**Summary of eMERGE SC Meeting: February 1st, 2023**

Zoom & In-Person

1. **NHGRI program official report | Robb Rowley (NIH/NHGRI)**
   1. Robb Rowley welcomed the group and congratulated everyone on accomplishments. He discussed PRIMED, eMERGE and ClinGen related to PRS efforts. Thanks to Ken Wiley for all of his help in the network, he is joining NCATS in February 2023.
2. **Announcements, opening remarks | Rex Chisholm (SC Chair, Northwestern)** 
   1. Updates of GIRA generation and return progress: 52 GIRAs generated to date, 27 GIRAs returned to date (12 in person, 15 by mail). Addressing technical issues discovered in Alpha and beta.
   2. Changes, lessons, and moving forward
      1. The CC uses a tracking log to document technical issues and fixes.
      2. Alpha and beta sites will present initial feedback during the GIRA panel.
      3. Content change requests and feedback are captured in the second tab of the log. CC is working with CARE group to discuss options to optimize formatting in GIRA v 1.1
   3. Expanded beta testing: Any site with sufficient data can now begin generating GIRA on their first 10 participants. Request that sites contact CC prior to initiation and document all issues. All sites should ramp up recruitment in order to meet the goal of 25,000 results by summer of 2024.
   4. Enrollment progress: 6,922 total enrolled.
3. **Panel: GIRA & Integration**
   1. **Return of Results & Early Lessons Learned | Nita Limdi (UAB), Eimear Kenny (Mt. Sinai), Wendy Chung (Columbia)** 
      1. Nita Limdi reviewed the GIRA generation process at UAB. UAB has been working closely with the CC as they performed the alpha launch of the GIRA. UAB has two FTEs working on MeTree.
      2. During the alpha launch, UAB discovered that when the GIRA is reviewed study staff must change the form status to ‘complete,’ then ‘save & stay’ for the PCE/Integrated Score and BMI to populate in the GIRA Review. The UAB team also discovered a mistake in the GIRA table regarding family history being incorrectly reported as not being used to determine high risk for afib, which has been corrected.
      3. As of today, February 1st, 2023, UAB has generated 47 GIRAs and returned 35. 12 GIRAs are pending review. An interesting finding is that out of the 47 GIRAs, 40% are men, and there have been three high PRS results for prostate cancer.
      4. Currently, the GIRA sorts conditions alphabetically if there are multiple high risk conditions on the summary of results page. Nita has suggested that multiple high risk conditions on one GIRA be sorted by risk category, with the most actionable risk at the top.
      5. The UAB informatics team, led by Jim Cimino, has created a mirror REDCap inside the UAB firewall. The reports are received into a shared drive, and a pharmacist attaches a cover note. The GIRA is then uploaded into Cerner automatically.
         1. Unlike EPIC, Cerner does not have a genomics module. UAB had to create a genomic medicine landing page. This maps into the genetics folders, and is where the GIRA reports are displayed.
      6. UAB is onboarding physicians to return results, and have walked them through how to access the GIRA reports in Cerner. UAB has created a cover note for providers to attach to GIRAs. For participants with high PRSs, the cover notes include infobuttons that link to an article that supports the PRS for that condition.
      7. The eMERGE UAB team sends an inbox message to each PCP upon high risk results being returned. The physicians had requested the team to wait one week in between notifying them and the participant, so they would have a chance to contact the patient.
      8. There is documentation in R4 following the return of results.
      9. Nita has begun to examine how the study will assess provider actions post GIRA return. One of the high risk prostate cancer PRS participants already has metastatic prostate cancer.
      10. As of yesterday, eight of the 22 physicians onboarded to eMERGE have been onboarded to the return of results process. UAB is using pharmacists in this role as many manage chronic diseases as part of care teams. Pharmacists are widespread in the community, and this would be beneficial if and when PRSs become standard of care.
      11. Because eMERGE is about genomic risk, Nita believes that the genomics risks of PRS and monogenic findings should be presented first on the summary of results page.
          * 1. ACTION ITEM: The CARE group will further discuss the order of risk result types presented on the GIRA summary of results page.
