**Summary of Steering Committee Meeting: December 2020**

December 10-11 via Zoom

**eMERGE Day 1: Thursday, December 10th, 2020**

* [Welcome and Logistics | Jodell Jackson (CC/VUMC), Rex Chisholm (SC Chair, NU)](#fbzurx616j3e)
* [Pediatric Condition recommendations | Sharice Wood (CCHMC), Elizabeth Bhoj (CHOP)](#5801c5rjc5jb)
* [Condition age ranges: Actionability & Returnability| Gail Jarvik (UW), Iftikhar Kullo (Mayo), Cindy Prows (CCHMC)](#tj6yznxas9bi)
* [Ethical Legal & Social Implication Considerations for the Prospective Cohort | Ingrid Holm (BCH), Richard Sharp (Mayo)](#4xp65flyr3kv)
* [PRS Pass/Fail Criteria | Eimear Kenny (Mt. Sinai), Patrick Sleiman (CHOP)](#ap1olhk5jf64)

**eMERGE Day 2: Friday, December 11th, 2020**

* Introductions/Overview
	+ [Opening remarks | Robb Rowley (NIH/NHGRI) & Teri Manolio (NIH/NHGRI)](#9y9y0wtg83vn)
	+ [eMERGE Network Overview: Priorities, goals, & progress | Rex Chisolm (SC Chair, Northwestern)](#5g8nlbhwugrs)
	+ [Comments from ESP Chair | Katrina Goddard (KPCHR)](#kix.g919li57xfpz)
* Retrospective validation
	+ [PRS WG | Eimear Kenny (Mt. Sinai), Patrick Sleiman (CHOP)](#vgymz8rd1uxb)
	+ [Genotyping WG (GDA deliverables) | Meg Roy-Puckelwartz (NU), Niall Lennon (Broad)](#oziuuematdfq)
	+ [Phenotyping WG| Chunhua Weng (Columbia), Wei-Qi Wei (VUMC)](#2ahz5d8gv2tt)
* Prospective study design
	+ [CARE WG– GIRA report & integration | Gail Jarvik (UW), Iftikhar Kullo (Mayo), Cindy Prows (CCHMC)](#sn0o7ypfyy8q)
	+ [EHRI WG– data integration/flow | Luke Rasmussen (NU), Bob Freimuth (Mayo)](#uiyjyobzf7p7)
	+ [Outcomes WG| Noura Abul-Husn (Mt. Sinai), Nita Limdi (UAB)](#2ap0of1151dx)
* [sIRB protocol | Digna Velez-Edwards (VUMC)](#cbztkqcp9mnq)
* [Input/Feedback from the ESP, general discussion](#m660v8fkz6nw)

[Action Items](#dpa3elhf1o1v)

[Decisions](#im5sqfquj9qj)

