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

June 22-23, Hybrid (Zoom & In-Person)

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

* 8:45-9:00 AM [Announcements, opening remarks | Rex Chisholm (SC Chair, Northwestern)](#7xjuvpwkusu7)
* 9:00-10:30 AM [Panel: Early Challenges & Successes in Recruitment](#6jvxjw813acz)
	+ Recruitment data summary | Wendy Chung (Columbia)
	+ Underrepresented groups | Nita Limdi (UAB)
	+ EHR based recruitment | Alexandra Miller (Mayo)
	+ Pediatric considerations | Cindy Prows (CCHMC)
	+ Discussion section | Wendy Chung (Columbia) & Ingrid Holm (BCH)
* [Workgroup breakout session one](#kix.bgtubp59mf33)
	+ 10:50-11:50 AM [Provider Uptake & Outcomes](#kix.c32jjlapdygt)
	+ 10:50-11:50 AM [PRS & Clinical Ops](#kix.wcaeeauhl626)
* [Workgroup breakout session two](#kix.bgtubp59mf33)
	+ 12:30-1:30 PM [Comprehensive Risk Assessment & Return](#kix.n0xav72dmddo)
	+ 12:30-1:30 PM [Phenotyping](#kix.1zta04nm4jtt)
* 1:30-1:50 PM [Scientific Presentation: High-throughput Assessment of Genomic Outcomes: Development and Validation of the HI-TAG Knowledgebase | Jodell Jackson & Josh Peterson (VUMC](#kix.yfyzobh7qkvi))
* [Workgroup breakout session three](#kix.bgtubp59mf33)
	+ 1:50-2:50 PM [EHRI](#kix.yf8asgaaz84j)
	+ 1:50-2:50 PM [R2/sIRB/ELSI](#kix.slcr5s9o6f4)

[**eMERGE Day 2: Thursday,** June 23rd, 2022](#kix.jdkhurb9mh65)

* 8:45-9:00 AM [NHGRI Program Official Report | Robb Rowley (NIH/NHGRI)](#kamuso9ax145)
* 9:00-9:45 AM [Touch4Life | Laura Crandon & Angela Brade](#sij1v4dod1ru)
* 9:45-10:15 AM [Clinical Operations | Katie Larkin (Broad) & Eden Haverfield (Invitae)](#80dv898jc7dg)
* 10:15-10:35 AM [PRS Workgroup Update | Eimear Kenny (Mt. Sinai) & Niall Lennon (Broad](#m0uz113ek10j))
* 10:55-11:15 AM [EHRI Workgroup Update | Luke Rasmussen (NU) & Robert Freimuth (Mayo)](#kix.yf8asgaaz84j)
* 11:15 AM-11:35 AM  [Scientific Presentation: The Northwestern e4 Application for Participants and Coordinators | Pierre Shum & Firas Wehbe (NU)](#kix.wyy7g0tvl0wo)
* 11:35-11:55 AM [Phenotyping Workgroup Update | Chunhua Weng (Columbia) & Wei-Qi Wei (VUMC)](#vzfsxf5rwvxh)
* 12:45-1:05 PM [Scientific Presentation: Polygenic Risk Score for Prostate Cancer Risk Prediction | Kerry Schaffer (VUMC) |](#ps447ikm7zao)
* 1:05-1:25 PM [CARE Workgroup Update | Gail Jarvik (UW), Iftikhar Kullo (Mayo), & Cindy Prows (CCHMC)](#tsnbs4ps81cs)
* 1:25-1:45 PM [Outcomes Workgroup Update | Nita Limdi (UAB) & Noura Abul-husn (Mt. Sinai)](#f1p7v99t0gki)
* 1:45-2:00 PM [Closing Remarks | Rex Chisholm (SC Chair, Northwestern)](#3i8wch688f9)

[Action Items](#kix.m4nlqta1yqbf)

**eMERGE Day 1: Wednesday, June 22nd, 2022**

1. **Announcements, opening remarks | Rex Chisholm (SC Chair, Northwestern)**
	1. Steering Committee Meeting Goals: Focus on Recruitment & Retention, all sites are now actively recruiting, Touch 4 Life is a minority recruitment group based around breast cancer, breakout groups will highlight challenges and propose solutions, start to think about the logistics of preparing for sample transfers, discuss current issues and barriers to GIRA return, workgroups will receive real time feedback from the steering committee.
	2. Network Progress Since February 2022
		1. All 10 clinic sites have begun enrollment and there are 825 participants in eMEREG IV enrolled as of June 15th, 2022, Invitae contracts were full executed at the CC, CCHMC, Mayo, & UW, VUMC & CHOP awaiting final signature at Invitae, Broad-CC DUA & MSA, all MeTEE DUAs, and all VUMC-site DUAs full executed, R4 data capture & parsing instruments for clinical variables, Broad, & MeTree data import tested and in production, Sites can begin sample order & transfer to Broad on July 5th, Invitae data capture instrument testing to begin shortly, GIRA platform build is in final stages of testing.