      12. Eimear Kenny discussed the GIRA data generation workflow at Mt. Sinai. Mt. Sinai has not yet returned a GIRA report but is working through the beta testing phase of GIRA generation. The study staff have found that the GIRA review process takes between 20 to 30 minutes, and the GIRA generation process takes between one to 45 minutes. Mt. Sinai has attempted to generate 16 GIRAs and has had 6 successful attempts.
      13. Eimear discussed the complexities that Mt. Sinai has identified in the RoR process and the specificities each scenario requires. Based on the current time spent, the team estimates they can generate 3 to 5 GIRAs per day, which ends up being 15 to 25 per week per genetic counselor in the study.
      14. Mt. Sinai has recommended a few changes based on beta testing.
          1. There are multiple reference documents being used for the GIRA review and generation process. The CC can collate the documents into a single file with more user friendly language, as opposed to the programming language, organized by condition. Errors in logic were found, which are currently being addressed by the CC.
             1. ACTION ITEM: The CARE group will review the return of results SOP to determine if additional information or language is needed to assist with site staff processing GIRA reports.
      15. Genetic counselors are returning results prior to results being sent to the participant and provider, and then imputed into the patient record. The GC documents the RoR in EPIC. Mt. Sinai is returning positive monogenic results to participants as soon as they are received, per their regulatory office guidance. The next steps for Mt. Sinai include thinking through how to handle the participants missing surveys and/or MeTree data. MGB has held samples for sending to Invitae and the Broad until the MeTree and survey data are complete.Out of the 16 GIRAs that have undergone the review process at Mt. Sinai, two have high risk findings for at least two conditions.
      16. Wendy Chung reviewed the beta launch process at Columbia. The team at Columbia have worked through ten samples through GIRA generation and provider notification. During the beta launch, the team worked manually for RoR. Following the beta launch and as the team becomes more comfortable with the process, the process will be automated. The GC spent 15 to 20 minutes manually verifying the GIRA, and post beta launch they are aiming for five to ten minutes. For the initial reports, Columbia contacted each participant by phone for both positive and negative results, to ensure the contact information was correct. In the future, the negative results will be returned automatically through the EHR, and only participants with high risk findings will be contacted by study staff.
      17. There is a known issue of family history of hyperlipidemia not being recognized as a family history of hypercholesterolemia. The CC is actively working to resolve this issue.
      18. Wendy realized the data warehouse used for Columbia’s clinical data is only updated quarterly, so data may be months behind. The Columbia team manually verified in EPIC if the labs were completed, and found that the majority of the time the labs that were missing in R4 were not actually completed in EPIC, so it was accurate. They do not anticipate having to manually verify in the future.
      19. One major challenge is that based on the recruitment locations at Columbia, half of their participants have had a change in provider since the initial survey was completed. Many providers are residents. This can change in the future depending on the location of recruitment sites. Cong Liu built a way for Columbia to identify the NPI of the provider from the participant survey. The NPI can be used to push the GIRA report out to the appropriate provider. Through this process, a significant number of providers were unable to be matched to an NPI number. The causes of this were found to include ambiguity in the provider name or misspellings.
   2. **GIRA Review Process | Scott Nigbur (Mayo)** 
      1. Scott Nigbur provided a high level overview of the planned GIRA review process at Mayo. Mayo has not returned any GIRAs yet. They have come up with this plan to optimize study team time while still generating accurate GIRAs. Mayo has a goal of 10 minutes spent on GIRA generation review per GIRA report. The plan for GIRA review is to review source data, which includes any data that is piped into the GIRA report, by the Mayo round table for the first ten GIRAs. The Mayo round table will consist of clinical research coordinators, post-doctoral fellows, research fellows, and Dr. Iftikhar Kullo. Following the first ten GIRAs, the Mayo round table will meet as needed to resolve any edge cases or disagreements.
      2. The next thirty GIRAs will have their source data reviewed by pairs of round table members. After this step, the Mayo eMERGE team will perform a self assessment to ensure the source data and logic have consistently been accurate. Upon passing this internal self assessment, the following thirty GIRAs will have just the GIRA review instrument and PDF reviewed by pairs of round table members.
