed by a new respiratory diagnosis or pulmonary functions they never had before).
   8. The screen will not be perfect which is why a chart review will be necessary at the time the specific concept was given to understand what really happened. This would create a group of patients with gold standard labels.
   9. In addition to temporal sequences, rules that do not need chart reviews that can inform a model will be tested on gold labels to classify patients with long COVID. The algorithm will then be sent to 2 test sites (Mayo and NU).
   10. In summary, upcoming steps include finalizing rules for rule-based labels, training, validating, and testing the algorithm locally at MGB, and testing portability of the algorithm at Mayo and NU.
   11. A consideration is looking at timepoints after July 2020 to see if some results really improved after there was a better consensus around COVID treatments. Since different medications were more common during different timepoints, timestamps can be used in temporal sequences so medications can have their own unique records. This will allow for analysis of healthcare utilization across time.
   12. Cases and controls will be used to differentiate those that truly have respiratory diseases. Controls will be defined as a gold standard set of chart reviewed patients which will have said they have respiratory issues after having had COVID. That group will be split up into 2 different groups with 1 just for testing at the end and the other to inform rules that will be developed. The smaller set of gold standard labels - those rules will be applied to the entire training set.
5. **Scientific Presentation:** **The Value of Population Screening for CDC Tier 1 Genomic Conditions | Greg Guzauskas (UW)**
   1. Tier 1 conditions have significant potential for positive impact on public health but routine population-based genomic screening is either not performed or recommended.
   2. Cost is at least $200 per test so the question is if genomic screening is cost-effective for the US population.
   3. Quality Adjusted Life Years (QALY) is the primary health outcome that combines survival times with the health impact of disease. Utility weights range from 0 (death) to 1 (Perfect Health)
   4. Incremental Cost-Effectiveness Ratio (ICER) takes the difference of cost from new treatment from old treatment and divides that by the difference in QALY. If the ICER is under a specified threshold, then it is considered cost-effective ($100,000 was used in this presentation).
   5. The three tier 1 conditions in eMERGE (Breast cancer, colorectal cancer, and familial hypercholesterolemia) all have a prevalence of 0.5% or less. Decision models for HBOC, FH, and Lynch syndrome were developed to combine decision tress and Markov models that track health and disease outcomes over their lifetime.
   6. Cascade testing module utilizes the known number of first degree relatives with a condition in the US.
   7. HBOC was the only tier 1 condition that showed a potential of cost-effective screening model in the younger population vs. older due to the increased option to take action.
   8. Combined models for screening for all three tier 1 conditions predict life-time costs are higher in younger populations and less costly in the older populations.
   9. QALY/100,000 screened suggest outcomes are better in younger populations. The incremental cost per QALY shows the highest cost-effectiveness in 40 years and younger.
   10. Single hereditary condition screens are likely cost-effective for HBOC but not LS or FH.
   11. Screening for all three conditions is likely cost-effective for adults under 40 years.
   12. Lower cost-effectiveness in older populations likely due to missed opportunities to prevent disease. The age range can be expanded if and when screening costs decrease.
   13. The Rational Integration of Polygenic Scores Model (RIPS) is a unified model for breast cancer, colorectal cancer, and cardiovascular events. This model will be shifted away from Mendelian disease to focus on understanding the complex interactions between the PRS and the prevalence of the risk in the general population.
6. **Network-Wide Outcomes & Analysis Planning | Noura Abul-Husn (Mt. Sinai) & Nita Limdi (UAB)**
   1. eMERGE is a prospective cohort of 25k individuals. Ten conditions are included in the study, including four that will be returned to pediatric participants.
   2. The Provider Uptake & Outcomes Workgroup has been working on patient and provider surveys as well as finalizing primary and secondary outcomes for the study. Network-wide primary outcomes will be reported to clinicaltrials.gov within three weeks from the beginning of recruitment (February 16, 2022).
   3. The primary research question is: Does receiving High Risk Report for common diseases influence the adoption of recommendations and clinical outcomes? The Network primary outcome is whether providers followed recommended actions for high risk individuals.
   4. Development of primary outcomes from proposed primary outcomes by phenotype. Phenotype leads were asked to identify process (primary), clinical (secondary), and intermediate (secondary) outcomes of interest on the outcomes by phenotype document. Three types of primary process outcomes were identified: orders (tests, imaging, or labs), referrals, and encounters. Data for order and referrals will be derived from the EHR while data for encounters will be derived from the post-RoR survey.
   5. Review of numbers for analysis (adults/peds/monogenic/polygenic expected)
      1. The study expects to enroll approximately 20k adults. Adult participants will receive both monogenic and polygenic risk (PRS) results. Approximately 500 adults are expected to have a high monogenic risk; about 25% of those are expected to also have a high PRS w monogenic risk.
      2. It is expected that about 4,680 adults will have only a high PRS, and approximately 3,700 of these may have (a) recommended action(s). Some phenotypes have do not recommend action until a specified age; there will be adults under that age who will receive a high PRS and not have any recommended actions at the time of RoR.
      3. Approximately 5,000 pediatric participants are expected to enroll in the study. Pediatric participants will only receive PRS results, not monogenic results. It is expected that about 650 will have a high PRS; roughly 590 will have recommended actions.
      4. Across all patients and phenotypes, it is expected that 4,292 participants will have (a) recommended action(s) and 19,170 will not have (a) recommended action(s).
   6. Development of secondary outcomes by phenotype
      1. Development of secondary outcomes is being completed via a process similar to that used for the development of primary outcomes. Phenotype leads will be directly consulted by the Outcomes co-chairs as part of the development process.
      2. Secondary outcomes will be intermediate and clinical outcomes (as applicable) for each phenotype.
         1. Intermediate outcomes focus on actions that occur after the process outcome. For example, ordering a test would be a process outcome and prescribing medication based on the results of that test would be an intermediate outcome.
         2. Clinical outcomes focus on actions that occur after the intermediate outcome (e.g., a new diagnosis of disease or days of school missed).
   7. CKD and CHD were reviewed as phenotype-specific examples of power and secondary outcome development.
7. **Workout breakout sessions**