	3. Immediate Network Challenges
		1. Cost reimbursement for high risk participants is complex and there will be site specific variations that come into play, subgroup to form and provide recommendations, global (and site) IRB amendment likely, consistent language & methods across sites will streamline amendments and reduce time, establish Outcomes variables required for each condition & methods for assessing, insertion of reports into site EHR, finalizing GIRA testing & launch GIRA platform, recruitment process improvement and IRB implications. Really want to strategize about what the right cadence is and what the right level of improvement in recruitment and retention is.
	4. Network Milestones for Next Six Months
		1. Finalize Invitae contracts at all sites, start the process of sample transfer to Broad & Invitae; receipt of data from all network partners to R4, get genomic data into AnVIL, get GIRA produced and begin return results. Trying to keep the time frame from recruitment to results as reasonable as possible – 6 to 8 months or so, respond to ESP recommendations & report out progress and remind everyone we have Sept 28th to 29th meeting already on the books
	5. Enrollment and Recruitment Timeline
		1. First return will maybe happen in September, currently estimating about 24 months to recruit the 2,500 participants at each site, last GIRA return will be in June of 2024.
2. **Panel: Early Challenges & Successes in Recruitment**
	1. **Recruitment data summary | Wendy Chung (Columbia)**
		1. The total number of participants recruited to date are 825 consented, roughly 59% of enrolled are female at birth, slightly over 53% enrolled are non-white.
		2. Roughly 60% of consented participants are female.
		3. Racial breakdown of consented participants are 47.8% white, 34.1% AA, 7.2% Hispanic, 3.5% Asian, 0.5% NA/AI, 0.2% Middle Eastern, and 5.9% identify as more than 1 race.
	2. **Underrepresented groups | Nita Limdi (UAB)**
		1. UAB validated multiple eMERGE IV conditions and enriched the African American datasets. Two papers are now accepted for publication. The goal is to recruit 75% minorities across all 10 sites.
		2. The IRB at UAB requires a partial waiver which turned out to be an advantage. Additionally, the IRB requires that the first outreach to patients must be done by a physician.
		3. UAB looked at the age ranges of patients and whether or not they showed up allowing planning of staffing and recruitment approaches.
		4. UAB restricted patients to well visits and recruited from 3 specific UAB sites with 3 physicians. While onboarding, physicians were concerned with how results would be shared and patients taking all the time in their 20-minute well visit appointments.
		5. The workflow begins with patient registration in the clinical trials system followed by clinical determinants extraction. Family history is collected using the MeTree software and the sample is collected and then shipped to Invitae and Broad. Patient surveys are conducted to collect social determinants and lifestyle. Everything will be put together to compute the genomic informed risk assessment report which will be brought back to UAB’s REDCap and embedded in Cerner. Once in Cerner, the patient and physician will be notified if the threshold is exceeded.
		6. Pre-recruitment includes screening patients for eligibility, sending the patients a signed letter one month before the appointment, and calling the patient by phone 1 to 2 weeks before the appointment. Patients can enroll online through REDCap.
		7. All high risk results will be returned by a physician during an in-person meeting and non high-risk results will be mailed/uploaded to the online portal.
		8. There are currently 329 participants and 9 physicians included in the study. Alabama has 67 counties with most of them having a medical utilization index of less than 62. Of the eMERGE participants, 80% come from Jefferson county (the most populous county in the state and where UAB is located).
		9. UAB will continue to allow online-self recruitment and work with the CC to ship samples, add tracking of sample collection and MeTree completion on R4, back up data, and create a timeline for GIRA reports to map out ROR/EMR integration.
		10. UAB has a dedicated time to speak with participants to go through the MeTree family history software. UAB, along with other sites, is concerned with the cost of dedicating so much time to go over MeTree with participants. UAB mentioned the average time taken to fill it out was 45 minutes and other sites are concerned the information being asked for is very specific and hard to collect.
	3. **EHR based recruitment | Alexandra Miller (Mayo)**
		1. Recruitment and GIRA Generation
			1. A custom report in Epic was created to identify eligible participants, a bulk message is sent to for the prescreen survey. A consent is sent out to those who complete the prescreen. A custom Epic order is created for the GIRA.
			2. Follow-up surveys for MeTree and pre-RoR survey completion are sent out through the patient portal.
			3. Samples are collected and sent to the appropriate lab.
			4. A custom Epic order is placed for the GIRA upload.
			5. A CSV is downloaded to obtain structured GIRA data.
			6. The custom Epic order for the GIRA upload will also notify participants of results being uploaded along with a CDS message being sent to providers.
			7. Mayo is also mailing results through their secured print facility.
			8. Post-RoR surveys will be sent out by email or patient portal.
			9. Mayo has implemented an Epic query for eligible participants that looks for:
				1. Age 13-74y
				2. Southeast MN resident
				3. Upcoming PCP appointment in the next 2 weeks
				4. Active patient portal
				5. Research contact permission
				6. A PCP listed in Epic
			10. Data transfer from R4 to Epic involves downloading a CSV file with labels which runs through APIs for PatientSearch, GetSmartDataElements, and SetSmartDataElements.