      3. The remaining GIRAs will have one round table member review their GIRA review instrument and PDF. Iftikhar has volunteered to review the first three de-identified CHD GIRAs from each site. Following this, CHD edge cases from non-Mayo sites can be reviewed and discussed by the Mayo round table. Mayo is putting effort into ensuring the eMERGE Mayo team is working together early on in the process to ensure the review process is consistent and cohesive. Mayo is focusing on training their staff at working through the already existing processes, rather than imagining new edge cases or scenarios. Mayo will also develop a local tip log specific to their site. This will assist in internal referencing and any new hires. Mayo has not sent any samples out to the Broad yet.
   3. **Edge Cases in the Wild | Matt Lebo (MGB)** 
      1. Matt Lebo reviewed edge cases that have arisen that the edge case group had previously discussed and accounted for. One expected edge case that came up was a high risk breast cancer PRS for a participant that did not meet the threshold for BOADICEA high risk. The breast cancer leads have proposed language to clarify that a high PRS alone does not result in high risk status for breast cancer in this study.
      2. There have also been multiple instances of a participant withdrawal after a clinical report was ready. This was expected, but not at the current frequency. Reasons for withdrawal include participants moving out of state. This also can occur at this frequency due to the length of time between participant enrollment and the time it has taken to return results.
      3. The Broad has identified seven instances of sex discordance, and the Broad is in the process of contacting sites. The Broad performs a fingerprint check on all samples which includes a sex chromosome check, which is compared to the sample, and the reported sex. In all instances of sex discordance, the fingerprint check matched the sex of the submitted sample, and the discordance was between the reported sex and the fingerprint.
      4. A newly identified edge case is a name discordance between R4 and the EHR. This has occurred in approximately 5% of participants, and was discovered in the UAB data. As a solution, UAB has created a weekly report that pulls names from R4 and UAB EHR and flags mismatches. These are then fixed before the two week record lock.
      5. An edge case that has not yet occurred but has a possibility of occurring is sex-chromosome aneuploidy from Invitae. Invitae is reporting these in the comments field, which is not a structured field being pulled into R4. This could potentially be flagged by the Broad and compared.
      6. Another edge case that has not yet occurred but should be discussed is the reclassification of monogenic variants. This is extremely unlikely that this would occur between the time the Invitae report is generated and the time the GIRA report is generated. If reclassification occurs, the instrument is locked in R4 and the Invitae results cannot be changed. Reclassifications will go through the Invitae portal. However, only the participants with high risk monogenic findings are being encouraged to create Invitae accounts. An alternative solution could be to change the ordering physician to the participant’s PCP, so any reclassifications would be sent to them.
      7. The issue of sex mismatch was discussed in eMERGE 3, and this phase of eMERGE should review the past decisions.
   4. **Return of Results Education | Sabrina Suckiel (Mt. Sinai) & Maya Sabatello (Columbia)** 
      1. Maya Sabatello and Sabrina Suckiel provided updates from the Education subgroup regarding RoR education. The original goal was to create educational material to address the needs for participants, providers, and study teams. The group created patient-facing material which included infographics and a website. The eMERGE website is for use by participants, study teams, and providers. The subgroup developed self guided content without audio for the study teams.
      2. The infographics were developed by Columbia to explain the GIRA components and results. The group used feedback and interviews to refine the infographics. The infographics are finalized and are available in Spanish and English. They are approved by the IRB. There is a manuscript on this work that is being submitted this week.
      3. John Connolly led the website development. There was a focus on allowing the website to be mobile friendly and disability accessible. The goal was to target all stakeholders. The website also repurposes existing material when possible. This includes eMERGE materials and external materials. It is available in both Spanish and English. The website has four major areas of consumption: Participants, the risk report, local site information, and FAQs for health care providers.
      4. The subgroup developed education to support clinicians, which include webinars and in-person introductions to the eMERGE study. This was influenced by work by the ELSI group.
      5. The education subgroup surveyed the sites to determine who is returning results by site. Most sites have genetic counselors involved in returning the GIRA.