**eMERGE Day 1: Thursday, December 10th, 2020**

* **Welcome and Logistics | Jodie Jackson (CC/VUMC), Rex Chisholm (SC Chair, NU)**
	+ The goals for Day 1 of the ESP/SC meeting were to:
		- Ensure that the network understands proposed age bands for each condition, and the downstream impact on each sample size.
			* The Co-leads were asked to complete GIRA sheets to start the discussion about the age bands of return for each condition, and to give estimates of how many participants will be impacted for each of those conditions.
		- The ELSI group will review inclusion/exclusion criteria, RoR as they have provided input for several Network decisions. The ELSI group will also discuss considerations the Network should make moving forward.
		- An additional goal of the ESP/SC meeting is to discuss and agree upon the metrics that will be used to evaluate the PRSs, and how the Network will determine if those PRSs will be confirmed and integrated into the final GIRA conditions.
* **Pediatric Condition recommendations | Sharice Wood (CCHMC), Elizabeth Bhoj (CHOP)**
	+ The Pediatric subgroup convened to address issues specific to PRS in pediatric populations.
	+ This subgroup evaluated the following conditions:
		- Obesity, Hypercholesterolemia, Hypertension, Type 2 Diabetes, Non-alcoholic Fatty Liver, Type 1 Diabetes, Lupus, Chronic Kidney Disease (CKD).
	+ The subgroup proposed three additional pediatric disorders: asthma, atopic dermatitis, and Crohn’s.
		- Crohn’s disease was excluded due to lack of actionability.
	+ There were two conditions removed due to the lack of PRS data: CKD and hypertension.
		- Although there is actionability in pediatrics, these two have different pathophysiology in pediatric versus adults so PRS validation inapplicable. They are not considered the same phenotype in pediatric and adult.
	+ Obesity has PRS validation and actionability in pediatrics.
	+ Hypercholesterolemia was found to be actionable for all age groups.
		- There is not a validated pediatric PRS but there is a possibility of applicability. This condition has the same pathophysiology as adults.
	+ Type 1 diabetes is actionable and has a validated PRS for pediatrics.
		- This condition is recommended for differential diagnosis due to the limited number of preventative measures. There is a monogenic disease that is oftentimes mis-diagnosed as Type 1 diabetes.
		- Children present with Type 1 diabetes with Diabetic Ketoacidosis (DKA). Including this condition could help catch this disease before severe DKA occurs.
	+ Type 2 diabetes is actionable across all age ranges.
		- The actions/interventions would be focused around prevention.
	+ Nonalcoholic fatty liver disease is pending PRS validation.
		- Actionability at younger ages is observed from a prevention standpoint. Outcomes measures include monitoring BMI and ALT measurements.
		- For NAFLD, we have poor predictive performance with the 1- to 10-SNP based scores that are currently available. There are at least 3 groups with significantly bigger studies than have been published, but the timing is working against us with regards to when that data will be released/available.
	+ Lupus has PRS availability that closely mimics type 1 diabetes with early identification of disease.
		- Actionability would be talking to families about screening and education opposed to preventing disease.
		- Allergy is more of an issue in kids than autoimmunity. Can potentially evaluate the kids with regards to allergy vs. autoimmunity in more research form. The incidence of SLE in children is 1/5000 or less.
	+ Asthma has a much higher prevalence in children
		- Actionability would be education on signs and symptoms of respiratory distress, specific flu vaccine intervention, and encouraging lifestyle modifications such as smoking cessation.
	+ Atopic dermatitis has PRSs available in pediatrics.
	+ The network discussed primary prevention vs. differential diagnosis in early disease in determining actionability.
		- It would be important for the PRS to have a high AUC for the differential diagnosis. This subgroup considered prevention and diagnosis. Weight was placed more heavily on one or the other depending on the phenotype.
	+ Breastfeeding recommendation for obesity comments:
		- Continuation of breastfeeding plus healthy weaning habits are some recommendations in place.
		- Breastfeeding is proven for lowering obesity in children.
		- Not all women can breastfeed, so we must be sensitive to not offending and relating not breastfeeding to obesity directly.
	+ The plan is to only return results once to participants so all PRS and GIRA need to be validated for results to be returned. The pediatric group recognizes that there will be a smaller list of conditions that will be returned to the pediatric participants.
	+ Discussion:
		- Hypertension and CKD are not going to be included in the pediatric group.
		- It is difficult to make a diagnosis of lupus in children.
			* A negative antinuclear antibody would rule out pediatric lupus. A high PRS could alarm parents when the chance of a child developing lupus is very low. There isn't a preventative strategy, the risk factors are not well understood. The peak incidence is at 35 years old. The AUC for lupus is low, a positive predictive value due to low prevalence will not be desired. This phenotype is a good condition to consider to further research but not return results in a clinical setting.
	+ The addition of asthma and atopic dermatitis:
		- For asthma you have ¾ of all kids present with recurrent wheezing, but only a small subset end up with asthma.