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

* 1. **PRS & Clinical Ops**

**Action Items:**

* + 1. Eimear will share the PRS/Genotyping MCS with the co-chairs, and then it will be circulated to the group to invite those interested to join the writing groups.
    2. Hypercholesterolemia, Obesity, and CHD must send a written description of the clinical association/validity study to Niall Lennon ([niall@broadinstitute.org](mailto:niall@broadinstitute.org)) and Maegan Harden ([mharden@broadinstitute.org](mailto:mharden@broadinstitute.org)) to meet NYS documentation standards. This can be a methods write up or a publication.
    3. Cong Liu will test the results empirically with the AoU data against the BOADICEA fixed parameters, once the AoU data is available.
  1. **Provider Uptake & Outcomes**

**Action Items:**

* Phenotype leads should revisit the [Outcomes by Phenotype](https://docs.google.com/spreadsheets/d/1zv_eHxnp5aVhMVeEiv5JdEt2LPnYUHPSGHIZTlRuTfg/edit#gid=34309240) spreadsheet **by Wednesday, February 16th** and ensure it accurately represents the final GIRA recommendations and related outcomes of interest.
* The Outcomes group will finalize the primary outcomes and submit them to clinical trials.gov by **Wednesday, February 28th.**
* Sofia will send out a Doodle poll and touch base with the Provider Surevy Subgroup co-chairs to determine the next meeting date(s).
  1. **Comprehensive Risk Assessment & Return**

