**Summary of Steering Committee Meeting: January/February 2024**

January 31 - February 1, Zoom & In-Person

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| **eMERGE Day 1: Wednesday, January 31, 2024** | |
| **Time** | **Event** |
| 9:00-9:20 AM | Progress, timelines, & goals | Rex Chisholm (SC Chair, Northwestern) |
| 9:20-9:45 AM | NHGRI Program Official Report | Robb Rowley (NIH/NHGRI) |
| 9:45-10:45 AM | Public controlled data access & discussion | Josh Denny (NIH) |
| 11:10-11:40 AM | Lessons & next steps from EHR Outcomes data pull | Shawn Murphy (MGB) & Wei-Qi Wei (VUMC) |
| 11:40 AM-12:10 PM | Discussion from the literature: Performance of PRS in screening, prediction, & risk stratification | Iftikhar Kullo (Mayo) & Eimear Kenny (Mt Sinai) |
| 12:45-1:05 PM | Clinical Operations Update | Katie Larkin (Broad) & Sienna Aguilar (Invitae) |
| 1:05-2:15 PM | Workgroup breakout session one  Recruitment & Return (CARE, R2/ELSI/sIRB, & QA/QC Taskforce)  Data Utilization (GRID) |
| 2:35-3:05 PM | Pediatric Outcomes | John Connolly, Shannon Terek, Margaret Harr (CHOP) |
| 3:05 - 4:15 PM | Workgroup breakout session two  Outcomes & Data (Provider Uptake & Outcomes, Phenotyping, & QA/QC Taskforce)  Manuscript development & refinement (CIRT) |
| 4:15 - 4:25 PM | Discussion and closing remarks | Rex Chisholm (SC Chair, Northwestern) |

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| **eMERGE Day 2: Thursday, February 1, 2024** | |
| **Time** | **Event** |
| 9:00-10:30 AM | Panel: Return of Results| Moderated by Cindy Prows (CCHMC) & Dan Roden (VUMC)  Return workflows across sites | Emma Perez (MGB)  GIRA return time, barriers, & lessons | All sites (5 minutes each)  Discussion & plans |
| 10:30 - 10:50 AM | Network data, Non-human subjects database, & outcomes plans | Jodell Jackson (VUMC/CC), Megan He (VUMC/CC), Nita Limdi (UAB), Dave Veenstra (UW) |
| 10:50 - 11:15 AM | Implementation and tracking of Provider survey | Georgia Wiesner (VUMC) & Ingrid Holm (BCH) |
| 11:45 - 12:00 PM | Discussion & closing Remarks | Rex Chisholm (SC Chair, Northwestern) |

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| **Other Links** |
| Action Items |