			* Physicians might be more inclined to treat with control medication rather than steroid/albuterol with a child that has a high PRS. No one has measured the efficacy of healthcare costs on kids.
			* If a PRS is available in this instance, something can be done about therapy for high PRS and if it would be financially beneficial. High PRS for asthma in children may make parents more inclined to modify environmental factors (flu, air purifier, smoking cessation) to help treatments.
			* How good is the asthma PRS performance? Does the PRS help distinguish subtypes?
				+ Allergic asthma is the highest proportion (~90%) in children.
				+ There is not a lot of research in diverse populations.
			* TOPMED has a large dataset on asthma.
				+ A comprehensive analysis has not been done, however there are GWAS data available, including a large proportion in Hispanic and African American populations.
		- Atopic dermatitis
			* This is a very common condition in pediatrics. This condition was originally dropped from consideration. Atopic dermatitis often occurs in the first year of life. Due to early onset, this condition may have less value than asthma.
	+ Hypercholesterolemia:
		- Dietary modification does not have a major impact, lowering only by ~5-10%. Intervention would include shifting the lipid screening to an earlier age. For monogenic FH, pharmacologic treatments are started after age 10.
		- Lipogenic cholesterolemia doesn’t usually appear until the early 20s, which would then be considered an adult-onset disease.
		- PRS can be used as a diagnostic test. However, when the prevalence is low, the number of false positives will outweigh the true positives.
	+ In summary:
		- NAFLD, hypercholesterolemia, and lupus will not be returned to participants under 18 years old.
		- **Action Item:** Asthma will be added as a condition in pediatrics.
		- **Decisions:** Atopic dermatitis will not be added to the conditions list.
		- **Decisions:** Only Type 1 and Type 2 diabetes, obesity, and asthma will be considered for pediatric return.
* **Condition age ranges: Actionability & Returnability| Gail Jarvik (UW), Iftikhar Kullo (Mayo), Cindy Prows (CCHMC)**
	+ One key element of the CARE workgroup’s mission is to develop a plan for return of results.
	+ The Network’s pragmatic trial intervention is the return of a CLIA compliant polygenic risk report, a CLIA compliant limited monogenic risk report, and a Genomic Informed Risk Assessment (GIRA) which will include family history information from MeTree.
	+ During the December 3rd PI meeting, the group discussed the results of the GIRA survey and the decisions were made for high risk designation.
		- High risk will be designed when the PRS for PRS for one of the conditions is in the top 1st or 5th percentile (instead of percentile, it may be relative risk but will vary with condition).
		- P/LP variant is present in a Tier-1 condition gene (additional genes clinically important in risk assessment TBD by PRS leads).
		- Actionable family history risk for one of a subset of conditions for which risk calculations are standard practice in clinical care.
	+ Further decision making is needed on which conditions family history risk will be used as a subset and if the risk needs to reach the same level as a returnable PRS.
		- It is still uncertain of how many more high-risk results there will be due to this change. The group will need to decide which high-risk designations will require in-person return.
	+ The GIRA report
		- For anyone not high risk, the group would prefer a label more descriptive or clearer of meaning of not high risk. The two labels proposed are “below study threshold” and “does not meet study criteria for high risk”. The report would include a statement defining that there was no high risk found and a template detailing the limitations of results.
		- The high risk GIRA will include a first page detailing the most important information: condition of high risk, evidence based recommendations to mitigate identified genomic high risk, and identify and treat early disease. The report would also include risk details (combination of clinical risk factors, monogenic, family history), evidence of interpretation, and limitations.
	+ There will be some return customization by groups: ancestry, age, and prior diagnosis.
		- For Ancestry, the group will first identify if we are able to validate PRS in the ancestry groups we will be enrolling and if not the PRS would be excluded from analysis and phenotypes would not be listed in the Methods.
			* There is additional consideration around if the Network should use participant’s self-reported race/ethnicity or genetic ancestry in deciding which PRS would be returnable.
				+ Clinicians would be relying on self-reported ancestry, genetic ancestry could be used in addition.
				+ In a local study done at Northwestern, there was a strong correlation between self-reported/EHR documented ancestry and genetic ancestry.
			* The PRS Validation workgroup is considering if only validated trans-ancestry PRS should be considered for return.
				+ There are a lot of mixed ancestry people, making trans-ancestry PRS the best solution.
				+ Trans-ancestry PRS is the personalized approach. Trans-ancestry approach doesn’t involve putting people into categories.
			* Customization layers to the report will add complexity and more opportunities for error.
		- Age customization will require disease risk not actionable in childhood or not actionable in adulthood to have no analysis of genotype and sequencing data. Customization based on prior diagnosis will not occur.