			11. To consent, an Epic report is run for participants that complete the prescreen but not yet consented.
			12. Biospecimen collection will be completed based on participant convenience.
		2. Pre-enrollment and consent
			1. Currently, Mayo has consented 76 participants out of 261 pre-screening forms completed.
				1. Age ranges from 25-74 years.
				2. Race is primarily non-Hispanic white at 96%.
		3. Approximately 95% of the potential participants have an active patient portal.
		4. Of participants that do not list a PCP in the pre-screen, most use the continuity clinic and see an intern and likely do not remember the provider’s name.
	4. **Pediatric considerations | Cindy Prows (CCHMC)**
		1. Ethical Considerations
			1. Ethical considerations include potential benefit for selected pediatric diseases for PRS and protecting children’s future autonomy. CCHMC considers interventions for asthma and obesity as actions that really need to occur during early childhood. For Type I Diabetes, which may have lower prevalence, kids can come in with DKA so identifying at risk kids can lower incidence.
			2. Additional considerations also include surveillance and intervention burden. For common disease in children, risks will be mitigated by primary care providers who are considering risks reported by eMERGE as well as medical history. Many interventions are also home-based (activity, healthy foods, etc).
			3. Nearly all parents expressed interest in learning their childrens’ PRS once they learned more but had concerns about age. Parents also identified barriers including intervention costs, transportation, time, and limits on adaptations parents can make to rental homes (for things like asthma prevention).
		2. It is important to remember parents are surrogate decision makers for children. Children's dissent should also overrule parent permission.
		3. One-to-one recruitment is what is primarily being used to initiate parental trust and answer questions.
			1. COVID had impacts on clinics and sick visits dominated in-person visits. Solutions include pre-screening clinic schedules for well-child visits and expanding additional sites. The consent process takes about 15-30 minutes depending on complexity and parent questions. For parents independently navigating R4, CCHMC is finding part 1 consent takes about 14 minutes and part 2 is even quicker. CCHMC is developing a 1 page information sheet with QR codes to the CHOP video and a CCHMC PRS video. It will also go directly to the FAQ (that will be provided with mailed letters as well).
		4. CCHMC/UC is targeting three primary care clinics with the highest percentage of African American children. CCHMC is using a community advisory committee to help with recruitment. Some suggestions include diversifying the study team, stressing face-to-face meetings, and tapping into community voices.
		5. Other challenges include children disliking blood draws and not getting them as often as adults. CCHMC is relying on saliva collection which must be observed to comply with CLIA. Shipping the kits for in-home saliva (which is observed virtually) is becoming a problem due to stolen or damaged packages.
		6. MeTree collection is more complicated when enrolling families, especially because you cannot copy information so every member of the family has to be completed.
		7. Some key suggestions for adult sites: Enroll younger children that do not have established health behaviors. Assure study staff conducting one-on-one parent permission and assent are trained to discuss studies with children. Plan to coordinate sample child blood or saliva collection and MeTree completion at the same visit.
		8. Health behaviors begin as children so it is worthwhile to enroll children, especially because parents are very motivated to help their children be healthy.
		9. CCHMC set different ages of assent to involve adolescents a lot more in the process of deciding whether or not they wanted to participate in the study.
	5. **Discussion section | Wendy Chung (Columbia) & Ingrid Holm (BCH)**
		1. MeTree Challenges
			1. Sites are telling individuals to be very focused on immediate family members which has been helping participants. Not having an “I don’t know” or “Unknown” option has been very challenging.
				1. Data integrity may be an issue and it takes a lot of time to go through family health conditions when some individuals do not understand what a health condition is. Participants in other studies have expressed concern answering “no” in place of “I don’t know” because their family members could actually have had a health condition they do not know about.
			2. Completing MeTree is taking a large amount of time and the other questions are going unanswered.
			3. UAB is taking elements from the survey and MeTree that are driving the GIRA report and trying to allocate analyst time to go through and look at concordance.
			4. Georgia Wiesner from VUMC used MeTree for a project called Forest which looks at family history to identify high risk for cancer. About half of participants will complete MeTree (the study is not dependent on having the information for the study). A specific set of instructions with screenshots has been helpful.
			5. There is no great way to redo the MeTree collection tool at this point in the study. A true subset can be created to allow for no responses for some questions.
				1. GIRA is about to be tested and everything is built out so the question is how long of a delay is acceptable to rebuild the data collection tools.
				2. A REDCap survey could collect the same data as MeTree that has a wider programming lift and important elements can be exported to MeTree all so the GIRA programming does not need to be changed.
			6. A working group should be created to quickly explore this to not delay the study but to come up with a solution and the minimum information needed to complete the family history.