**eMERGE Day 1: Wednesday, January 31, 2024**

1. **Progress, timelines, & goals | Rex Chisholm (SC Chair, Northwestern)** 
   1. Meeting Goals: Returning GIRAs & Data Access
      1. Day 1 will focus on data access and utilization. This will include public controlled access overview, lessons and next steps for EHR data pulls, and the performance of PRS in the literature.
      2. Day 2 will focus on the return of GIRA. This will include a panel on return methods across sites, identification of barriers and sharing of lessons. The Network will also hear about the development of the Provider Survey.
      3. Days 1 and 2 will include information on measuring impact with information on pediatric outcomes and Network data & outcomes plans.
   2. Enrollment Progress
      1. Recruitment is on track for June 2024.
      2. There have been 21,879 participants enrolled.
         1. 13% pediatrics.
         2. 47% racial and ethnic minorities.
         3. 66% female at birth.
         4. 12% sexual orientation minority.
      3. The Network should focus the remaining recruitment effort on meeting diversity metrics, including for pediatrics.
      4. Sharing lessons learned over the past six months improved recruitment across the sites. This method should be translated to increase return rates.
   3. GIRA Returns
      1. There have been 5,707 GIRA returned (4,489 adult and 1,218 pediatric).
         1. 1,780 (31.3%) were high risk returns. This had been modeled at 25%. Of the high risk returns 899 are High PRS, 118 are P/LP Monogenic, 1027 are due to Family History, 71 are due to BOADICEA. Family history is having a big impact.
      2. The Network has a long way to go in returning GIRA in order to hit the Network target of 25,000.
         1. As sites transition from recruitment to return, we anticipate the rate of return to accelerate. The current projection is that by August 31, 2024 the Network will have only returned 19,340 GIRA.
      3. **ACTION ITEM**: Sites need to send as many samples as possible to the Broad and Invitae by April 30th, 2024.
         1. The current projection for Invitae samples is 19,340 samples by 8/31/24. The monthly rate in order to meet the return goal is 1,517 samples.
            1. The goal is to get to 17,000 Invitae samples by the end of April, due to funding.
         2. The current projection for Broad samples is 22,911 samples by 8/31/24. The monthly rate in order to meet the return goal is 2,009 samples.
   4. Accomplishments since September 2023
      1. The Network has achieved 85% of the recruitment goal. All sites are returning results, with 5,707 returned as of January 26th, 2024. There are 10,938 PRS reports and 9,383 Invitae results in R4.
      2. The Non-Human Subjects Database has been developed and is in alpha testing. The EHR outcomes data freeze has been collated, with a goal of release to the Network in mid-February 2024.
      3. Multisample VCF (genotyping data) has been released on AnVIL.
      4. The provider survey has been implemented in R4.
   5. Study Goals and Challenges
      1. Ensure target recruitment of underrepresented individuals is met.
      2. Release the EHR outcomes data and begin initial outcomes QA/QC measures.
      3. Share lessons learned for returning GIRA to increase efficiency across the Network.
      4. Minimize passive withdrawals and missing data.
      5. AnVIL data analysis and utilization for prospective and discovery analysis.
      6. Goal: Recruitment completed by June 2024. There is a current deficit of 3,121.
      7. Goal: Return completed by October 2024. There is a current deficit of 19,293.
2. **NHGRI Program Official Report | Robb Rowley (NIH/NHGRI)** 
   1. The need to send samples to Broad and Invitae as soon as possible was re-emphasized.
   2. The eMERGE network is collaborating with AnVIL to utilize cloud resources for analysis of eMERGE network data and serve as a use case for other consortia in the future.
   3. The need for an increased rate of GIRA return was re-emphasized. Recruitment rate increased substantially after similar issues with the rate of recruitment were discussed at a previous steering committee meeting.
   4. In August 2024, the eMERGE network will submit a budget extension request to the NHGRI.
   5. To mitigate data sharing risks, the eMERGE network (1) updated publication guidelines, (2) created a list of ICD/CPT codes for redaction to prevent undue risk to participants, and (3) conducted a risk assessment for the Non-Human Subjects database to prevent participant re-identification.
   6. The focus is now on managing access to retain trust throughout the process of (1) NIH approval and monitoring, (2) data requisition, and (3) data deposition.
      1. While there have been allegations of data use misconduct reported to the NIH, there has been no evidence of harm discovered in these cases.
      2. There is a multi-step NIH approval and monitoring process.
         1. A data use agreement, which is co-signed by the PI and institution, is submitted to a data access committee and approved based upon Data Use Limitations.
         2. The Data Use Certification Agreement includes information about the Data Use Limitations, sponsoring NIH institution / center, responsible data access committee, study description, and suggested acknowledgement statement.
         3. Requestors are authenticated using eRA commons and reviewed to ensure that they meet additional requirements.
         4. Breaches of data or inadvertent data released must be reported to the DAC within 24 hours, and a written report with incident details and a remediation plan must be submitted to the DAC within 3 days.
      3. The data requester must abide by certain requirements.
         1. The requestor must (1) be in good standing with the institution and funding agencies, (2) have PI information posted on the public dbGAP website, and (3) agree to follow the relevant regulations and laws.
         2. The investigator must use the data appropriately, subject to review by the institution.
3. **Public controlled data access & discussion | Josh Denny (NIH)**
   1. The All of Us research program mission is to accelerate health research and medical breakthroughs. Getting data out to as many people safely and responsibility is important to the program.
   2. There are over 759,000 participants and over 539,000 biosamples. After COVID, the program gained the ability to reach participants all over the country in addition to brick and mortar recruitment.
   3. Types of data collected include EHR data, participant surveys, physical measurements, biosamples, and wearable data.
   4. In addition to EHR data from participants, data can be shared via patient portals which was launched in 2022.
   5. The All of Us approach in the beginning was to bring researchers to data using a cloud-centric approach.
      1. There are 4 tiers beginning with a public tier with a data browser with summary statistics aggregate counts.
      2. There are two tiers with raw data including a registered and controlled tier. The controlled tier has obvious PII removed but does have real dates.
      3. There are ancillary studies going on now and planned for the future with individual biospecimens and participant data.
      4. A fifth tier will be added with information not in the controlled tier that will need to be requested on a project specific level.
   6. The data browser is accessible across the world with high level aggregate data. All the data is in OMOP. The researcher workbench allows for analysis in a Google cloud using R and Python. IRB approval is not needed and this is open to academic health care and not-for-profit organizations. This is now available across the world.
   7. Current data available to researchers through All of Us contain one of the largest sets of whole genome sequences widely available to researchers including over 312K genotyping arrays, 287K EHR, and 413K survey responses.
   8. Institutions sign a master agreement and there are about 60 institutions currently. A mandatory training and a data user code of conduct contract is also needed.
   9. There are over 8,600 registered researchers and over 8,500 active projects. All accounts have 2 step verification and identity verification. The median time for onboarding from the application is 5 days. For each workspace, users must share the primary purpose of research. Planned scientific questions, and anticipated findings. Anyone looking at the workspace can flag it for any concerning reasons.
   10. The Research Access Board review for compliance with the terms of data use by completing audits. Researchers can also submit papers or abstracts. This is not a scientific review board but more so making sure there is no stigmatizing information being shared. The board approves or provides recommendations for changes to be made and can freeze workspaces that need to be reviewed/edited.
   11. In March 2021, VUMC PhD student, Patrick Wu presented a dissertation on repurposing drugs using gene expression signatures and EHR data. He questioned if this could be replicated and he was able to do so with similar results. The scripts were put into the All of Us environment and because of the standardization, it worked well.
   12. Things that have worked well so far include the recruitment of researchers, the NHSR model to facilitate rapid access, the Research Access Board regular reviews and feedback, and the use of R and Python with tools like Hail, Plink, and Regenie. Next steps include more diversity of tools like SAS and RStudio, the controlled tier plus for more granular data access, becoming more pipelined, and drop-in datasets (as opposed to an annual release).
   13. The review, gate, or approval of individual papers is not a role that can be sustained. All of Us is working to bring in pediatric data in addition to ancillary studies. The next data release will be coming late 2024 with new data including a life functioning survey, remote height and weight, and racial and ethnic subcategories.
   14. eMERGE decided to redact certain types of data from the health record. All of Us also redacts codes for things like violent crimes and vehicle accidents which can be found in the resource pages. All of Us has not had many issues with misuse of data. The most common thing found is cells less than 20 being shared in papers. There have been some cases with flags in research descriptions that could use some amendments and those have always been done.
   15. The diversity of the All of Us participants is a strong characteristic of the program. The diversity metrics for All of Us can be found here. The All of Us publications can be found here and the projects directory can be found here.
   16. For All of Us data access, international data access users go through identity validation unless it is not possible in certain countries.
   17. Anyone who is part of the All of Us study has access to genetic counselors any time and results are shared with participants via genetic counselors. There is also a national directory for referrals.