		- The group is proposing to return Mendelian negatives as they are useful for care and family members.
		- There will be limitations text to contextualize, “below study threshold for high risk.”
		- As a research program, data will be analyzed even if not returned or added in the clinical report.
	+ PRS analysis and return customization for pediatrics (<18 at enrollment).
		- They will not receive results if PRS is not validated for their ancestry or there isn’t a trans ancestry score.
		- Disease risk needs to be actionable during childhood before return.
		- There may be conditions with disease risk actionable during childhood but PRS not validated for childhood onset disease: CKD, Hypercholesterolemia (LDLR, APOB, PCSK9 sequencing relevant), Hypertension, and NAFLD.
		- Ethical issues reduce enthusiasm for pediatric clinical implementation (e.g. depression).
	+ Most impactful age ranges of actionability for conditions ranging from 0-80 years of the target population for prospective cohort.
		- Site suggested actionability by age from the GIRA concept sheets completed by the condition site leads.
		- The lower age range for adults keeps changing making customization by age a factor.
	+ Margaret Harr presented a mock GIRA report including a study summary page, disease risk results, PRS summary page, GIRA summary page, and final study information page.
		- The GIRA report will include a study summary page highlighting the diseases where participants are at high risk by PRS, monogenic, or family history. Clinical actions and pertinent positives are up front.
		- The disease specific risk results will be noted on one page for each disease where the patient was identified as high risk.
			* Red boxes will be used to highlight categories at high risk. Only boxes where that risk category was assessed will be displayed (e.g. monogenic results will be shown only for Tier 1 conditions).
		- The PRS summary page will list all diseases for which PRS was calculated. The result will be dichotomous noting “high risk” or “not high risk”.
			* The page will include details on high risk cut off for each disease. The page may be populated with structured data from Broad or Broad pdf inserted. It may be site dependent on if this page is included.
		- The GIRA summary page will list all diseases for which risk was evaluated.
			* Results will be separated by high risk or high risk not identified.
			* There will be template language explaining the meaning of “not high risk” for each disease.
		- A final page will include information about the study, methods, and limitations.
	+ In summary:
		- **Decisions:** The group reviewed an early draft GIRA report and will initiate a subgroup to finalize a GIRA template.
		- **Decisions**: Trans-ancestry PRS should be prioritized and validated when possible.
		- **Decisions:** One report will be returned and participants cannot opt in or out of a particular condition, it will only be customizable by age grouping.
		- **Decisions:** Educational materials will be provided to participants that already have a condition but the PRS/GIRA indicates that they “do not meet study criteria for high risk.”
		- **Action Item:** A GIRA report subgroup will be formed to develop and finalize the GIRA format.
* **Ethical Legal & Social Implication Considerations for the Prospective Cohort | Ingrid Holm (BCH), Richard Sharp (Mayo)**
	+ There are two aspects of ELSI in eMERGE.
		- ELSI research studies in the first two years.
		- ELSI in the prospective cohort.
	+ Year 1 ELSI Projects
		- There are several adult patient domains.
			* They can be grouped into three potential collaborative domains.
				+ Beliefs, Attitudes, Baseline Perceptions
				+ Baseline Knowledge
				+ Preferences, Readiness
		- All of the clinical sites are doing participant focus groups and/or participant interviews.
			* This allows for a lot of overlap in study design, which lends itself to possible collaborations.
		- Year 1 ELSI Projects Summary
			* VUMC has completed their ELSI project.
			* There is tremendous subject matter and methodological strengths across sites.
			* Each site has their own primary aims, yet are collaborating across sites.
				+ Interview guides and focus group guides are being shared in the [ELSI subgroup Google Drive.](https://drive.google.com/drive/u/1/folders/1iNLjy5sHnpBPpwp_jxQjKBEsYdIGzLp6)
	+ ELSI Topics in the Prospective Cohort
		- ELSI of protocol design decisions.
			* Year 1 projects are meant to inform the implementation of the PRS. However these projects might not be completed prior to the sIRB being submitted.
			* A percentile score in the PRS is not meaningful. Relative risk should be displayed on the report and should be presented separately for different populations.
			* The ELSI subgroup would like to provide input on the limitations of PRS language for both the PRS report and the GIRA.
		- ELSI topics in the prospective cohort
			* There are a number of areas that the ELSI group can be involved in the prospective cohort.
			* Embedded ELSI themes in eMERGE include:
				+ Enrolling ethnically, racially, and socio-economically diverse populations; participant preferences; consent; post-RoR surveys.
	+ ELSI issues are involved in all aspects of eMERGE and should be considered in all workgroups.
	+ Discussion:
		- If the network uses the transparently PRS, how would that affect reporting.
			* In regards to assessment of how the Tran ancestry PRS perform in different groups:
				+ Which groups should we be assessing?
				+ Other things besides ancestry matter and should be communicated on the report.