      6. The subgroup developed a [Return of Results Content Guide](https://docs.google.com/document/d/1nQdx2vvRLP4HxHGJg68fSp8Uqic5mgFECovUK_R0aE0/edit?pli=1), which is a self-guided educational resource. This includes links to educational materials developed by eMERGE and outside sources.
      7. Alexandra Miller led a mock RoR session to pair GCs with RAs to build comfort with the RoR process. Shannon Terek led the development of a [Return of Results Talking Points](https://docs.google.com/document/d/18fcE89rcuT25qHZrCWsyCNa1iWFHbSH5/edit) document, which can be used by study staff returning results. This is not meant to be prescriptive language, but a way to provide alignment across sites. This was circulated to the CARE workgroup.
      8. Sabrina and Maya created and circulated an assessment of the developed materials, preparedness, and future needs of study staff returning results. Out of the ten respondents, all felt either somewhat or very prepared to review the GIRA packet with participants. A few respondents indicated they felt not prepared for returning a pediatric PRS result. Half of the respondents requested RoR roundtable discussions to assist in RoR preparedness.
      9. The next steps for this subgroup are to transition the subgroup meetings into roundtable discussions regarding the RoR experiences every two weeks. It is expected that whoever is returning the GIRA results will walk the participant through the entire GIRA report, including the care recommendations. In eMERGE 3, a GC returned the results, followed quickly by a clinical encounter. Based on these findings, it was proposed that a RA can return the results and contextualize the risks, but do not talk about specific actions that can be taken. The clinical encounter would determine the specific actions to be taken.
   5. **General Q & A, Discussion**
      1. The group discussed the issue of missing data. There is the MeTree rescue survey that can be implemented once the IRB is amended. Excluding participants with missing data has cost and time implications. It may be important to examine the reasons participants are missing data. For example, sites are concerned that these participants are the ones with barriers to accessing computers or time constraints. Excluding these participants also biases the population to those without barriers to healthcare access. Participants with missing data in their GIRA causes their GIRA to be less equal to complete GIRAs. It would be helpful to collect the list of data needed for clinical reports and determine if the missingness can be mitigated. Data missingness is dealt with regularly in this field. Currently, if a participant selects ‘intersex’ or ‘prefer not to answer’ for assigned sex at birth, text will display explaining that they will not receive complete results. This can be expanded for missing BMI or other variables needed.
      2. ACTION ITEM: The network should focus on brainstorming mitigation strategies that would allow the critical missing data to be picked up in targeted ways.
         1. There is already language in the GIRA qualifying how missing data affects the report. The GIRA currently has a section for ‘conditions not assessed’ for conditions with failed PRS reports. Breast cancer can be added to this section when it is missing the appropriate data.
      3. The group discussed the question of high PRS for breast cancer alone not triggering a high risk GIRA. In the future, very few high PRS would trigger actionability on their own. Integrated scores will likely be needed for use at the point of care.
         1. ACTION ITEM: The breast cancer phenotype leads will discuss the question of a high breast cancer PRS not triggering a high risk GIRA return, and adding language to explain the discrepancy between having a high risk PRS but not receiving a high risk GIRA for breast cancer.
            1. This has been completed.
         2. A suggestion was made to add additional language explaining both the missing data elements of BOADICEA and the high PRS/not high risk report on the report. The only elements required for the BOADICEA score are the sex at birth being female, date of birth, height, and weight.
4. **Science Presentation: Conducting transgender-inclusive research in genetics | ST Bland (VUMC) & Kate Mittendorf (VUMC)** 
   1. ST Bland introduced the Family History and Cancer Risk Study, or FOREST, as well as definitions used in the talk.
   2. Why it matters: health disparities and trust.
      1. Up to 1 in 3 TGSD people report negative health experiences due to gender identity within the previous year. Up to 1 in 5 report having been denied healthcare because of their gender identity. About 1 in 4 reported delaying needed care as a result of fear of discrimination.
   3. Part of this story stemmed from analysis of sex and gender data collection in FOREST.
      1. Legal sex, sex, birth sex, and gender identity pulled from different sources under different conditions lead to mismatches in the record. Pronouns and gender-congruent “updated” names are not collected.