   18. The All of Us has a “passport” access to data. A barrier for getting into dbGaP for eMERGE is the initial entrance. When consenting participants, eMERGE would like to make it known that data will be shared so updating data to dbGaP or other research sites is more accessible.
       1. It may be helpful for All of Us to write a paper around the consent process. There is a video with a quiz in addition to the written consent which is helpful for knowing the participant knows how the consent works and what it means. The eMERGE consent form is not as broad and the REDCap form indicates that participants are not spending much time reading it.
   19. All of Us does a post return questionnaire around satisfaction and an open text box. The study’s initial documentation states that it is not supposed to evaluate outcomes.
   20. There are always challenges with both terminology standardization and labs/meds robustness. All of Us has tools available on a researcher workbench with code snippets and other well built support functions for these challenges and others.
   21. **ACTION ITEM**: eMERGE Network PIs are being asked to discuss public data sharing for eMERGE and come up with a list of concerns and recommendations.
4. **Lessons & next steps from EHR Outcomes data pull | Shawn Murphy (MGB) & Wei-Qi Wei (VUMC)**
   1. Accomplishments from the phenotyping workgroup in the past few months have included gathering the outcomes from EHR data files from all sites and exploring the use of large language models for referral data extraction.
   2. The outcomes from EHR data will be combined and shared with the network via an AnVIL workspace.
   3. A lesson learned from the most recent data pull is that sites may not all have the same formal language for labs and medications making it challenging to map to the EHR and pull the data.
      1. The group decided to collect all mediation data based on drug class however this will not solve the problem of certain medications not being properly mapped to RXCUIs. To solve this issue, the outcomes workgroup or condition leads will create a list of keywords for different conditions that can be used to pull these medications.
      2. Another option discussed is submitting all medications to the CC and cleaning the data with the help of the CC and condition leads. This would allow for all medication data to be held at the CC in the case of the medication list changing in the future.
      3. Sensitive topic medications will be redacted at the site level prior to the data being sent to the CC (like the network did for the CPT and ICD codes for the outcomes from EHR data pull).
   4. Another lesson learned was how to pull referral data in a short observation window which is important for outcomes analysis. The group has been looking at summary data from VUMC and UAB to decide how each site will also gather summary data for reviews.
      1. The group is beginning with CVD and sharing site summary data with the condition leads and outcomes workgroup for feedback.
      2. After finalizing a strategy for the referral data retrieval, it will be expanded to other conditions.
      3. Reasons the group is not using NLP for referral data extraction is that the group cannot have a basic assumption that the referral data has been documented by a physician in notes. Also, NLP takes significantly more time than a regular rule based algorithm, as the network learned during eMERGE III.
      4. Instead of NLP, the group has been exploring the use of large language models to extract referral data. There are many publications from researchers inside and outside of the eMERGE network on the use of large language models for phenotyping.
         1. Shawn Murphy is leading this discussion and is exploring different models and everything will stay local to the sites. This approach can also be extended to other data like the medications that are challenging to extract discussed earlier.
         2. The key to successful large language model use is giving the model a good prompt. Additionally, the models run better on GPUs but can also run well on CPUs.
5. **Discussion from the literature: Performance of PRS in screening, prediction, & risk stratification | Iftikhar Kullo (Mayo) & Eimear Kenny (Mt Sinai)** 
   1. Hingorani et al paper Performance of polygenic risk scores in screening, prediction, and risk stratification: secondary analysis of data in the Polygenic Score Catalog garnered a lot of press and was critical of polygenic risk scores.
   2. As background, there is substantial overlap between controls and cases when looking at polygenic risk scores. This is a known limitation.
   3. The conclusion of the paper is strongly worded and states “Polygenic risk scores performed poorly in population screening, individual risk prediction, and population risk stratification. Strong claims about the effect of polygenic risk scores on healthcare seem to be disproportionate to their performance.”
   4. The paper uses a metric called detection rate for 5% false positive which they called DR5. The authors say the acceptable rate is 80. This means a screening test is really good if you can detect 80% of the people with only 5% false positive.
      1. The paper used CHD as an example, indicating that the detection rate is far below 80%.
   5. Data was presented in three contexts: Population screening, Population risk stratification, and Individual risk prediction.
   6. The paper made several arguments:
      1. PRS are poor screening tests. Rebuttal: They are not a screening test. They are a (valuable) risk variable.
      2. Common diseases are ‘oligo’ or ‘mono’ factorial. Rebuttal: Common diseases are multifactorial.
      3. Common diseases are ‘simple’. Rebuttal: Common diseases have a complex etiology.
      4. Only age should be used, not multivariable risk equations. Rebuttal: Age by itself is not enough.
      5. For DR5 of 80 you need an odds ratio of 12. Rebuttal: Such odds ratios are rare in common diseases.
      6. Use statin for everyone, at a certain age. Rebuttal: This is ‘imprecision medicine’.
      7. The idea that you should predict weather by looking out the window. Rebuttal: Weather prediction requires multiple inputs.
   7. The authors made the statement “Enthusiasm surrounding PRSs might have been encouraged by pressure on academia to demonstrate a tangible health effect after decades of research investment in human genomics and by commercial opportunity.”
      1. As a response it could be argued that a common misconception about polygenic risk scores is that they are a diagnostic/screening test, when in fact a PRS is just one more probabilistic risk variable.
   8. Strengths of the paper: It provides a statistical view of PRS as screening tests. There is visual and statistical back up of their case as to why PRS are poor screening tests. There is considerable scholarly contribution to the statistical properties of screening and screening tests.
   9. Weaknesses of the paper: It is a somewhat regressive view. It ignores >100 years of epidemiologic research into complex diseases. It is a simplistic view of common disease risk prediction. It ignores complexity. The paper ignores the probabilistic nature of all risk. It ignores patient perspectives.
      1. Feedback to the paper was brushed off. Authors responded “The three responses to our article do not alter the conclusions of our paper or alter our view that the effect of polygenic risk scores on healthcare has been overstated.”
   10. Discussion:
       1. We should be cautious about not overstating the individual importance of polygenic risk scores relative to something else.
       2. PRS does have unique properties that make it an important risk factor. PRS is not an independent predictor of great magnitude.
       3. In talking to participants, indicate that if you have a high PRS along with age or other factors, that is when to talk to your doctor about a screening test.
       4. There is the question of how to integrate PRS with other risk factors for those diseases where we don’t have the kind of equations like we do for diseases like CHD.
          1. It would be very difficult as a Network to attempt to make risk calculators for these other phenotypes. Epidemiologic studies are very restricted in minorities. The All of Us data is not mature enough to use yet.
       5. The challenge is to continue to articulate that polygenic risk scores provide a risk over time. It is not a dichotomous yes or no.
       6. Polygenic risk scores are not a diagnostic test despite the paper treating it as if it is.
6. **Clinical Operations Update | Katie Larkin (Broad) & Sienna Aguilar (Invitae)**
   1. Katie Larkin presented updates from the Broad. There was a backlog in December 2023, which impacted 1,200 samples. All these samples now have results. Through investigation of this backlog, the Broad identified additional samples that had silently failed through the imputation process. These should all be closed out relatively soon.
      1. The Broad has updated their internal monitoring system in order to catch and respond to these failed samples in the future. Over ⅓ of sample submissions are experiencing metadata issues, which adds a stop step prior to accessioning.
         1. Sites should ensure samples are not shipped to the Broad clinical lab prior to R4 metadata upload. Uploaded metadata should be double checked. Sex at birth and race are required. Raquel Jacobs (rjacobs@broadinstitute.org), Fanny Dao (fdao@broadinstitute.org), and Katie Larkin (klarkin@broadinstitute.org) are available to assist in onboarding new clinical coordinators or to answer any questions.
   2. The actual fraction of samples at high risk match to what was expected. The expectations were based on the assumption of no correlation between conditions. There are 19 samples that are high risk in three conditions, 12 of those include T2D.
   3. Sienna Aguilar presented updates from Invitae. The failure rate of the last quarter, 9/1/23 - 12/31/23, was presented. Saliva samples have the highest failure rate, consisting of around 2% for both complete failures and sequencing-only reports. Sequencing-only reports are when del-dupes are not being reported. Sienna reported that in general, the eMERGE failure rates are not seeming to deviate from what Invitae typically experiences.
   4. There have been two incidental findings as of 12/31/23, one of a possible clinically significant gain of X chromosome, and a possible clinically significant loss of X chromosome. These were found through a request for sex discrepancy data.
   5. Approximately 2% of the cohort has a positive monogenic finding. This includes both types of APOB. There are seven gain of function APOBs.
      1. **ACTION ITEM**: The Invitae team will review the data to determine if there are additional findings for gain or loss of X chromosomes as those data are not easily access in their current database so numbers presented may under represent the true findings.
7. **Workgroup breakout session one**
   1. **Recruitment & Return (CARE, R2/ELSI/sIRB, QA/QC Taskforce)**