There will be different relative risk ranges across the ancestry groups.

Each PRS would only need to be calculated once per phenotype.

* + - * Regarding trans ancestry, calculate PRS and report it as meeting the threshold or not and then define what the threshold means.
				+ This suggests a uniform threshold with a different interpretation by ancestry.
				+ Communication on what is happening at the threshold will need careful thought on crafting this language.
			* A transethnic PRS might go against the intent of the eMERGE project.
				+ One thought is that the group is to oversample minority and underrepresented groups to strengthen the science in these groups.
				+ The GIRA and PRS workgroups have noticed that the transethnic PRS scores are performing better than ancestry-specific PRSs in some conditions.
				+ A large study with 1.5 million participants (not yet published) that created a statistical methodology that accounts for the contributions across other ancestries.

The odds ratios will be lower in those of African ancestry.

The report could state that the score takes into account the ancestry in the four ancestry groups and let the participant identify which group they identify with.

* + - * + The PRS group suggests that the PRS is validated in groups that have sufficient data.
				+ Careful thought needs to happen on how to report ancestry that might conflict with one’s self-identity.
			* There is a placeholder for the transethnic score on the GIRA mock up.
				+ What will be reported if the Confidence Interval overlaps with 1?

A decision will need to be made on what to report prior to the reports being returned.

This also reflects the state of the current data or lack thereof.

* + - * + A reason why trans-ancestry PRS performs better than ethnic-specific scores is due to leveraging the large European datasets.
				+ Genetic ancestry will be used in the models to develop trans-ancestry scores.

The reporting will not need to know the ancestry or self-reported identity of the participant.

The information for different population groups where the science supports valid information.