   4. Kate Mittendorf shares case examples from FOREST to demonstrate the issues that arise from the aforementioned mismatches. Many reasons for these mismatches, from misunderstandings to the patient’s choice not to disclose information. More inclusive wording, like “sex assigned at birth” rather than “birth sex” can encourage more transparent participation. Strive to avoid “othering” questions and statements.
   5. Implication of sex and gender in eMERGE. Thus far, about 2% of participants have identified as TGSD. Projects to 500 individuals by the completion of the study. These fields impact GIRA recommendations and MeTree family history risk computation. GIRA display depends on sex recorded in the eligibility survey. One participant was identified as undergoing a gender change during the course of the study. These changes are reflected in the EHR and the individual’s name. This brings up the ethical issue of potential unexpected disclosure to HCP, as well as participant contact and push to records. Congruent names are important for syncing data across sources. Also impacts people with name changes for other reasons. Consider adding a variable to allow participants to include name they wish to be called during the study, while maintaining a legal name field.
      1. Recommendations: Allowing TGSD to be a part of these research studies. Additional recommendations contained in the QR link.
      2. Sex and gender are becoming less static variables. Opportunity to learn from this going forward.
      3. Questions: Advice on how we should think about how we handle the current sample vs record mismatches?
         1. Can use recommended language in communication back to participants. Informing people what the data is used for is helpful for building trust.
5. **Presentation: Operations update of Broad & Invitae, lessons learned | Niall Lennon (Broad) & Sienna Aguilar (Invitae)** 
   1. Niall Lennon and Chris Kachulis provided the Broad update. The Broad has received samples from 8 different sites and are ready to receive samples from all sites.
   2. There have been 5 tests not performed out of the 2314 samples received. Regarding sex concordance, the process at the CLIA lab is to check for the internal possibility of sample swap on a sex discordance case. If the internal check shows that it is concordant, the submitting site would be notified to perform the second level of checks. There have been seven incidences of sex discordance. In two of the instances there were two samples submitted on the same plate, which highly indicates a submitting lab sample swap.
   3. The processing turnaround time (TAT) has reduced over time. Most sets are completed within three weeks.
   4. As the Broad receives more consistent sample submissions, it will allow them to provide more consistent turnaround times.
   5. It is important to remember when examining the p-values that there are ten independent tests occuring. The numbers are what was expected when assuming the conditions are independent of one another. The Broad has been tracking the correlations between the PRSs. The largest and most significant correlations are T2D-CHD, T2D-BMI, and BMI-CHD. These have become highly statistically significant. The z-scores are meeting normal distributions in general. Going forward, the Broad will continue to accept partial plates, with a minimum of 15 samples per plate. This is different from what was initially requested, but as the Broad has become more comfortable with their workflow they are now able to be more flexible. The partial plates allow for the Broad to rework any samples that need re-running.
      1. ACTION ITEM: Sites are able to send partial plates when ready, with a minimum of 15 samples per plate, to the Broad.
   6. Sienna Aguilar presented sample updates from Invitae. Invitae has received 1,473 total orders, with 936 completed.
   7. Early lessons learned from this process include gDNA. Invitae has noticed some gDNA sample issues. These can be caused by non-standard tubes or non-ideal gDNA samples. Invitae has [documentation](https://view.publitas.com/invitae/f168_invitae_optimizing-for-dna-sample-success/page/1) available for DNA sample success. Invitae has noticed that if the first gDNA sample fails, and the site sends a second sample that was collected at the same time as the first sample, that second sample will likely fail as well. The preferred workflow is that a blood sample would be sent in lieu of a second gDNA sample, or a gDNA sample from an alternate date of collection.
      1. ACTION ITEM: The Clinical Operations workgroup will discuss the proposed workflow for sites submitting a second sample after an initial gDNA sample failure.
   8. Sienna has been in communication with sites sending gDNA. Invitae is asking sites to adhere to the gDNA shipping schedule in order to limit the amount of gDNA samples they are receiving on any given day to 50. The samples are currently being received at a manageable cadence. Sex concordance checking at Invitae is a routine part of the clinical assay.