**Action Items:**

* N/A
  1. **Phenotyping**

**Action Items:**

* The *Deprecated Triglyceride [Mass/volume] in Serum or Plasma* LOINC code 3049-4 needs to be confirmed by the Type II Diabetes lead site, MGB, by **Friday, February 18, 2022**.
* It would be helpful to provide equations so conversion into correct units can be done if necessary. Mayo is providing unit conversion equations in cases of unit errors by **Friday, February 18, 2022**.
* If each ICD code is linked to the corresponding allergen LOINC code, that would solve this issue. CCHMC is mapping the codes to include with the DD by **Friday, February 18, 2022**.
  1. **EHRI**

**Action Items:**

* The CC will schedule meetings with condition leads once family health history and clinical risk text has been finalized.
* The EHRI workgroup members can start working on a “many to one” roll-up variable to aid in mapping **by 3/11/2022.** Condition leads to sign off on finalized text on family health history and clinical risk so the CC can schedule a meeting with the condition leads so the developer requirements can be finalized.
* The EHRI workgroup members can start working on a “many to one” roll-up variable to aid in mapping of the GIRA **by 3/11/2022.**
  1. **R2/sIRB/ELSI**

**Action Items:**

* The co-chairs will follow up with Lori and Teji regarding a completion dashboard for participants in MeTree.
* Julia Wynn will draft a listserv of study personnel at each site who are involved in recruitment.

1. **Care & GIRA progress | Gail Jarvik (UW), Iftikhar Kullo (Mayo), & Cindy Prows (CCHMC)**
   1. The GIRA care recommendations have been agreed upon and locked.
   2. Harmonization of healthy lifestyle language across recommendations was approved.
   3. Each GIRA section will be separated by a header and also be used as a page break. These sections are for the summary age, risk specific result pages, risk specific patient education pages, methods and limitations, and FAQs.
   4. A GIRA cover page was developed to provide a brief study overview, sections of the GIRA, and site contacts. Only sections that are in the GIRA will be listed on the cover page to make the report more customized to the participant.
   5. The CDS subgroup is working on language that will go to providers and participants to notify them about new items placed in the EHR regarding eMERGE.
   6. The GIRA content pages are still under development but are close to being finalized.
   7. Monogenic risk text being placed on page one of the risk reports is being considered.
   8. Genetic counselors are returning monogenic high risk and this should be indicated in the high monogenic risk text.
   9. It may be helpful to primary care providers for some type of checklist or treatment considerations included in the risk box.
   10. Further design and language discussion will take place in a future workgroup meeting.
2. **Closing remarks | Rex Chisholm (SC Chair, Northwestern)**
   1. Things to still consider surround how we handle monogenic risk return, timing, and outcomes analysis.