3. **Workgroup breakout sessions**

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

* 1. **Provider Uptake & Outcomes**
	2. **PRS & Clinical Ops**
	3. **Comprehensive Risk Assessment & Return**
		1. **Action Item:** An encounter note template will be created by Margaret Harr and Alex Miller to be shared with the group.
		2. **Action Item:** Each condition lead should review minimal family history requirements needed in column D from this spreadsheet and work with Margaret Harr (CHOP) to define survey needs.
	4. **Phenotyping**
	5. **EHRI**
	6. **R2/sIRB/ELSI**
1. **Scientific Presentation: High-throughput Assessment of Genomic Outcomes: Development and Validation of the HI-TAG Knowledgebase | Jodell Jackson & Josh Peterson (VUMC)**
	1. Background
		1. eMERGE III enrolled 25,000 patients and 4.2% (1,042) returned a variant and 479 patients had a pathogenic or likely pathogenic variant. Patients were excluded for missing data. Focused on top five conditions: Breast Cancer, Colorectal Cancer, Cardiomyopathy, Arrhythmia, Familial Hypercholesterolemia. The process outcomes examined are specific steps that lead to an outcome. Examples included screening, diagnosis and procedure processes
	2. HI-TAG (High Throughput Assessment of Genomic outcomes) was used to group outcomes
		1. Chart review was very time consuming and can’t be conducted on public databases. Sites performed a manual chart review and CPTs were collected for three years. HI-TAG groups CPT codes into tags potentially flagging as diagnostic, screening, or procedure outcomes. The HI-TAG process was intensive and cross-checked and verified with domain experts.
	3. Validation analysis compared results from CPT/HI-TAG to the manual outcome review.
		1. Looking at positive predictive value and sensitivity, diagnostic and procedure had a lot of missingness. Screening comparisons showed good results: 60-80%. There were some tags such as Breast Cancer and FH that showed discrepancies.
		2. Additional chart review looked at discrepancies. Timing: Chart review did not look at the same time period as CPT review. Billed Procedures: Related but not same procedures and ambiguity. Missingness: External results that didn’t show up in CPT or procedure were listed in the chart but CPT code was not present.
	4. Procedure rates using HI-TAG cpts were compared after return of results
		1. Analysis did a one to one matching on age, sex, and site to compare procedure rates. Significantly more services delivered for four conditions (Not FH) post RoR compared to Pre RoR for P/LP variants. When compared to those without variants four conditions (not BC) showed significantly more health services delivered compared to those without variants. Difference in difference analysis examined change in services among participants with P/LP to those without - significant findings in: Arrhythmia, Cardiomyopathy and Colorectal Cancer. HI-TAG knowledge base can be to examine outcomes on de-identified common variables. We saw an increase in rates of services post return in the eMEGE III data set for three of the five conditions examined.

**eMERGE Day 2: Thursday, June 23rd, 2022**

1. **NHGRI Program Official Report | Robb Rowley (NHGRI)**
	1. Genomic Learning Healthcare Systems Virtual Meeting - hosting a virtual meeting August 31st to September 1st, 2022, 11 a.m. to 5 p.m. ET
		1. Meeting to discuss progress since the National Academies meeting in 2015, as well as to identify generalizable solutions to genomic medicine implementation challenges experienced
	2. Updates:
		1. The budget for NIH has increased by 5.3% since FY 2021 (1 billion dollars of that increase is for ARPA-H)
		2. FY 2023 budget for NIH is proposed to increase by 8.9% to 49 Billion (5 billion dollars is included for ARPA-H)
		3. The budget for NHGRI increased by 3.8% since FY 2021
	3. Advanced Research Projects Agency for Health (ARPA-H)
		1. The purpose of ARPA-H is to benefit the health of all Americans by catalyzing health breakthroughs that cannot readily be accomplished through traditional research or commercial activity. Summer of 2021 OSTP and NIH published a commentary in *Science* and engagement activities were launched to gather community feedback. FY 2022 in March omnibus with $1B made available for 3 years. Director of ARPA-H to be Presidentially appointed (no one has been appointed yet). In April 2022 ARPA-H transferred to the NIH. The ARPA-H Director will report to the HHS Secretary
	4. Funding Announcements
		1. Advancing Genomic Medicine Research. Stimulate innovation and advance understanding of when, where, and how to implement genomic information and technologies in clinical care. New R01 and R21 funding opportunities – application due dates: August 1st, 2022; March 13th, 2023.
		2. Dissemination and Implementation Research in Health (DIRH) Pars. Support studies that will identify, develop, and/or test strategies for overcoming barriers to the adoption, integration, scale-up, and sustainability of evidence-based interventions, practices, programs, tools, treatments, guidelines, and policies. New R01, R21, and R03 funding opportunities – application due dates: October 16th, 2022; February 16th, 2023.
2. **Touch4Life** **| Laura Crandon & Angela Brade**
	1. The Touch4Life organization advocates for women, especially under-represented women, to get involved in breast cancer research.