6. **Science Presentation: Realizing the potential of secure and decentralized harmonization of clinical and genetic data for precision medicine | Gamze Gursoy (Columbia)** 
   1. When combining multimodal data, such as genetic and clinical data, there are several barriers. Multimodal data have distinct formats and there is the potential for security concerns. Blockchain helps with these challenges by using flexible data objects (JSON) which provides enhanced security and immutability and decentralizes control to increase statistical power.
   2. A blockchain network consortium could be created with data from institutions who share records. The use of secure cryptographic tokens would allow for secure sharing of data. Challenges for this consortium model include high latency, large storage overhead, high energy use, and difficulty in usability for researchers. Indexing multimodal data to enable efficient querying. Each query is a transaction which needs to be approved. This can result in long wait times and high latency. The data can be indexed so retrieval is quicker using nested database indexing.
      1. In the example shown, data is split into nested databases: EHR-clinical, Genetic, and Audit tables. For the EHR clinical table, the OMOP common data model is used and connected to concept groups. A person view is a duplicated stream of the data organized by person. This allows for getting results on specific patients quickly. A genetic variant view allows for selection by coordinates. The audit view shows who used what kind of data by login ids.
      2. When a query is performed, the blockchain contains information about which data stream to use to access information. This allows for cohorts to be created using hash tables to find person IDs. For example, a researcher can identify patients with SNPs using the variant view to find a list of person IDs. Using those Ids, the EHR level can be extracted using person view.
   3. Overcoming challenges of the blockchain. To overcome the challenge of storage, additional patients are added in blocks with a low storage growth rate. A proof of authority system allows for a lower energy usage. This can be done when the institutions are trusted and an audit is performed on usage.
   4. User-friendly front-end [Precisionchain.g2lab.org](http://precisionchain.g2lab.org) (Username: [test@test.com](mailto:test@test.com) password: test-ME). Examples were shown demonstrating how to select and build a cohort based on inclusion criteria based on clinical factors and gene information.
   5. A demonstration was shown applied to an ALS cohort.
      1. Data from the ALS consortium (1,575 patients across 26 institutions) were used to show a relationship between age of onset and variants. In order to show a statistical significance, data is needed from 20 sites, emphasizing the need for data-sharing and a block-chain solution.
7. **Workgroup breakout sessions**

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

* 1. **CARE** 
     1. For CHD, when looking at a report that is not high risk, the group discussed whether or not sites should still see and review the integrated score
        1. If the GIRA is not high risk, we don’t want to see the elements for the integrated score. A review of every report including low-risk reports would add to the review burden for sites. The score is being generated for all patients if the items are present to calculate the score. The score can still be used in calculations and metrics. The patients aren’t going to see the score if they are not at risk for CHD. The question is specific to whether the site should see the score as part of a thorough review. For early GIRAs, every aspect should be reviewed. For the alpha and beta sites, some sites were doing a separate score calculation manually and using the QC table to see the variables being used. Some sites were also going back into the EHR. The calculation does not affect whether or not the patient will get the report. Data integrity will be checked in the patients who are high risk.
        2. **Decision: We do not need to review the elements for the score if the patient is not at high risk for CHD. R4 will hide the CHD portions**. The high-risk reports will be reviewed during the alpha/beta sites to confirm workflow and computation accuracy.
     2. Many education pages are specific to PRS. The group discussed whether or not these should included for patients who are high-risk due to other triggers.
        1. For monogenic results, Invitae produces supplemental pages that will be provided to the participant. This could be printed or emailed for return of results. The invitae report contains a link. The genetic counselor may print additional education pages from the link.
        2. For family history education, we could provide no education pages and the provider would need to speak about it or we could provide the education pages that have a lot of information about PRS and a separate bullet about family history. The education page for breast cancer is not based on PRS, it is based on a high integrated score. For all other cases, if PRS is high, the education page will be shown. For colorectal, no education page will be shown in any circumstance.
        3. For sites that have already returned GIRAs, the group discussed the need to re-return based on the changes to the education pages. The group decided that it is up to the sites and it will not be mandatory to re-return GIRAs based on changes to education pages.