**eMERGE Day 2: Thursday, February 3rd, 2022**

1. **Invitae Custom Panel Update | Eden Haverfield & Tara Schmidlen (Invitae)** 
   1. Invitae will commit to providing the custom proactive 16 gene panel for eMERGE. This panel includes the first tier population screen plus the five additional requested genes. Invitae is planning to have this available by the end of March, but there is not a firm timeline. Tara and Eden are working internally at Invitae and will provide updates as soon as they are available.
   2. The panel will be present in Invitae’s online provider portal as the Invitae eMERGE Panel. The goal is that as sites are trained on the Invitae portal, the panel will be pre-populated within the healthcare provider portal.
   3. The contracting with Invitae and the CC is still in progress. Sites will have to complete individual site-Invitae contracts once the main CC-Invitae contract is finalized. The site-Invitae contracts must be in place in order for sample order and shipment to occur.
   4. Invitae will be providing logistics training to sites. This logistics training will not be provided until the contracts are signed.
   5. The Clinical Operations subgroup monthly meeting will be addressing logistics, sample requirements, site specific information, and eventually report outs of sample statistics.
   6. Invitae client services have not been educated on the eMERGE study. Tara and Eden will continue to be the point of contact for Invitae.
   7. Invitae prefers receiving saliva as a sample over gDNA. Saliva can be stored longer, and there have been supply chain issues with the tubes for gDNA.
   8. Heterozygous carrier results will be returned to participants.
      1. Carrier status will be reported for LDLRAP1. The report would be designated as carrier status.
      2. APOB loss of function variants, which are not associated with familial hypercholesterolemia, will be reported as clearly not associated with FH.
      3. This also applies to the LMNA variations that are not associated with afib.
      4. No VUS are reported.
      5. The network must consider this while finalizing the GIRA report.
   9. The Invitae clinical reports do not contain care recommendations.
   10. Since VUMC is the coordinating center and an eMERGE site, there will be an ancillary contract with VUMC that will be used as a template for the rest of the site-Invitae contracts. Once the site contracts are ready, Invitae will distribute them to site PIs or site legal teams.
   11. The eMERGE custom panel will be handled exactly the same as the rest of the Invitae proactive panels. All variants are fully interpreted, and VUS are unreported. The same level of detection as diagnostic testing applies to the eMERGE custom panel, which includes sequence-based changes and copy number changes. Invitae has offered to present on their variant interpretation procedures and processes. Their framework has been published and can be distributed upon request.
2. **RA Training Update | Digna Velez-Edwards (VUMC), Ingrid Holm (BCH), & Wendy Chung (Columbia)** 
   1. The hope is for a “soft launch” for recruitment to occur sometime around mid-February.
   2. Research Assistants (RA) have been trained in a series of training meetings organized by Julia Wynn, Maya Sabatello, and others.
   3. There will be a weekly coordinator meeting set up for RAs to discuss issues and successes and have questions answered at the start of recruitment.
   4. The training design was a didactic slide presentation with poll questions added at the end to gauge participant understanding of eMERGE concepts. Most participants in the training were able to correctly answer the poll questions and feel comfortable with data safety and other concepts taught.
   5. The participant-facing website build has started. A vendor has been selected and url established (emerge.study) with 86 unique pages already developed. The website will be available in English and Spanish. Content development is underway with emphasis on repurposing existing sIRB approved material where applicable. Sites are encouraged to send images and content to further enhance the website design and information provided.
      1. The plan is to have the website built and ready for use prior to the Spring Amendment planned for March 2022.
3. **R4 & End-to-End Testing Overview | Josh Peterson (CC) & Jodell Jackson (CC)**
   1. eMERGE needed a customizable, secure data storage environment with the following capabilities:
      1. Distributed research data capture, management of identified data in a secure environment, interfaces to external partners to centralize structured data, automated data transfer and EHR integration features, and an agile and rapid development and accessible build team.
   2. REDCap was chosen for eMERGE because of its advantages, including that it is already established as a research data environment in most academic centers and it has application programming interfaces (APIs) for connections with sites and vendors. Potential hindrances of REDCap include that it has limited flexibility to generate dynamic reports and its ability to push structured information into EHR is limited.
      1. R4 is the eMERGE REDCap project and stands for the following study elements and their listed components:
         1. **Recruitment**: consent, study metadata, prescreen, baseline, and pre-RoR surveys
         2. **Results**: PRS report, Invitae report, family history pedigree, baseline EHR data
         3. **Risk Reduction**: GIRA, outcomes surveys and data
   3. New EHR import features for REDCap
      1. FHIR data transfer (clinical data interoperability)
         1. REDCap is set up with a basis in recruitment and allows for direct data capture from participants.
         2. Data access groups allow for site-only access, controlled at the investigator level.
         3. CDIS can be used to incorporate clinical data directly into site’s local REDCap projects (it is best suited for recent data).
         4. FHIR can ingest HL7 and JSON messages from external partners.