	2. The team includes professionals with clinical, technical, and educational backgrounds.
	3. Due to the broad biodiversity in the AA gene pool in the US, it is important to encourage women of color to participate in clinical trials so relevant data is collected and the data pool is enriched.
	4. Black women are 42% more likely to die from breast cancer and the causes need investigation.
	5. Lack of diversity in research can be divided into lack of trust, barriers to participation, and a less inclusive approach to recruitment.
	6. Mistrust in research is due to events as recent as the Tuskegee Syphilis Study (1932-1972).
		1. Building trust requires locality consciousness and culturally relevant messaging that is genuine and not opportunistic.
		2. Entities tend to use the ‘logical trust’ model that uses broad recruitment strategies that are data driven on who to reach out to.
		3. ‘Emotional trust’ builds on social relationships and shows authentic concern.
	7. Survey results show that sites are using a filter to show diverse populations within their area. Results also indicate that biobank and in-person recruitment is working well. Technology barriers, unassisted pre-screen and enrollment leading to missing data, and COVID restrictions are impeding recruitment.
	8. A focus group with black women revealed that physician recommendations provided the highest motivation to participate in research trials. Specialist providers can be approached for participant recruitment and not just focusing on the PCP.
	9. Other effective methods to improve motivation to participate in clinical trials include emphasizing that this may positively impact people like them and may provide life saving treatments.
	10. Emotional trust and engagement: Social relationships and emotional connections with churches, colleges, and community organizations can help build emotional trust.
	11. Demonstration of goodwill in the community by creating community circles, aligning with community partners, listening to the community, among others, can help improve trust as well.
	12. Essential value of the clinical trial is important to communicate to help build emotional trust as well.
	13. Culturally relevant messaging that includes images and vernacular that resonates within the community, hyperlocal messaging, and patient focused messaging helps to build an inclusive approach in recruitment.
	14. Recommendations for increased and sustained engagement:
		1. Continue using methods that are working well for the specific site.
		2. Develop a social connectivity framework and infrastructure.
		3. Enhance current messaging to make emotional connections to target populations.
		4. Segment new trust measures for each engagement channel.
3. **Clinical Operations | Katie Larkin (Broad) & Eden Haverfield (Invitae)**
	1. Broad
		1. Katie Larkin has replaced Maegan Harden as the Clinical Operations Co-chair from the Broad. All sites have executed contracts with the Broad, and all sites should have instructions and training for how to send samples. Candace Patterson (candace@broadinstitute.org) and Mike DaSilva (mdasilva@broadinstitute.org) are available for ongoing support.
		2. Sample Submission
			1. The Broad is accepting DNA extracted from blood or saliva sent in the 2D barcoded tubes. Each site should have 2,500 tubes previously provided by the Broad. The 2D barcodes are linked to the Broad LIMS, and the metadata will be uploaded into an order in the R4 portal. Samples must have a min of 40 uL at 60 ng/uL to allow for QC testing.
			2. Sites must submit samples in sets of 95. The tube rack will have one slot open for a positive control.
			3. A shipment tracker will be used by the Broad to confirm they have received sample shipments.
		3. Samples undergo an internal QC process.
		4. Results are reported to R4 via API once they are signed out. The research data outputs will be available to the network through AnVIL.
		5. The Clinical Operations group will monitor and report out monthly the number of samples received, in process, and completed. The average turnaround time will be reported along with the percentage of high PRSes.
			1. The target turnaround time from sample intake to report release is 4-6 weeks.
		6. The Broad will be able to start receiving samples the week of July 5th.
			1. This process will be a pilot. Sites are asked to send one set of 95 samples initially. If sites have fewer than 95 samples please reach out to Candace prior to sending.
		7. Ancestry or population is not being put into the pipeline.
		8. ACTION ITEM: Niall and Eimear will discuss offline regarding the ability to perform surveillance on PRS scores across population groups as the study is ongoing.
		9. There are a priori expectations of the proportion of high risk individuals, which should be able to be monitored. The CC can add this monitoring metric to the R4 dashboard.
		10. ACTION ITEM: The PRS workgroup will work on creating power calculations to determine the sample size needed to examine differences in the proportion of the high risk bin across conditions.
		11. Sites can send samples to the Broad as part of the pilot phase, regardless of participant MeTree completion.
	2. Invitae
		1. Tara Schmidlen and Eden Haverfield reviewed the Invitae workflow and process. Invitae has been distributing information regarding the Invitae portal to sites upon contract executions. They will also be reviewing the order process on the next Clinical Operations subgroup meeting.
		2. Tests can be canceled at any point up until data is uploaded into the Invitae platform. Once the data is uploaded, Invitae has an ethical duty to disclose any medically actionable results. If the participant withdraws after the samples are sent, no GIRA will be generated. If the data has already been uploaded, the clinical report will be returned.
		3. Invitae can provide saliva or blood collection kits at no charge via [their website](https://www.invitae.com/request-a-kit/#/). These are provided with FedEx prepaid labels. Blood and saliva samples can be received by Invitae any time with no maximum.