        4. The language is confusing if the reason why the patient is being returned is due to family history. Especially if they are only receiving results by mail. Although the PRS figure is large, it is still important to share the risk information. The pages are static and cannot be changed based on the different risk types. Conditions that are triggered by family history have a bullet describing the risk. The provider needs to provide context that the PRS score is irrelevant for this page if it is due to family history.
        5. **Decision: If the patient is receiving a GIRA due to monogenic risk only, do not show the education page. If there’s any other type of risk factor (PRS, IS, FHH) that triggers the risk, we should show the education page. That would not include colorectal under any circumstance.**
     3. (4:49) Invitae reclassification- How should patients be informed of reclassifications?
        1. Patients change their doctor but there is still an obligation to report if something new comes up. In eMERGE 3, certified letters are sent to the last known address to attempt to maintain communication.
        2. When returning a monogenic result, patients should be encouraged to set up an Invitae account. This could be added to clinician education, GIRA report, or cover letter. We want the patient to take ownership of future communication. Edits to the consent form may be needed to reference the Invitae portal. This may also be relevant for patients who initially receive a negative report. **Action Item: Discuss with Invitae if they could add info about reclassification to their report.**
  2. **EHRI & Clinical Decision Support** 
     1. R4 Alpha/Beta Feedback
        1. When data is imported by upload or by API, the REDCap “save hook” does not always appropriately update calculated fields that are based on these items. When data is uploaded by bulk upload, calculated fields don’t always cooperate as expected. Save needs to be done on any instrument in the project (which causes calculations to take place). Northwestern plans to upload the clinical data once but will account for the potential for doing it more than once.
     2. CDS
        1. Sites have been surveyed asking if they will be able to tell if the GIRA was viewed in the EHR. Northwestern has engaged the Epic team and they have indicated it is not possible. The access logs can be used as well. Northwestern is treating the GIRA as a lab and lab results should be automatically timestamped. They will be able to tell if someone was able to view the message which has a summary of the high-risk results from the GIRA. Mt Sinai and Vanderbilt are planning on putting GIRAs in the media tab so they are audited as they are opened. Vanderbilt can only do this at the study end, not routinely. Mayo is following up with local Epic contacts to confirm. Mayo would have to build an interim based education website to link as a resource and type of CDS for clinicians. They were told journal websites would cause a challenge since it is external (this is most likely a security and policy issue).UAB has an info button software however it is a bit tricky to use. Tracking for the individual link clicks may not exist but UAB will confirm. No user/patient information is passed but the log files should be able to confirm as well. One of the parameters includes being able to tell if the click was done by a patient or provider. Sites using Epic may be able to discuss collecting access data together to find a solution.
     3. Implementation Progress and Barriers
        1. Columbia’s Epic IT team is providing a custom solution to allow for sharing of providers. Currently, the NPI registry is being used to search provider names but was an issue with finding providers listed in survey responses. At CCHMC, most recruitment is from resident clinics where providers don't fully align with providers listed in the EHR.
     4. eMERGE & PRIMED Collaboration
        1. The breakout topic during the joint meeting will discuss cloud resources and data sharing with a focus on AnVIL. The goal is a 1 year cross-network collaborative project that aligns with existing work and could result in a future supplement or grant proposal. Where the outcomes data is planned on being analyzed and the addition of social determinants of health can be topics of collaboration. Security and privacy for previously submitted datasets is a project idea. AnVIL data cannot be linked back to participant data but there are always risks with genotype data. What the mechanisms for returning the GIRA in patient records look like in the long term future should be considered.

1. **Presentation: Outcomes update since ESP meeting | Nita Limdi (UAB) & Dave Veenstra (UW)** 
   1. eMERGE will be informing participants that are at high risk that they should take clinical action. Those that are not high risk will be informed via mail or EHR (still being decided). Feedback from the external scientific panel was around outcomes in general and setting a clear set carefully documenting variation across sites. Site based effects will be noted when doing analyses.
   2. The outcomes group is specifically interested in the recommendations clinicians adopt and any intervention patients receive based on those recommendations and then whether or not patient outcomes were improved.