      1. Two privacy breaches have occurred at two separate sites. These were reported as protocol deviations to the site IRB and to the sIRB. The sIRB is requesting a Network-wide plan to prevent this from happening again. Many sites check identifiers to verify the report has been uploaded to the correct participant. Sites vary on whether this is done manually or electronically. Additionally, some sites have implemented a preview feature during upload.
         1. **Decision:** The Network plan is to confirm three identifiers prior to uploading a report to the EHR. This should be validated either electronically or by hand.
      2. Sites were asked to fill out the GIRA RoR site factor grid in order to get some perspective regarding barriers and hurdles to RoR as well as ideas for rate acceleration.
         1. The time required for GIRA review has decreased as sites have moved out of beta phase, but it is still a time consuming part of the process.
         2. The amount of FTEs returning results at sites varies. There are likely discrepancies with site FTEs devoted to RoR due to these staff having other duties. Sites could consider narrowing training scope to have staff focus on a certain piece of the process (e.g. GIRA review or return calls). Sites might redistribute staff once the recruitment phase is complete.
         3. Automating parts of the process (e.g. automated upload and messages for negative GIRAs) has saved time at sites.
         4. Scheduling a return call can be time consuming due to missed calls, canceled appointments, etc. The majority of results are being returned via televisit. Some sites have implemented cold calling participants by calling once and again a second time right away if the participant does not answer. A message is left after the second call.
         5. Sites have found it difficult to estimate how long a return appointment will take. Sites typically budget an hour for return appointments. This can include notes.
         6. High risk results based only on family history are mailed to participants. Positive family history is usual care for a physician and should be able to explain to their patients.
         7. Participants with high PRS for breast cancer and low BOADICEA receive a courtesy call. These calls are taking approximately as long as the other high risk PRS result calls.
   2. **Data Utilization (GRID)**
      1. Megan He walked the group through the NHS Database SOP and Database.
      2. The database was created as a location for comprehensive eMERGE network data. This database has direct identifiers and contextual data redacted in order to share data across the network. The NHS database will be available in REDCap and in AnVIL. The NHS database will mirror the R4 Portal, with the caveat of some variables being redacted within instruments due to sensitive or identifiable data. Only age-at-event will be included in the NHS database. The database only includes data from participants who are currently enrolled and not withdrawn.
      3. The REDCap database will refresh nightly. If a participant withdraws after the NHS database is released, their new status will be reflected the following day. Data can be exported through reports or API. Users will not be able to edit any fields in the project.
      4. Megan reviewed the NHS database on REDCap. The race breakdowns will look different than in R4 due to the previously decided collapse. With the date fields, the CC has added an asterisk to certain fields to denote when ‘age at event’ is being used versus what would have been a date in R4. Users can filter for if the family history rescue survey was completed.
      5. It will be important to ensure versioning is accessible and viewable in AnVIL. The REDCap NHS database will likely persist following this round of eMERGE.
      6. The network is not performing standardization for participant entered survey questions. Data captured from the EHR is being standardized using OMOP. These will be important considerations to how the data will be transferred and be usable in ACR.
      7. The CC is seeking beta testers for the REDCap NHS database prior to provisioning access to the entire network. There should be at least one volunteer from each site. The CC will provide the beta testers access to the REDCap project. The beta testing will be for a few weeks. During this time, real data will be pulled in, and beta testers will be able to export data and run reports. General instructions for how to work in the database and export data (such as only certain variables or filtering select participants) will be provided in the NHS SOP. This is beta testing for the REDCap, not for genomic data available on AnVIL.
      8. It was proposed that there should also be a beta testing period when all the data types are available in AnVIL, prior to network-wide use. Data being pushed to AnVIL would be easiest to start as a csv. The NHS data dictionary should be included so that it is clear what the variables and headers mean.
      9. The NHS data will assist with QA/QC to organize risk factors and to drive power analysis. The eMERGE ID will be used in the NHS database.
      10. The data will be combinable in AnVIL, not in the REDCap database. The outcomes data will be disseminated through AnVIL.
      11. Moving forward, it will be important to consider how the different extractions of overlapping data will be linked and used together, for example linking survey and ICD data. This practice would be a good fit for the GRID workgroup. Standardization or transparency would benefit the data use. The NHS data is limited to what is in the survey data and will not include raw data files (JSONs) from partner sites. There will be a way to determine the data source in the data dictionary.
      12. The GRID workgroup should stay in close contact with the Outcomes workgroup in regard to the NHS database use. The QA/QC Task Force will be examining the data in a different lens.
      13. The phenotyping workgroup will need to be involved in defining outcomes and specific data definitions.
      14. While there will not be EHR data in the NHS database, there will be GIRA risk status which can be used before final outcomes definitions are established. For example, a participant record could show they are at high risk for CHD due to PRS and FHH.
   3. Adam Gordon presented on FHH data in eMERGE. There is a backup survey or MeTree survey that are completed either by the participant or by study staff on behalf of the participant. The backup survey is completed in R4, and MeTree is piped into R4.
   4. The raw FHH data, which are JSONs with PHI, are kept in the site instances of R4. The derived FHH data, which is binary true/false and defined by the condition leads, is placed in the NHS database. Users have the ability to download each individual’s JSON file at their site through R4. Adam is proposing that this group tackle the task of taking all of the JSON files within each site and making them into a usable de-identified analysis-ready dataset.
   5. There is no breast cancer derived FHH data in the NHS database, due to that FHH being piped directly into BOADICEA.
   6. It is also important to remember that ‘false’ could mean either the participant does not know their family health history, they skipped the question, or they do not have a family history of that condition.
   7. The NHS database will only contain true/false FHH data from R4. Pedigrees contain more thorough and more granular information on the participant’s FHH, for example age of diagnosis. The raw JSON output contains PHI, and is a mix of structured fields and free text entry.
   8. MeTree collects demographics such as race and ethnicity. The network is not currently planning on comparing the reported MeTree demographics to the reported survey demographics. It will be a challenge to convert the raw JSON output into a parsable format.
   9. The workgroup must determine the format, content, and implementation of MeTree data aggregation. Since the JSON files contain PHI, each site must use a uniform method to process the data prior to centralizing.
   10. **ACTION ITEM**: The workgroup should develop a script for each site to run to de-identify the MeTree JSONs. These de-identified files will be merged across sites without identifiers.
8. **Pediatric Outcomes | Priyanka Marpuri, Jasmine Purcell, John Connolly, Shannon Terek, Margaret Harr (CHOP)**
   1. Background, Pediatric Recruitment and Workflows
      1. Recruitment (across Network): Currently, there are 2,743 pediatric participants enrolled. The goal is 5,000. CHOP is enrolling 100% pediatric. All sites are now recruiting children. The majority of participants are from underrepresented backgrounds.
      2. Return of Results
         1. So far, across sites, we have returned 1,209 GIRAs to participants.
         2. CHOP has returned 935 (86%) not high risk results and 151 high risk results (14%).
         3. The majority of participants who had a high risk ROR had a ROR with a phone or video call with a genetic counselor.
         4. Of those with a high risk condition, the rates of each condition are relatively equal between the 4 conditions (20-27%) with 9% being at high risk for more than one condition.
         5. Prior condition prevalence varies by condition: Asthma (37%) and Obesity (74%), Type 2 Diabetes (3%), Type 1 Diabetes (0%), Multiple conditions (77%)
      3. EHR Integration
         1. A workflow for EHR integration was shared and applies to not high risk and high risk results being integrated into EPIC. First, the risk result is entered as structured data and the PDF is linked. The provider and patient are notified through basket and myCHOP messaging. The return of the result visit is scheduled if applicable and documented. If applicable, Clinical Decision Support pop-ups provide guidance and education during a well-visit regarding high risk conditions. Information is tracked via action logs and clinical decision support actions. Additional information was shared about the ROR visit, CDS guidance and tools and tracking in the EHR.
         2. There are multiple data sources and access points at various locations. It is important to know what information is accessible to understand how results are impacting care.
         3. Once results are uploaded, tracking information is captured regarding whether the results were viewed by the providers and caregivers.
         4. Smart elements from the clinical note, and problem lists and notes are also available.
         5. At the PCP well visit, information about the GIRA access, and outcomes are collected.
   2. Provider Outcomes Capture
      1. EHRI workflow: Two important sources used include Clarity (Microsoft SQL server database) and an access log that shows who has accessed orders associated with the participant.
      2. Preliminary Data
         1. Of 841 participants at CHOP, 33% of participants did not access the result in myCHOP and 9% did not have myCHOP. The results will be emailed to the participant.
         2. 60% of participants did view results. About 85% of these were not high risk results.
         3. Additional info was shared regarding how many days passed before participants viewed the results. 63% viewed the results within 1 day. The average time is about 10 days.
         4. Using access logs, information was able to be captured for 83% of participants. CHOP is continuing to investigate how to capture more information.