		4. Invitae will not be providing collection kits for sites sending gDNA. Invitae can only receive gDNA in batches of 50 or less per day across the entire network. Invitae has created a shipment schedule that will be shared with sites as their contracts are executed.
		5. More details on this process can be found in the Sample Management and Submission SOP.
		6. For sites sending gDNA, Invitae is requesting a smaller pilot batch of 5-10 samples. Sites must inform Tara prior to shipping this smaller pilot batch of samples.
		7. Invitae portal accounts will provide shipping status updates. Once the results are released, the notification will be emailed to the HCP and/or delegate. This notification will not include the report content, it will just convey that the results are available. The PDF reports can be accessed in the HCP portal. This includes sample failure notifications.
		8. Invitae provides a [peer-to-peer clinical consult service](https://www.invitae.com/en/providers/talk-to-an-expert).
		9. There has not been a time limit imposed on additional sample submission following sample failure. The time-out would be the completion of study, and may be site dependent.
		10. P/LP findings for EPCAM, APOB, LDLRAP1, and LMNA will be flagged and will require manual review.
		11. CNV failures will not prevent monogenic results from inclusion.
		12. TP53 possible mosaic results are flagged by Invitae on the report, and Invitae will accept additional tissue types for further analysis. Contact the [clinical consult team](https://www.invitae.com/en/providers/talk-to-an-expert) if this occurs.
		13. Eden Haverfield (eden.haverfield@invitae.com) and Tara Schmidlen (tara.schmidlen@invitae.com) will be the first point of contact for Invitae.
		14. The turnaround time for these tests is up to 21 days but on average around 12 days.
		15. Saliva samples collected now can be entered in the HCP portal, but should not be sent to Invitae.
		16. Sites would like to try to get the GIRA and Invitae reports generated as close together as possible for them to be returned together. It is acceptable for a separate return for some participants to receive their positive monogenic results independent of their polygenic and GIRA results. The PRS report would not require a separate return. Monogenic results have clinical guidelines for return. The Broad would prefer for sites to send samples as soon as they are ready, in plates of 95 samples, as the Broad is not limited on genotyping capacity.
	3. Luke Rasmussen provided an update on the Redox API. He is piloting the Redox through NU. There is sample code on GitHub that can be circulated to those who request it.
4. **PRS Workgroup Update | Eimear Kenny (Mt. Sinai) & Niall Lennon (Broad)**
	1. The network previously decided on focusing on representation on different genetic ancestry groups in the high risk categories for all eMERGE conditions. The All of Us cohort data uses the same exact array for PRS imputation so it was decided that it could be used for an ancestry adjustment model.
		1. The All of Us training cohort consists of data from 6,885 All of Us GDA arrays. It is balanced by population groups with the exception of South Asian ancestry. The cohort also contains many individuals with a high level of genetic admixture.
		2. The purpose of using the genetic ancestry to calibrate the model is to achieve the 5% in the tail of the distribution.
	2. The PRS and Breast Cancer group has been working together to work out the parameter set and it has been updated based on the 308 sites reported out by the eMERGE IV poepine.
	3. A PRS flagship paper abstract has been submitted to AASG and PRS selection, optimization, validation, and implementation manuscript is now in an advanced draft. Tables and figures are being refined and planned submission is the end of July.
		1. Additionally, four manuscripts describing PRS development at sites have been submitted, one has been accepted, and three are published. Moreover, sites have three unpublished manuscripts, one is under embargo, and two have a planned submission of July.
		2. The ClinGen common disease workgroup is also very interested in the publications since this is technically the first application of the standardized PRS tool the ClinGen group adapted being used in eMERGE.
		3. A list of the publications can be found in the document here. They will also be added to the eMERGE website in the future for easy access. Additionally, they should be added to the PRS grid document hereso the CC can keep track.
5. **EHRI Workgroup Update | Luke Rasmussen (NU) & Robert Freimuth (Mayo)**
	1. Current and Future Directions
		1. Collect Network requirements (data, workflow, EHR integration), define specifications for report artifacts (PRS, monogenic, GIRA). Support Network WGs as needed (Outcomes, CARE, PRS, GIRA)
	2. Hackathon on June 14th, 2022 & Next Steps
		1. A change control process needs to be defined for R4. A site development/testing mirror of the production project should be created. Code may be shared across sites regarding populating EHR instruments and retrieving GIRA data elements. The workgroup will begin drafting minimal JSON specifications for the GIRA data elements.
	3. CDS Workgroup update
		1. Areas of commonality: everyone is notifying providers of high risk, almost all by EHR messaging (only one intends to disclose over email). Sites are unsure if they will be able to deliver the provider survey via EHR. The majority of sites plan to put the Invitae results into the EHR, but this may not be done at the same time the GIRA is placed in the EHR.
		2. Next Steps for CDS:
			1. Share methods across sites of tracking if GIRA was opened. Determine what structured data elements sites need for CDS. Document differences in decision workflow and use of CDS. Share CDS resources and strategies among sites. Ultimately, the workgroup will consider publishing “Lessons learned: on CDS implementation and impact of different approaches to RoR/CDS on outcomes.