* + - **Action Item:** Likelihood of utilizing trans-ancestry PRS for the conditions of interest should be confirmed and reported out by the February 2021 steering committee meeting.
* **PRS Pass/Fail Criteria | Eimear Kenny (Mt. Sinai), Patrick Sleiman (CHOP)**
	+ Challenges and Considerations
		- The goal of the PRS workgroup is to evaluate the scientific validity of the PRS to bring forward to the clinical trial next year and to inform pass/fail criteria for particular scores.
		- Polygenic risk scores are a relatively new science and one of the biggest challenges is that the readiness of PRS for implementation varies considerably among conditions but the field is very rapidly evolving.
		- There is no agreed upon best practices for developing PRS and reporting performance.
		- The dearth of genomic information for non-European populations relative to European populations in the genomic databases is creating issues of generalizability and optimizing performance across populations.
		- When moving from research to clinical testing, there are new considerations for assessing technical validity, robustness, and ability to implement pipelines.
	+ Leveraging Evolving Data, Methods, & Standards
		- The PRS group has a lot of expertise in addition to access to myriad external datasets to help with validating and optimizing scores. This is particularly important for developing PRS that will work well in diverse populations.
		- The group includes method developers that have developed emerging methods for multi ethnic PRS (published and unpublished).
		- As a community, there are developing standards and when possible, the group will adhere to those emerging standards.
	+ Evaluation Process
		- The PRS workgroup first did a deep dive into literature to look at PRS validity under consideration.
		- A focus on time and resource dedication is important for timeline development and for the eMERGE Network to adhere to. The workgroup is now validating the proposed PRS.
	+ Overview of 16 Conditions
		- Prevalence for the 16 conditions range can vary considerably, ranging from 1% to 45% in population based estimates in adults. For conditions that are less prevalent the GWAS sample size is much smaller.
		- SNP based heritability is very important for PRS. For most of the conditions, SNPs range from 7-25%. For some conditions (those more rare), this is unknown which does not give a clear idea of reasonable predictions of heritability.
		- There is a mixture in terms of GWAS generation. A small proportion of samples are from non-European ancestry populations.
		- Not all conditions have validated polygenic risk scores. So far, there are validated published PRS fr 11/16 conditions. Without a validated PRS, it is difficult to know what the baseline performance will be but for some conditions there is optimism to get there.
		- For populations in which scores have been validated, 50% of validation only occurred in European ancestry populations.
		- For some conditions, newer emerging studies are expected to be released within a timeframe that will fit with this study (depression, LDL cholesterol, obesity). For others, like NAFLD, although studies are known, they may not be released in the short term.
		- The ability to improve upon risk prediction is very data dependent. Sites have been very proactive about setting up collaborations to put together multiethnic validation datasets.
	+ Impacts on PRS Performance
		- The main things that impact PRS performance are the heritability and in this specific case for PRS, it is SNP based heritability. Sample size is extremely important because even when heritability is high, out of sample prediction is expected to be low unless discovery samples sizes are very big.
			* As sample size increases, there is a tipping point that needs to be surpassed in order to maximize the heritable component of the trait which tends to be very big for human populations.
		- There are many steps and choices in generating PRS that include tuning and calibration which can all be improved upon.
		- In the last year, method development and more sophisticated methods, like Bayssian. Recently as well, methods have been performed on the same datasets to allow for comparability.
	+ Establishing Pass/Fail Criteria
		- The metrics cannot just be curated from the literature so the group decided to do their own standardization to understand baseline performance forPRS under consideration.
		- A pipeline has been built that will take UK Biobank data and take scores that are under consideration by PRS to standardize method application.
			* Implementing the polygenic risk scores in a CLIA lab needs to be highly considered. The pipeline can help implement technical filters for a more robust way of predicting performance.
	+ Impacts on PRS Performance in Diverse Populations
		- When there is a very large GWAS and meta analyzing and fine mapping takes place with data from diverse populations, a better performance occurs.
			* Fine mapping includes using SNPs and effect sizes usually using Bayesian approaches to put a prior probability on any one of those SNPs being the causal SNP. Although it is time consuming, it is known that polygenic risk scores work much better when using causal SNPs.
			* There are a number of trans ancestry scores performing between because of newer methods (ridgePRS, CaliPRS, PRS-CSx, PRS using LAI, and more) because they have been fine mapped across ancestry groups.
		- Developing a trans ancestry score for each condition, particularly those that have proven more difficult due to data constraints, may not be feasible with the current eMERGE timeline.
	+ Future Plans
		- The group has established a pipeline to generate baseline metrics using UK Biobank and eMERGE III data. This same pipeline will be used to evaluate multi ethnic PRS methods and approaches. This will support sites to make data-based or statistical improvements of their polygenic risk scores.
		- Future plans also include supporting sites to implement pipelines on Terra/AnVIL in collaboration with the genotyping workgroup in addition to integrating PRS into GIRA with the CARE workgroup.
		- The group could focus on implementation for the phenotypes that have the best data but then continue to do the science and research as the data becomes available. Within the 5 years of this study, more and more GWAS will be published in non-European populations.
			* Currently, Abdominal Aortic Aneurysm, Atrial Fibrillation, CRC, NAFLD, Prostate Cancer, and Stroke only have GWAS on European populations.
				+ Abdominal Aortic Aneurysm and Atrial Fibrillation have larger GWAS in the works while NAFLD does not at the moment.
			* With the current timeline, it may be best to choose 6 or 8 very robust conditions to move ahead with implementation. Additionally, implementing what can be now with a later date for implementation of the additional conditions may be best so they do not dribble out over time.
			* The group should consider/explore 2 releases and rounds of return (1 now and 1 in a few months).
				+ Although this option would include two rounds of outcomes measuring, it would allow for longitudinal engagement of the cohort which would encourage retention.
				+ During informed consent, the list of conditions would need to be included.
			* **Action Item:** Determine the feasibility of returning the GIRA report twice to participants to accommodate PRS validation later in the project.