         5. It is an existing platform that is familiar to many sites and investigators.
      2. Sites have to set up FHIR data transfer, but it is a substantial improvement on previous methods. The CC will support FHIR data transfer and any standard way to import or input data for eMERGE. EHR data should be imported into site’s local instances of REDCap and then pushed to R4.
   4. R4 data flow
      1. The CC is the only eMERGE site that receives data from Invitae & Duke and is covered by the DUAs to house data in R4 from Broad and Invitae and Duke. Clinical sites then enter/push data to Invitae & Duke directly.
      2. The Broad will handle de-identified versions of Monogenic BAM and VCF files from Invitae.
      3. Data will eventually be de-identified and pushed to ANVIL (details are in development).
      4. R4 generates study IDs and stores links between family members.
      5. Sites should have local instances of REDCap so they can customize and easily exchange data between their instance and R4.
      6. Overview of data flow: Sites and participants directly enter data. R4 intakes PRS PDF and structured data. R4 intakes monogenic PDF and structured data. R4 intakes family health history data for GIRA. GIRA combines data using condition logic.
   5. Future builds: The risk reduction element will be built out next. It includes the dynamic GIRA logic (BOADICEA & PCE pending).
      1. Sites will be instrumental for testing logic and edge cases. Initial testing is expected to begin in April.
      2. The instruments used to capture return metadata are TBD.
      3. EHR data capture for outcomes variables needs to be defined and approved.
      4. Target finalization by summer 2022 to ensure enough time for building, testing, and editing.
   6. Needs from PIs over the next three months include:
      1. Working with the CC to sign off on GIRA logic and GIRA\_KB variables. (February)
      2. Pulling down partner test data to ensure data capture protocols are working between R4 and sites. (March)
      3. Testing GIRA generation and all combinations of dynamic text display. (April)
      4. Alerting the CC if any issues arise during initial recruitment period.
4. **Phenotyping Workgroup Update | Chunhua Weng (Columbia) & Wei-Qi Wei (VUMC)**
   1. Major accomplishments of the Phenotyping Workgroup: Finalizing clinical data elements, establish protocol for data quality control, complete common data refreshment which is available for GWAS, PGRNseq, WGS, and Exome Chip and include demographics, initialize gold standards repository, crete phenotyping algorithm metadata, complete NLP manuscript resubmission.
   2. Clinical data elements DD: The DD is limited to GIRA requirements, it avoids data duplication from other sources.
      1. Demographic info including participant ID, first and last name, and DOB are being collected for data matching purposes.
   3. Plan for quality control: Each site needs to capture and correct egregious errors. A plan for this quality control was reviewed by the workgroup.
   4. Gold standard repository
      1. The highly valuable gold standards data that have been collected throughout eMERGE can be very valuable for future studies. The plan is to collect manual cart review case and control status and create a gold standard repository so the data can be used in the future.
      2. Related algorithm ID, case control status, and the review date will be collected.
      3. A sufficient description of the metadata algorithms is important,
      4. There are many different Type II Diabetes algorithms on PheKB and which one can be used for projects.
      5. The plan includes defining a metadata framework to enrich cohort descriptions.
5. **Scientific Presentation:** **Developing and Validating a Genome Informed Risk Assessment Tool for Coronary Heart Disease | Mohammad Saadatagah (Mayo)**
   1. Currently, the ACC and AHA recommend using the Pooled Cohort Equations to estimate the ten year absolute risk of CHD. Genomic risk is not incorporated into the PCE.
   2. Mayo has developed an Integrated Score for CHD that incorporates PRS into the PCE.
      1. The UK BioBank was used as a cohort. The 10 year PCE was calculated. Then, an individual's ancestry specific CHD PRS was estimated. With these, the integrated score was calculated. Finally, the integrated score was compared to the PCE for risk prediction.
      2. Participants with prevalent ASCVD and/or taking a lipid lowering medication are excluded from the PCE and IS calculation.
   3. The integrated score will not be calculated on participants with a history of ASCVD, those who are taking a lipid lowering medication, and participants outside the age range of 40-79.
   4. eMERGE participants with a high integrated score, or high family history, and not a high PRS or monogenic findings, will have a high risk GIRA returned via letter.
      1. 15%-20% of eMERGE participants are estimated to have a high risk family history.
      2. 10%-15% of eMERGE participants are estimated to have a high integrated score.
   5. The integration of PRS in the PCE will reclassify almost 10% of participants.
   6. Individuals with a high IS and low PCE are at a higher risk of future CHD events than those with a low IS and high PCE.
   7. The risk of CHD in the top 5th percentile of CHD PRS is similar to those with monogenic family history of CHD.
   8. The study did not examine the interaction between family history risk and genetic risk. Participants were classified as either having monogenic, polygenic, or family history risk. The overlaps were not examined, but participants were classified based on the highest risk category (monogenic > PRS > family history).
   9. The CHD is examining how many participants become reclassified into an actionable risk category.
   10. It is difficult to examine the predictive power of the PCE over time, as participants with ASCVD events are disqualified from the PCE. As participants age, incidences of ASCVD increase.