6. **Scientific Presentation: The Northwestern e4 Application for Participants and Coordinators | Pierre Shum & Firas Wehbe (NU)**
	1. Background
		1. Local app created to track and integrate workflow across multiple platforms. Workflows are integrated to combine participant and coordinator data
		2. Functionality: Participant portal contains a sequential list of items that are required for the patient to complete study. Links out to redcap instruments. A coordinator portal allows for linking to medical records and completing admin tasks. Shows status of patients as they move through instruments. Allows for export and completion of tasks.
	2. Demo Application [Recording link](https://zoom.us/rec/share/yuj2UhUgxD8SOSNk0ivW904KgplsXrYnuHf6iUWZPGCMr31S3A6UCxcIAg_QZ--P.dVtRYrbm_dTZApGh) Timestamp: 02:22:00
	3. Lessons learned: Be agile and work for each module one at a time-minimum viable product, Redcap API and open source flutter were key to success, Recommend hackathon and communal code sharing.
	4. Questions
		1. Can other sites take advantage of this? What barriers exist? Staffing up and getting the correct expertise for setting up.
		2. What committees and approvals are needed? Needed permission to add to medical record but limited other oversight required.
		3. Limited ability for other sites to adopt. Northwestern has a clinical trials management system that does not exist at other locations.

1. **Phenotyping Workgroup Update | Chunhua Weng (Columbia) & Wei-Qi Wei (VUMC)**
	1. There are three major components of the finalized guidelines of the clinical data elements for GIRA.
		1. The data dictionary defines what data is being collected from the EHR, with the terminology, description, unit, and type of data. The minimum and maximum values are defined.This also details what data is required for the GIRA. The workgroup generated example data to assist sites in understanding what the EHR data should look like.
		2. The notes and quality control component is very important. The QC will occur prior to data submission to R4. This section details the QC parameters. For each clinical data element, the workgroup has detailed a short description of what the data should look like, with units and a normal range. If a participant’s data is outside the range, it will trigger a chart review.
	2. The workgroup is currently developing and defining a phenotyping algorithm metadata framework.
		1. The intent is to help researchers choose which phenotype algorithm to use for different applications to select the best fit for their research. Version one of the framework contains a general description of the algorithm, the technical description of the algorithm, and the phenotype performance.
		2. The group is testing this framework on a list of phenotypes (Diabetes mellitus 1, diabetes mellitus 2, hypertension, heart failure, myocardial infarction, atrial fibrillation, acute kidney injury, chronic kidney disease, and colorectal cancer).
		3. This framework has gone through multiple reviews within the network. The plan is to finish the annotation by late July. Following completion of the annotation, the workgroup will review and assess for further refinements or improvements.
		4. ACTION ITEM: Please reach out to Chunhua Weng (chunhua@columbia.edu) and Wei-Qi Wei (wei-qi.wei@vumc.org) if you are interested in working on the phenotyping algorithm metadata framework annotation.
		5. PheKB is a repository of the phenotyping algorithms. This framework is designed to help catalogue and evaluate the phenotyping algorithms, to help facilitate the retrieval of related phenotyping algorithms. For example, there are multiple phenotyping algorithms for type 2 diabetes. This framework can assist researchers in further specifying search parameters to find the algorithm they need.
		6. It was suggested that the framework include version number and validation dates. The framework already includes the algorithm publication date. The manual chart review results repository is collected, which includes validation data. The phenotyping workgroup will formalize guidelines on how to use this with R4.
2. **Scientific Presentation: Polygenic Risk Score for Prostate Cancer Risk Prediction | Kerry Schaffer (VUMC)**
	1. Over time, there has been a shift in the use of PSA (prostate-specific antigen which is a blood test used primarily to screen for prostate cancer) as a screening tool. This has resulted in overdiagnosis and overtreatment which has caused anxiety, high financial burdens, and bodily complications.
	2. There is a large push in focusing on high grade cancers that are likely to cause morbidity and mortality in patients.
	3. A new emphasis on shared decision making for medical procedures has increased interest in decision and clinical prediction tools to help men make informed decisions on prostate biopsies.
		1. A calculator that can be found online that calculates risk based on age, PSA level, digital rectal exam, race, family history, and prior biopsy status. The calculator predicts high grade disease, low grade disease, and benign findings.
	4. Prostate cancer is known to be a highly heritable condition and genome-wide association studies have identified numerous common SNPs associated with prostate cancer risk.
	5. A tool was developed using a meta-analysis of prostate cancer (paper can be found [here](https://www.nature.com/articles/s41588-020-00748-0)).
		1. The study wanted to evaluate whether validated multi-ancestry polygenic risk would improve risk prediction for the outcome of clinically significant cancers on prostate biopsies compared to the clinical predictor calculator.