         5. Other information that was captured using logs includes specialist review, non-clinical personnel interactions, and participant review of the results.
         6. Clinical Decision Support accommodates multiple workflows. The provider has multiple access points. An example was shared showing orders for best practice alerts for specific conditions and external links about the study.
   3. Network-wide Outcomes
      1. This analysis is based on preliminary data from CHOP and focuses on feasibility of approach.
      2. One of the primary questions is to look at whether or not there is enough power to answer outcome questions.
      3. Pediatric Conditions Overview: It was estimated that 12.5% high risk of pediatric participants would be high risk for one or more conditions (620). PRS is required for pediatric participants to be at high risk.
      4. Power Analysis:
         1. Type 1 Diabetes: There were 16 high risk vs 825 non-high risk so far (2%). Primary outcomes analysis so far indicate that there will be enough power to show differences in groups. For example, half of participants had autoantibody screening and there is an increase in counseling in the high risk group.
         2. Type 2 Diabetes: There were 23 high risk vs 818 non-high risk (3%). An analysis graph was shared showing who in each group received interventions. Based on the numbers so far, there is not as much of a difference as with type 1 diabetes. There may be more power as more participants receive interventions and more are enrolled. Additional analyses will need to account for age due to prevalent diabetes and recommendations that differ based on age (12-17).
         3. Asthma: There were 34 high risk vs 807 non-high risk (4%). Several outcomes are based on the Post-ROR survey data to assess what recommendations were made regarding risk mediation. So far, there is little difference between the groups and insufficient power. At this time, there appears to be a large amount of missingness for EHR asthma related outcomes.
   4. Additional Outcomes
      1. There is a Parent Interview Study at CCHMC and CHOP to assess parents’ understanding of recommendations of disease risk.
      2. There is also a Provider interview study at CHOP looking at the impact of CDS and infrastructural support.
9. **Workgroup breakout session two**
   1. **Outcomes & Data (Provider Uptake & Outcomes, Phenotyping, & QA/QC Taskforce)** 
      1. The phenotyping workgroup has been discussing an alternative option to manual chart review. Large language models to extract outcomes data are being explored. All notes from participant EHR for some time period within PRS score return would need to be collected. The smaller the number of notes is better to handle however missing important details on entire notes needs to be taken into consideration. Local and public large language models are being explored and how to go through the mechanics of the calculations are being discussed. There are large language models that come without a business language and are for multiple business practices. It is straightforward to build extensive libraries for using large language models.
      2. Since there is an issue with pulling medications without RxNorm codes, large language models could be used to pull that data as well. Implementing a large language model pipeline would help resolve similar issues in the future without having to rebuild the pipeline unlike NLP which looks at a special record expression and then has to be rebuilt for its next use. Also, unlike NLP, a large language model is a learning model so if a gold standard of chart review is used, the model will know what to look for in future use. Next steps include taking a look at notes on consented patients and understanding what is needed to extract from the notes and to accomplish using a large language model followed by coordinating with the outcomes group.
      3. Doing manual chart review to double check that the large language models are extracting the correct information will be important since manual chart review is the gold standard. Manual chart review can be used to do positive and negative predictive values and all the calculations that determine the quality of the large language model. Large language models can also use vector embeddings for words that are close to the one being searched.
      4. The link here will load Python code and can take sites through using a large language model on local machines. Sample notes can be found here and here. The large language models can be run without a GPU in a reasonable amount of time. Most of the work is being done by looking up the embedded meanings of the words in the vector database so building the vector database will most likely be the most work. Sentences from notes will be put into the vector database so that the process can find if a patient had a referral to a specific specialist. This will be called the indexing phase. The meanings and embeddings of the words are being loaded as a series of strings.
      5. It would be a requirement for all eMERGE sites to have the same large language model available on each site for security reasons. Sites would most likely be unable to do this without supplemental funding so that will be discussed in a future outcomes workgroup meeting.
      6. The QA/QC group is looking into doing chart reviews on 20-40 patients depending on the number of potential errors anticipated and whether the errors would be systemic within specific sites or affecting all sites. The manual chart review slides can be found here.
         1. It may be helpful to select high risk patients for conditions for which referrals are one of the outcomes so that two goals are being accomplished at once. Although, it may be better to use a more randomized approach to which participant charts are reviewed.
         2. Since referral outcomes are important to only a few phenotypes, charts can be chosen for the phenotypes that are expected to use referrals as an outcomes variable.
         3. The groups will discuss this topic and the options in more depth in subsequent work group meetings.
      7. The outcomes workgroup has been discussing the idea of condition leads doing a quality assessment of available non-human subjects data and being discussing possible outcomes.
         1. The outcomes from EHR data will compiled in the next few weeks and the NHS database is in alpha testing. The multi-sample vcf data is already on AnVIL. Within the next month to 6 weeks all data will be on AnVIL. After the NHS data is available, a snapshot of the cohort’s self-reported sociodemographics should be available in 20,000 eMERGE participants.
   2. **Manuscript development & refinement (CIRT)** 
      1. The CIRT workgroup acknowledged the passing of Eta Berner, who was a co-chair of the CIRT workgroup and a respected leader in the community.
      2. In the CARE breakout session, there was a discussion about two instances where the incorrect report was uploaded to the patient EHR. To prevent future instances of incorrect reporting being uploaded to the patient EHR, each site will automatically or manually validate the MRN, name, and date of birth. Mayo and CHOP manually validate MRN, name, and date of birth information. MGB has a step of manual override to confirm the name.
      3. Sites differ in whether the process of uploading reports to the EHR is manual or automated.
         1. Mt. Sinai uses an automatic process to upload not high risk reports and manually upload high risk reports. For the automatic upload of not high risk GIRAs, an EPIC inbox message is sent to the provider and patient with the GIRA as an attachment. For high risk GIRAs, the GIRA is linked to the patient encounter.
         2. UAB manually uploads reports but has plans to automate the process. The infrastructure for genomics reports was not available on Cerner and needed to be built. One hurdle for automation is selecting the correct encounter for the patient.
         3. CCHMC is in the process of automating report uploads but UC performs uploads manually. UC uses “document-type tags” so that the reports are more easily searchable.
      4. Sites were given the opportunity to discuss information or tools that would have been helpful to automating the integration of report data with the EHR in a discrete, standardized form. There was not a lot of support given to the EHR upload process due to the perception that REDCap (R4) was going to be the main driver. Clearer standards for EHR integration should have been defined in the RFA.
      5. With the exception of Broad data, the results (including GIRA results) did not come in discrete lab data and could therefore not be used as flags. Inclusion of a JSON file for overall GIRA results, similar to partner data, would have been very helpful. There is variability between sites about whether the Broad report must be uploaded as a separate report.
         1. CHOP uploads discrete data to the EHR manually.
         2. Mayo uploads discrete data to the EHR using Smart Data Elements to incorporate genomic indicators to tie a genomic result and a CDS rule. This is similar to the process of the genomics module in EPIC but has a few key differences. There is more control over automatic data flow into the EHR. Some of the EPIC tooling that is required to get the data in can be bypassed. The data is not editable by other users of the system. Links to the PDF reports of the genetic results are sent in an in-basket message to providers.
      6. There is variability between sites on whether the non-discrete GIRA is linked to an orderable, encounter, media tab, or other result.
         1. Mayo needed to link the non-discrete GIRA to an orderable in order to have the variable in the EHR in order to trigger a CDS.
         2. MGB and VUMC needed to link the non-discrete GIRA to an encounter so that the report was available within the patient portal. It is helpful to include instructions to patients for how to access the GIRA.
         3. Mt. Sinai is able to attach the GIRA PDF to the MyChart message.
      7. In future studies, the genomics module could be used to incorporate genomic data but not all sites have this module active. While there are guidelines for monogenic results, there is no clear clinical guidance for PRS reports. Site specific decisions ultimately matter.
      8. Site specific decisions ultimately matter when determining where research results should be incorporated in the EHR and requires coordination with other medical specialties.
      9. Most sites are either adding monogenic results or no study results to the “Problem” list. One site is adding integrated risk scores to the problem list.
      10. While the overall goal is to put together a manuscript concept sheet, the focus of the paper is still in discussion. Potential focuses of the manuscript include “lessons learned” and how clinical PRS can be integrated into the EHR. There is an existing manuscript concept sheet regarding site specific IT infrastructures to support the eMERGE IV study, including for data collection and pushing results to the EHR.