   11. Early analyses suggest that the CHD PRS is more predictive at earlier ages, but further analysis is needed to learn more. Almost all risk factors weaken with age.
   12. In the graph of incident CHD events, participants with prevalent disease prior to age 30 were excluded.
6. **PRS & Clinical Ops Workgroup Update** 
   1. The PRS workgroup meetings are now monthly and those continue to support scientific discussion and reporting outreach activities. There is a new meeting bi-weekly, the Clinical Operations meetings.
   2. Currently the PRS workgroup:
      1. Continues to support papers under development and conditions on the research track, contributes to PRS reports supporting the certification process at Broad, evaluates the clinical implementation pipeline, develops concept sheets on implementation of PRS testing for 10 conditions, supports discourse on scientific developments in PRS methods, particularly in trans-ancestry populations, and does outreach activities that include inviting external speakers.
   3. The Broad’s foundational validation of the GDA plus imputation is approved by the laboratory director and by NYS CELP.
   4. The eMERGE conditions have completed supplemental validation and are being written up for medical director review.
   5. eMERGE has formally been categorized as a demonstration project of All of Us meaning eMERGE is able to access and use All of Us cohort data before it is publicly available. All of Us genotyping uses exactly the same Global Diversity Array and pipeline as eMERGE so provides a good reference panel for ancestry adjustments. The All of Us genotyping data is being recalled right now with an updated manifest and updated cluster file which is expected to be done with the Broad data in the next few weeks.
   6. Supplemental validation includes accuracy and precision measurements on sets of arrays with match genome data. The PRS performance in the eMERGE I-III dataset is also evaluated for each condition.
   7. Breast Cancer proposed an alternate adjustment and the BOADICEA group provided fixed adjustment parameters. After further discussion, the group prefers to keep all phenotype adjustments the same. The group will go through with the exercise to check for extreme differences in the adjustment that would be performed and discuss further from there.
   8. Conditions where the score does not have a publication listed on the validation document (CHD, Hypercholesterolemia, and Obesity) need to provide a written description of the clinical association/validation study that was done at the Broad so it is on record.
   9. Validation documents should also include the rationale for cutoffs for each condition.
   10. Clinical Operations Group
       1. The goals of the group include: Progress updates on clinical sample flow from sites to Broad and Invitae and reports back to sites (number of samples received/failed, recurring issues that require review from the network, etc), identification of issues with clinical workflows (before they are launched), scoping any changes to be implemented in clinical pipelines, updates on deposition of data (BAMS) into AnVIL for research.
       2. There is a portal/page that will report metrics like how many participants have been recruited and other general metrics so the CC can have a discussion with the Clinical Operations group about including additional information.
7. **EHRI & CDS Workgroup Update | Luke Rasmussen (NU) & Robert Freimuth (Mayo)** 
   1. At this point in time, EHRI has completed work on collecting network requirements, defining specifications for report artifacts, and support for other network workgroups.
   2. The workgroup has identified some roadblocks and pending decisions, such as report generating systems capabilities, reports, and dependencies on driving use cases and decision support.
   3. GIRA integration dependencies still need structured formatting, order process, result process finalized.
   4. Once these are finalized, the measured outcomes can be determined.
   5. The workgroup has identified ways to move the IT field forward as well. A structured format data dictionary informing an HL7-FHIR standard is one topic that can be used to advance the field.
   6. Current direction of the workgroup includes finalizing content specifications for a structured GIRA report, planning and documenting site-specific data flows, and integration of CDS for participants and providers.
   7. Future direction of the includes identifying and consideration of applicable existing standard specifications such as HL7 FHIR standards.
   8. The CDS subgroup is co-chaired by Eta Berner (UAB) and Emma Perez (MGB). Goals for this subgroup include harmonizing site plans for implementation where applicable and documenting similarities and differences.
      1. The CDS subgroup will also meet to discuss RoR workflow, potential impact of workflow and CDS on outcomes, share CDS resources and strategies, and consideration of publishing “lessons learned” on implementation and/or impact of different CDS manuscripts.
      2. For individuals interested in joining the subgroup, email Lynn.
      3. The scope of CDS has changed in some ways by modifying the concept from strictly “clinical” and broadening it to decision support in general. The first step in this approach could be to just get the information into the EHR and then decide how to implement CDS for that information. GIRA can be used as one of the sources for CDS.
      4. The CDS should not be just an alert notifying that a report has been entered into the EHR.
8. **Closing Remarks | Rex Chisholm (SC Chair, Northwestern) |** 
   1. Discussion on the marker paper and who will lead that was raised. The CC will put in a MCS for sites to join and write outlining the network goals for this phase.
   2. The PRS group is also working on a marker paper outlining their metrics and selection criteria for the prospective cohort conditions.
   3. Workgroups are encouraged to think about network-wide papers they plan to publish.