		2. Data from VUMC BioVU was used. The study first confirmed that prostate cancer PRS were associated in BioVU with cancer cases in the overall BioVU population. It did associate and discriminate for prostate cancer.
		3. Prostate cancer was defined as individuals with two ICD codes for prostate cancer and the control was males with a PSA measurement but no prostate cancer ICD codes.
		4. A cohort of males was developed who met with a urologist for an evaluation of elevated PSA seeking to determine if the PRS was associated with any prostate cancer on the biopsy. The cohort included males ages 40 to 80 and excluded anyone with organ transplants or prior biopsies. The cohort began with 39,274 males with genotyping and concluded with 655 participants after chart reviews and exclusions. The popuation’s median age was 63 and included a median PSA of 5.3. There were 47% with no cancer, 52% with cancer and 27% with higher grade prostate cancer.
		5. The prostate cancer risk was significantly associated with the diagnosis of any cancer and grade group greater than two cancer.
		6. For the outcome of any cancer, the PRS improved discrimination compared to a model that only included age.
		7. Next steps include cohort and prospective studies that can help determine outcomes and goals. Additionally, PRS scores can be developed for high grade cancers and include racially diverse populations.
		8. Over time, patients converting to higher grade cancers is approximately one third. Patients may want to know of lower grade cancers early but age range, number of biopsies, and negative consequences should be considered.
3. **CARE Workgroup Update | Gail Jarvik (UW), Iftikhar Kullo (Mayo), & Cindy Prows (CCHMC)**
	1. Current CARE challenges include patient related clinical research costs, return pipelines, and MeTree considerations.
	2. The Medical Cost Coverage Subgroup will meet on the 1st and 3rd Tuesdays at 2:00pm ET.
		1. The critical decision that needs solving is how much uniformity will be required across the network.
	3. The return pipeline will include participant cover letters, RoR sheet with key discussion points for GIRA high risk returns, phenotype agnostic encounter not templates, and provider notifications of high risk results.
	4. Messaging should be specific so providers do not overlook the In-basket message and language should be consistent across the Network.
	5. When interviewed, providers felt more comfortable with monogenic results and who the participant may be referred to compared to the polygenic results.
	6. Key points to be covered by the provider can be shared so messaging is consistent. Since most sites are using genetic counselors to return results, messaging will likely be consistent.
	7. MeTree concerns include time costs on study staff and several conditions using family history to trigger a high risk return (afib, prostate cancer, CKD, breast cancer, and CHD).
	8. A small subgroup will be formed to review the minimal data necessary for family history needed for family health history. A REDCap alternative to MeTree has been discussed but for now won’t involve R4 programmers.
	9. It should be considered that if a participant has trouble completing MeTree, they may have issues completing the REDCap survey. Non-technical solutions should be pursued to minimize changing study design and affecting outcomes.
4. **Outcomes Workgroup Update | Nita Limdi (UAB) & Noura Abul-husn (Mt. Sinai)**
	1. Primary outcome is uptake of healthcare recommendations among these groups. Number of new diagnoses and risk reducing interventions or treatment intensifications for and secondary outcomes.
	2. Are we going to return results 1:1 high touch to any control participants? When we have 5000 enrolled and some RoR experience within that first 5000.
	3. Manuscript concept sheet: The Outcomes co-chairs are creating a manuscript concept sheet for the Outcomes marker paper; a writing group will be formed soon. The manuscript will cover several topics, including: how outcomes were selected and harmonized across phenotypes, where the outcome data will come from (surveys, from patients/providers, data from EHR), regression discontinuity design for analysis, the randomized control group (related to the 1:1 Live GIRA return to control group decision), a detailed discussion of comparator groups (high risk to not high risk, how we will adjust for related conditions), a walk through of preliminary power calculations for both phenotype-specific and phenotype-agnostic analyses under different assumptions of uptake in the high risk versus not high risk group.
	4. Ongoing challenges: Currently, the Provider Survey Subgroup is working with its Outcomes parent group to decide timing and frequency for the provider survey. The workgroup is also collaborating with other groups on several other issues: methods and timing of results (with CARE workgroup), site-specific communication strategies (with CDS and EHRI workgroup), reimbursement for recommended actions (with new Cost subgroup).
	5. Future challenges
		1. Noura is stepping down as the Outcomes co-chair; Dave Veenstra (UW) and Nita Limdi will be the co-chairs going forward.
		2. Outcomes plans to finalize provider surveys and operationalize after RoR soon.
		3. The workgroup plans to consider how medical care costs/reimbursement may impact outcomes and factor it into the analysis.
		4. The group will work with phenotype leads and the phenotyping workgroup to capture outcomes of interest from EHRs or surveys.
5. **Closing Remarks | Rex Chisholm (SC Chair, Northwestern)**
	1. Condition leads must review and submit the minimal family history collection by the end of next week to the CC. The CC will also be collecting any participant raised issues.
	2. Sites should ensure they are sharing single site publications with the coordinating center and the NHGRI. The CC and NHGRI will help publicize publications.