   3. The 3 main questions asked condition wide are (the first 2 will be tied to a 6 month survey and the last to a 12 month):
      1. Are clinicians more likely to make recommendations in high risk groups compared to controls?
      2. Are patients more likely to receive risk-reducing intervention?
      3. Are patients with existing disease more likely to be diagnosed?
   4. eMERGE will have data beyond 6 months for participants so looking at receipts of interventions will be done when possible.
   5. The ESP also made recommendations on interim analysis beginning when the network reaches a prespecified milestone (potentially enrollment of 5,000 (20%) participants). The interim analysis can inform overall outcomes as well as process improvement. Sites that have recruited more patients will probably contribute more from the interim analysis. A minimum from every site will be defined.
   6. Type II Diabetes
      1. The outcome being measured based on return of results is whether or not there were more orders for HgbA1C or a fasting blood glucose based on the high risk return. A more downstream outcome is whether a patient did the test leading to a new diagnosis and ultimately being prescribed new medication. The current analysis analyzes all patients together but one of the prespecified questions, for the common conditions, is in patients who had prevalent disease asking if there was additional testing resulting in closer monitoring thus improving blood glucose control.
   7. Coronary Heart Disease
      1. CHD has a similar framework to Type II Diabetes. There were 16 patients at UAB who had high family history risk for CHD and 3 with high PRS for CHD. Could one of the prespecified questions be does high family history risk return result in additional testing?
   8. Hypercholesterolemia
      1. The awareness is a lot higher than for CKD however looking at testing lipid profiles in patients who have high PRS for Hypercholesterolemia to see what it would do to the new diagnosis provided that awareness is around 70%.
   9. Prostate Cancer
      1. Out of 47 people that are 40% men, 3 of them had PRS for prostate cancer. In all 3 cases, physicians were doing PSA testing. PSA testing was hoped to be tracked on the patient survey.
2. **Science Presentation: A Polygenic Risk Score for Chronic Kidney Disease in African American Populations | Alana Jones (UAB)**
   1. Kidney disease in the US, 14% of adults in the US have CKD. 13.8% White adults have CKD, while 18.9% Black adults have CKD. Black adults have a ~4 fold higher risk of progression to ESRD.
      1. Cause of these disparities is social, but important to understand genetics in disease risk. Predominant representation in GWAS, development, & evaluation is European ancestry. European-derived PRS as less accurate in non-European populations. Current trajectory is likely to exacerbate existing disparities in CKD diagnosis and outcomes.
      2. Rationale for project: By developing PRS in AA populations, we can potentially close a disparity in genomic risk prediction.
      3. Developed 10 different sets of summary statistics. Best result was using eGFR GWAS with a sample size of 66,000 AA individuals. Description of Development and Evaluation of model and compared to published eGFR/CKD PRS. Shared baseline statistics from these reports.
         1. 1 SD increase in PRS associated with 35% greater odds of CKD. Accounting for APOL1 status and excluding G2s improved prediction.
      4. Evaluation.
         1. Consistent associates in TOPMed. PRS threshold-dependent increase of odds of CKD. Inclusion of APOL1 did not change the effect but improved standard error and AUC.
         2. Does PRS performance vary by eGFR equation?
            1. Using the updated eMERGE score was significant in HyperGEN. Similar association is CDK. Greatest performance was the multi-ancestry cohort.
      5. Summary:
         1. AA-speicifc eGFR eGFR PRS significantly predicted prevalent CKD in cohorts of AAs. Sensitive to known risk factors. Performance improved by accounting for APOL1 status.
         2. For PRS developed prior to eGFR equations, predictive performance varies. Small samples size, exclusion criteria, and self-reported rates listed as study limitations.
      6. Future directions:
         1. Evaluate capacity of PRS to predict longitudinal outcomes. Compare existing clinical risk algorithms. Integrate with other -omics approaches.
      7. Take-home messages:
         1. Multi-ancestry approach superior to single ancestry approaches. GWAS sample size matters. Need to address possible misclassification of CKD based on prior eGFR equations. PRS improve CKD risk prediction after accounting for traditional risk factors.
      8. Question: Is it possible to generate combined scores with PRSs? That’s part of the ultimate goal.