**Action Items**

**PRS & Clinical Ops:**

* Eimear will share the PRS/Genotyping MCS with the co-chairs, and then it will be circulated to the group to invite those interested to join the writing groups. The MCS will be submitted to the CC when finalized.
* Hypercholesterolemia, Obesity, and CHD must send a written description of the clinical association and validity study to Niall Lennon ([niall@broadinstitute.org](mailto:niall@broadinstitute.org)) and Maegan Harden ([mharden@broadinstitute.org](mailto:mharden@broadinstitute.org)) to meet NYS documentation standards.
* Cong Liu will test the results empirically with the AoU data against the BOADICEA fixed parameters, once the AoU data is available.

**Provider Uptake & Outcomes:**

* Phenotype leads should revisit the [Outcomes by Phenotype](https://docs.google.com/spreadsheets/d/1zv_eHxnp5aVhMVeEiv5JdEt2LPnYUHPSGHIZTlRuTfg/edit#gid=34309240) spreadsheet **by Wednesday, February 16th** and ensure it accurately represents the final GIRA recommendations and related outcomes of interest.
* The Outcomes group will finalize the primary outcomes and submit them to clinical trials.gov by **Wednesday, February 28th.**
* Sofia will send out a Doodle poll and touch base with the Provider Survey Subgroup co-chairs to determine the next meeting date(s).

**Phenotyping:**

* The *Deprecated Triglyceride [Mass/volume] in Serum or Plasma* LOINC code 3049-4 needs to be confirmed by the Type II Diabetes lead site, MGB, by **Friday, February 18, 2022**.
* It would be helpful to provide equations so conversion into correct units can be done if necessary. Mayo is providing unit conversion equations in cases of unit errors by **Friday, February 18, 2022**.
* If each ICD code is linked to the corresponding allergen LOINC code, that would solve this issue. CCHMC is mapping the codes to include with the DD by **Friday, February 18, 2022**.

**EHRI & CDS:**

* Condition leads to sign off on finalized text on family health history and clinical risk so the CC can schedule a meeting with the condition leads so the developer requirements can be finalized.
* The EHRI workgroup members can start working on a “many to one” roll-up variable to aid in mapping **by 3/11/2022.**

**R2/sIRB/ELSI:**

* The co-chairs will follow up with Lori and Teji regarding a completion dashboard for participants in MeTree.
* Julia Wynn will begin drafting a listserv of study personnel at each site who are involved in recruitment.