**eMERGE Day 2: Thursday, February 1, 2024**

1. Panel: Return of Results| Moderated by Cindy Prows (CCHMC) & Dan Roden (VUMC)
   1. **Return workflows across sites | Emma Perez (MGB)** 
      1. Sites are now all returning results based on the risk categories.
         1. High Risk GIRAs that are a result of high risk monogenic, high PRS, or High BC integrated score are returned with a ROR with the study team.
         2. GIRAs that are not high risk or high risk only due to family history are returned passively. There is some difference by site regarding monogenic overrides.
         3. Sites settled on providing a courtesy phone call for participants with a high breast PRS but not a high integrated score.
         4. Early in the return process, some sites were contacting all participants or participants with family history only. Exception for one site offering return to all Spanish speaking patients because many pages in the GIRA are not available in Spanish. All sites contact the participant’s provider about a high risk based on PRS/monogenic/IS
      2. Contact with Provider: 7/9 sites contact the provider about family history only GIRAs. 6/10 sites contact the provider about not high risk GIRAs. 9/10 sites do NOT email PCPs about stand alone Invitae or Broad report, unless positive Invitae result.
      3. GIRA Location in EHR and standalone reports: Most sites put the GIRA in the media tab with 3 sites putting them in results. 7/9 sites always put Invitae in as a standalone report. 2 sites are doing it conditionally if Invitae is positive or if GIRA generation is delayed. 3/10 sites put in the Broad as a standalone report. 1/10 sites put the pedigree in as a stand alone report.
      4. Data integration types and Forms of CDS: 8/10 sites are integrating non-discrete data from the GIRA. For sites uploading stand alone broad and Invitae reports, these are all non-discrete data. 2/10 sites use BPAs. 1/10 sites use order sets. 1/10 sites use smart buttons. 4/10 sites input monogenic results as problem lists.
   2. **GIRA return time, barriers, & lessons | All sites (5 minutes each)** 
      1. The RoR GRID summary was reviewed, following updates after the recruitment and return breakout yesterday.
         1. The network-wide average times for a high risk GIRA return were reported:
            1. GIRA prep / data checking review: 20.9 minutes.
            2. Days to schedule 1:1 review: 12.8 days, with some sites cold calling. The time for scheduling return appointments, which may be conducted by staff outside of genetic counselors, is not accounted for but is a significant effort. Return visit: 28 minutes (14-54 minutes on average). Post return process: 24 minutes.
         2. The average time needed for a not high risk GIRA is 20.8 minutes.
         3. There are approximately 3-4 FTEs for the return process at each site, which is more than what was initially budgeted for.
         4. The total time for needed high risk GIRA return is ~1 - 1.5 hours and total time for not high risk GIRA is ~30 minutes.
            1. For the remaining 19,000 GIRAs that need to be returned, with an estimated 25% high risk excluding FHH only, it will take 7,125 business hours to complete return at all sites. For participants with multiple high risk results, time needed to return will be increased but not doubled.
      2. Since the network average time for each step of return was discussed, sites did not present these slides during the site reports and site specific metrics can be reviewed on the slides.
      3. CCHMC
         1. Rate limiting steps: Internal biobank delays, early reliance on saliva collection which required resampling, trying to coordinate RoR to families and shipping family vs individual samples, “Family” refers to multiple family members enrolled in the study, as a parent needs to be present for return of results for a pediatric participant. EHR upload process to two institutions (CCHMC + UC).
         2. Current implementation for increasing efficiency: Samples are shipped individually rather than by family, GIRAs uploaded to EHR in bulk (working on automated process), results are returned to individuals instead of coordinating with the whole family, research blood draw added to clinical draws when possible.
         3. Plans for increasing rate of return: Monthly shipments, rather than waiting to fill the samples, increasing the number of research draws that occur at the same time as clinical draws, more locations / areas for blood draws, adjusting physician schedules as needed for RoR, considering cold calling.
      4. CHOP
         1. Rate limiting steps: Uploading metadata to R4 for Broad ordering, Broad backlog, variable time for GIRA generation in R4 (ranging from 5 minutes to 24 hours), manual process of placing GIRA into EHR, scheduling RoR appointments.
         2. Next steps for increasing efficiency: Goal is to finish RoR by October 2024 (240 GIRAs returned per month), identify R4 issues with Broad upload, expand on EHR automation, RoR “Clinic times” where genetic counselors hold two 3-hour blocks dedicated to RoR (GIRA generation, setting visits, etc).
         3. CHOP has 2.75 FTEs (genetic counselors) on the team.
         4. CHOP is experiencing a site-specific issue where Broad Orders are only being uploaded once but results in duplicate instances for certain samples, which need to be manually deleted. At other sites, the Broad Order upload can time-out resulting in the need to re-upload metadata again. This results in duplicate samples,, which need to be manually deleted, if the code does not catch and prevent re-upload of the same sample ID.
            1. UW mentioned that they are having an issue with metadata which is entered in R4 not piping over to the Broad Order instrument and needing to be re-entered.
            2. The Broad and R4 teams should work together to identify issues with the Broad API resulting in the time-out when placing Broad Orders.
         5. Invitae orders cannot be bulk ordered, which adds time needed to add orders.
         6. GIRA generation time is on average 15-20 minutes. GIRA generation occurs in a REDcap queue which includes other REDCap projects outside of R4. Sites should let the CC know when there are periods of extreme slowness with R4 generation. REDCap has been moving storage to cloud servers and other systematic changes which has results in some of the more extreme slow down periods.
      5. Columbia
         1. Columbia is still calling participants who are high risk due to family history only. Columbia believed that other sites were calling family history high risk only and will discuss how to proceed going forward. Since other sites are not calling, it will be important to think about consistency for outcomes for return. The recommendations for family history high risk only (follow-up with primary care provider) are included in the GIRA and are mailed or sent via patient portal at other sites. These follow up calls are quick and occasionally the participants provide further relevant information about the family history.
         2. There is a difference in time needed for return of not high risk results to adult and pediatric participants. The follow-up steps for pediatrics are all manual, while these steps are automated for adult participants.
         3. Many of the rate limiting steps are similar to what was reported by CHOP and CCHMC.
         4. Columbia does not schedule return appointments, and relies on cold calling participants.
         5. Factors that increase timelines for return: Periods with no Broad results followed by many results at once, genetic counselors needing to be involved in other aspects of the study and other studies,
         6. Current implementation for increasing efficiency: Cold calling participants, few people returning results in an efficient workflow with less variability, if the opportunity to return multiple GIRAs at once (family relationships on R4), Columbia has not actively tried to hold results to return to families, but does take advantage of the opportunity when possible. The family relationships instrument is used to track participant relationships.
            1. Automated RoR pipeline for not high risk result, the automated pipeline saves approximately 20 minutes per participant.
         7. Next steps for increasing efficiency: Experienced research coordinator to assist with post-RoR follow up tasks , moving the efforts of a recruiter (MD, native Spanish speaker) to working on return, it would be useful to determine whether linking of GIRA return to a telephone encounter rather than a visit affects how likely the provider is to read the note and results.
            1. Columbia and CHOP forward the note from the telephone encounter to providers.
      6. MGB
         1. For returns, MGB has 1.5 FTE genetic counselors and 0.1 FTE research coordinator for mailings.
         2. Rate limiting steps: Delayed Broad reports, determining which GIRAs are actually ready to review, internal reporting of GIRAs which are ready to review can be confounded by sample failures or females which need height and weight entered to calculate BOADICEA. Not wanting to generate too many high risk reports, since there are only 1.5 GCs dedicated to return, scheduling RoR appointments, MGB institutional guidelines indicate that not high risk GIRAs must be mailed to participants (not permitted to use patient portal, and not best practice to use email.
            1. Columbia sends both not high risk and high risk GIRAs as encrypted emails, with instructions on how to open the email.

There are no read receipts to track opening of the emails.

* + - * 1. CCHMC was mailing results but will be moving to emails since participants were not receiving the mailed reports.
      1. Current implementation for increasing efficiency: GCs will self-assign record IDs to own and review, automatic scheduling of return appointments (linked to GC schedule) used by 25% of participants.
      2. Next steps for increasing efficiency: Once recruitment ends, have more RAs and GCs help with return.
      3. There have been previous discussions in the field about whether cold calling with health results is appropriate, since participants may not be prepared to receive results when they answer. Columbia and UAB provide context for the call up front to ensure that participants are ready to receive results and speak in a friendly and calm tone. Cold calling for CHOP is a last resort after not being able to schedule an appointment, so participants should be aware that a call is coming. Follow-up interviews for another study at Columbia indicated that families preferred to receive information via a cold call rather than needing to make appointments.
    1. Mayo
       1. Mayo is manually uploading GIRAs via a custom order to participant EHR and notifying participants and PCP via patient portal. Not high risk GIRAs or high risk due to family history only utilize this virtual return process with no RoR appointment. High risk GIRA (PRS or monogenic) utilize the virtual return process and an RoR appointment with a genetic counselor or study coordinator. The time needed for a high risk RoR appointment is up to 30 minutes. The total time for the RoR process can take up to several hours, with an average of 20 minutes.
       2. Rate limiting steps: Variable times needed for GIRA generation, risk score validation (BOADICEA and PCE), missing information which requires participant recontact, participant response timeline.
       3. Current implementation for increasing efficiency: Collaboration with external teams as early as possible, due to the need for a custom order, Mayo needed to build an API and structured data workflow. Study staff specialize in specific study steps, but remain flexible.
       4. Next steps for increasing efficiency: Increased specialization of RoR processes, train additional staff on RoR processes, continue to document errors to allow the team to review and resolve, and shifting focus to RoR.
    2. MPHC
       1. Rate limiting steps: Variable times needed for GIRA generation, preparation for RoR, participants do not always answer the phone call.
       2. Current implementation for increasing efficiency: Internal tracking of GIRA to determine where each GIRA is in the generation / return process.
       3. The goal is to complete enrollment by March 2024 and then shift the focus to RoR.
    3. Mt Sinai
       1. The time for return appointments for a high risk result ranges from 7-50 minutes and depends on the type of result and condition.
       2. Rate limiting steps: Time needed to schedule appointments to return high risk results, about 25% of participants are no-shows for the RoR appointment, resulting in staff needing to spend more time to re-prepare for the RoR appointment. GIRA Review (edge cases, following up on error log entries to close the loop), Passive results (MyChart and provider messages must be generated and sent manually).
       3. Factors that increase timelines for return: Time needed for GIRA review and errors has improved, new staff training and re-training current staff, competing study demands for RoR staff, lab turnaround time, internal and network-wide technology issues.
       4. Current implementation for increasing efficiency: Added staff time for returning not high risk results, API bulk upload of batched not high risk reports into Epic, staff experience.
       5. Next steps for increasing efficiency: Setting staff targets for GIRA return, streamlining the process for high risk returns, adding a final call attempt to return to participants, moving focus from recruitment to return.
       6. There is not too much bioinformatically to automate the GIRA review process, since it often requires identifying missing data. Duplicates can be identified bioinformatically. The network should consider a method to automatically identify female participants with missing height / weight preventing BOADICEA calculation. UAB does QC check for missing data when Broad Orders are uploaded so that missing data can be resolved during the time needed for sample processing.
    4. NU
       1. Rate limiting steps: GIRA review, GIRA return, appointment times can be variable which makes scheduling difficult, preparation time is needed for appointments, which is wasted if a participant doesn’t pick up for a cold call, Lab -time needed to place Invitae orders manually, technical issues with R4.
       2. Current implementation for increasing efficiency: Temporary workers who are specialized in one step of the return process.
       3. Next steps for increasing efficiency: Automated upload to the EHR, double calling during cold calls to increase the rate of answering.
    5. UAB
       1. UAB was involved in the alpha testing process of GIRA generation and return, had a temporary pause for QC, and then re-started returns with a current temporary increase in PharmD effort.
       2. Rate limiting steps: Manual upload of GIRA and Invitae reports to the EHR, attempts to reach participants for return of high risk, Invitae reports not crossing over the REDCap (1.2% of GIRAs), manual checking of FHH which require age component (5.6% of GIRAs), parity issue with BOADICEA which requires Canrisk calculation (0.7% of GIRAs).
       3. Current implementation for increasing efficiency: Temporarily added more staff to return with specialized roles for return. One FTE PharmD can return ~130 GIRAs per month, and UAB currently has temporary additional effort to increase the rate of return to ~200 GIRAs per month. One PharmD is focused on generating and returning non-high risk results so that these can be returned efficiently without interrupting returns of high risk results.
       4. Next steps for increasing efficiency: Automatic upload of GIRA and Invitae reports to EHR.
       5. UAB’s projections with added FTEs anticipate that returns can be completed by October 2024. Withdrawn participants are removed from the queue so return staff have an accurate number of GIRAs to return.
    6. UW
       1. There are 2 genetic counselors (0.5 FTE each) and research coordinators and assistants working on return of results.
       2. Rate limiting steps: Broad results delay, manual upload of reports, data missingness, unresponsive participants, oversight and troubleshooting needed for all high risk reports, variable time needed for GIRA generation.
       3. Current implementation for increasing efficiency: Multiple staff generating GIRAs and collecting missing data, GCs staggering availability for RoR appointments, high volume of GIRAs ready to generating, high volume of samples collected.
       4. Next steps for increasing efficiency: Higher Broad throughput expected, automated GIRA upload to EHR, transition staff from recruitment and sample collection to RoR, recruitment of adults is almost completed.
    7. VUMC
       1. Rate limiting steps: Pipeline from REDCap to Epic, the automated process of uploading the GIRA to the EHR using Onbase can require up to 2 days. Rescheduling participant no shows, REDCap issues, edge cases which require review prior to GIRA generation.
       2. Current implementation for increasing efficiency: More staff effort (genetic counselor) focused on GIRA generation, shifting genetic counselor effort to return after recruitment is completed, cold call RoR.
       3. Next steps for increasing efficiency: Booking page and text messaging to schedule RoR appointment.
       4. The goal is to finish RoR in August 2024 and use the remaining two months for scheduling appointments.
  1. **Discussion & plans**
     1. There are several common issues in the RoR process that are slowing the return of results at sites.
     2. R4 can be slow at times.
        1. **ACTION ITEM**: The CC will look into whether there are specific days or times that are extremely busy within R4 to potentially find more efficient times to generate GIRA.
        2. Sites should keep in mind that R4 speed is dependent on factors outside of R4. There are many other REDCap projects that impact this.
        3. The REDCap team is currently looking into different storage mechanisms to hopefully help with lags in REDCap as a whole.
     3. The potential to develop a way to automate return of not high risk results could be investigated.
     4. **ACTION ITEM:** Columbia will discuss as a group not returning high risk family results in person in order to increase efficiency.
     5. Some sites are planning to repurpose staff once recruitment is completed to return results.
     6. It could be helpful to designate staff for specific parts of the RoR process, including GIRA review, GIRA generation, RoR, uploads etc.
     7. There are several issues that are not in site control. These include delays at the Broad and Invitae and difficulty in scheduling RoR appointments.
     8. Potential solutions to increase RoR rate include:
        1. The use of rapid call backs.
           1. Several sites have found success in calling back immediately if a participant does not answer on the first call. A message is left after the second call if the participant still does not answer.
        2. Potential shared training sessions between sites for increased efficiencies and tips. It could also help to narrow the training scope of staff (for instance, only training staff to review GIRA).
        3. Instituting a QC step to make sure the data being sent to the Broad is complete prior to being sent.
           1. Some sites indicate that the data that should be coming from R4 automatically is missing.
           2. **ACTION ITEM:** The Broad should work with sites to increase efficiencies in metadata transfer including reviewing API issues and connections to R4.
     9. **ACTION ITEM:** The CARE workgroup will meet on 2/5/24 and generate a comprehensive list of RoR barriers and hurdles and brainstorm potential solutions. The list will then be discussed on the PI call on 2/15/24.

1. **Network data, Non-human subjects database, & outcomes plans | Jodell Jackson (VUMC/CC), Megan He (VUMC/CC), Nita Limdi (UAB), Dave Veenstra (UW)**
   1. The goal of eMERGE is to make the most amount of data accessible while balancing privacy and utility for both genetic and phenotypic data. In eMERGE III, the network started putting data into the cloud among other things.
   2. eMERGE is looking to stay on the forefront of large scale data analysis, access and usability.
   3. If eMERGE members need access to workgroup listservs, publication hubs, etc., they can contact the CC to receive those permissions. When it comes to having access to data, the CC has extra verification steps to allow for data access including the verification of a manuscript concept sheet if the data will be used for a specific project.
   4. The network has EHR based outcomes data which had a data freeze start in August, non-human subjects R4 data (NHS database) which has all the survey data and structured results, and genomic data on both sequencing and genotyping data (The Broad put a multisample dataset on AnVIL with about 6,500 samples).
   5. Discussions will begin taking place in the next month around allowing for collaboration with other networks for cross network analyses and other discovery projects.
   6. A recent AnVIL clinical resource project charged with improving support of the clinical genomic research community is using eMERGE as a flagship test case led by Matt Lebo and Robert Carroll. They are working with the GRID workgroup so anyone with questions please reach out to Sofia Labrecque.
   7. The NHS database will include data from R4 without any identifiers (names, locations, free text, HIPAA data or dates). For dates, age at event will be used. All currently enrolled non-withdrawn participants will be included.
      1. The family relationships instrument is brought over as well so linking parents and children will be available in the NHS database.
      2. All participants will be identifiable by eMERGE ID so they can be linked to the AnVIL data as well.
      3. The REDCap data will be updated on a nightly basis but the NHS data living on ANVIL will be updated with data freezes. For REDCap access, email Megan He and for AnVIL access, email Alanna DiVietro.
      4. The database will be going through final testing soon and the CC will be asking for at least one person from every site to beta test. During the beta testing, members can think through creating reports that might be useful to sites.
      5. The outcomes from EHR data will be used for downstream analysis with the use of multiple data types (EHR, NHS, R4, and genomic data).
      6. Each phenotype lead needs to confirm the variables needed for outcomes are being captured between now and June so there is preliminary data for the June steering committee meeting.
      7. Adjustments to the outcomes from EHR data pull process or pipelines should be documented to ensure successful final analysis.
      8. **ACTION ITEM**: The eMERGE condition leads will report out at the June 2024 steering committee meeting (similar to the pediatric presentation on day 1 of this winter 2024 SC meeting) outlining an assessment of key variables and outcomes analysis plan.
2. **Implementation and tracking of Provider survey | Georgia Wiesner (VUMC) & Ingrid Holm (BCH)** 
   1. Ingrid Holm presented on the HCP survey implementation progress. There was a 40% HCP response rate in eMERGE III.
   2. The goal of the survey is to identify if providers perceive the GIRA report as useful for clinical care. The survey was developed as a subgroup of the Outcomes workgroup. The survey implementation group has representation from each site.
   3. High risk GIRAs generate a survey link in R4 for the HCP survey. Because this survey is only live now, and was not live at the start of the RoR process, it will be provided to HCPs who may have already seen a participant with a high risk GIRA. Going forward, only one survey will be sent to each HCP receiving a high risk result participant.
   4. The survey is not currently being provided to HCPs receiving not high risk GIRAs.
   5. The group decided that the EHR upload date will be considered the date of return.
   6. In the compilation of site data, some variables will be able to be shared with the network and some will not be able to be shared between sites.
   7. Sites must confirm that the HCP has not received a previous survey invitation. If a provider had received a previous survey invitation and never completed that survey, they would not be eligible for another survey.
   8. The survey was initiated January 16th, 2024. Each site will develop their own go-live date based on when their local processes are developed.
   9. UAB has distributed 12 provider surveys, and NU has sent out two.
   10. Each site has a different way to identify the providers who are linked to each participant.
   11. There is no target for the number of completed provider surveys per site, as there is a large variability of providers between sites.
   12. The 2-4 week timeframe after the GIRA being uploaded to the EHR was developed in order to provide the HCP time to review the GIRA. The large interval of 4 weeks was initiated to provide sites time to find the HCP. The IRB protocol does not include a time frame for contacting the providers. Sites are able to provide the HCPs with the survey before 2-4 weeks.
   13. The group is not collecting the information of providers who do not respond centrally, but sites have the ability to track this.
   14. It would be interesting to examine characteristics of providers who do not respond to the survey across the network.
   15. Due to this survey going live after RoR had begun, the network has the opportunity to compare the behavior of HCPs prior to receiving the survey with their behavior after.
   16. The group has begun discussions on direct guided interviews with HCPs, which was performed in eMERGE III.
   17. The group will discuss experiences with distributing the HCP survey since the go-live at their next meeting.
3. **Closing Remarks | Rex Chisholm (SC Chair, Northwestern)** 
   1. The discussion regarding the need to accelerate the GIRA returns provided important information and generated specific action items to assist in meeting our return deadline.
   2. eMERGE and the CC has done a lot of work building an infrastructure to compile a large amount of information into a report and sending it to the providers and participants.

**Action Items:**

**Sites:**

1. Sites need to send as many samples as possible to the Broad and Invitae by April 30th, 2024.
2. eMERGE Network PIs are being asked to discuss public data sharing for eMERGE and come up with a list of concerns and recommendations.
3. The eMERGE condition leads will report out at the June 2024 steering committee meeting (similar to the pediatric presentation on day 1 of this winter 2024 SC meeting) outlining an assessment of key variables and outcomes analysis plan.

**Clinical Operations:**

1. The Invitae team will review the data to determine if there are additional findings for gain or loss of X chromosomes as those data are not easily accessed in their current database so numbers presented may under represent the true findings.

**CARE:**

1. The CC will look into whether there are specific days or times that are extremely busy within R4 to potentially find more efficient times to generate GIRA.
2. Columbia will discuss as a group not returning high risk family results in person in order to increase efficiency.
3. The Broad should work with sites to increase efficiencies in metadata transfer including reviewing API issues and connections to R4.
4. The CARE workgroup will meet on 2/5/24 and generate a comprehensive list of RoR barriers and hurdles and brainstorm potential solutions. The list will then be discussed on the PI call on 2/15/24.

**GRID:**

1. The workgroup should develop a script for each site to run to de-identify the MeTree JSONs. These de-identified files will be merged across sites without PHI.

**Decisions Made:**

1. The Network plan is to confirm three identifiers prior to uploading a report to the EHR. This should be validated either electronically or by hand.