**eMERGE Day 2: Friday, December 11th, 2020**

* **Introductions/Overview**
	+ **Opening remarks | Robb Rowley (NIH/NHGRI) & Teri Manolio (NIH/NHGRI)**
		- The eMERGE External Scientific Panel Members include:
			* Katrina Goddard, PhD (Kaiser Permanente Center for Health Research) (External Scientific Panel Chair); Kim Doheny, PhD (Johns Hopkins University); Stanely Huff, MD (Intermountain Health); Janina Jeff, PhD (Illumina); Lisa Parker, PhD (University of Pittsburgh); Vandana Shashi, MBBS, MD (Duke University); Clesson Turner, MD (Uniformed Services University of the Health Sciences).
		- The Network has published a paper titled “*Strategic VIsion for Improving Human Health at The Forefront of Genomics”.* This publication highlights the commemoration of the 38th anniversary of the Human Genome Project.
			* + The four major areas of the new strategic vision covered in this publication are:

Guiding Principles and Values; Robust Foundation for Genomics; Breaking Down Barriers; Compelling Genomics Research Projects.

* + - The NIH partners with the ACMG to sponsor the NIH-ACMG Fellowship in Genomics Medicine Program Management.
			* This fellowship involves the collaboration of these entities: The NHGRI, The National Heart, Lung, and Blood Institute, The National Institute of Minority Health and Health Disparities, and the *All of Us* Research program.
			* The goal of this fellowship is to increase the pool of physicians, genetics counselors, nurse practitioners, and physicians’ assistants trained in the management of research and implementation programs in genomic medicine.
			* Two qualified clinicians are selected annually to acquire credentials and experience in leading genomic medicine at NIH and other organizations.
				+ Applications for the two-year fellowship program are due annually on December 1st. Anyone interested in applying should contact Sylvia Garvey (acmgfellowship@nih.gov).
		- This past June and July, there were new R01 and R21 funding opportunities in genomic medicine and genomic counseling made available.
			* The Advancing Genomic Medicine Research and Genetic Counseling Research are soliciting applications that stimulate innovation and advance understanding of when, where, and how to implement genomic information and technologies in clinical care.
				+ New applications will be accepted beginning March 2021. Applications are also being accepted regarding assessing strategies to optimize the counseling process in the context of limited resources. The next application due date is in July 2021. It is strongly encouraged to include ancestral diverse and underrepresented participants and populations in these applications.
	+ **eMERGE Network Overview: Priorities, goals, & progress | Rex Chisolm (SC Chair, Northwestern)**
		- The eMERGE Network has published 691 papers since its inception.
		- There are 880 network and site projects that are currently active, and 181 publications are in development. There have been 1517 external downloads of eMERGE dbGaP data.
		- An important part of eMERGE is allowing the research community to reuse data that the network collected. Phase I and Pre-phase II datasets have been used extensively.
		- Three additional datasets are now available in dbGap for public controlled access:
			* eMERGEseq (Phase III: n=24,956)
			* GWAS and structural variation (Phase I-III; N = 105,108)
			* This data will be used in eMERGE for PRSs and broadly by the research community.
		- eMERGE network aims include:
			* Calculating validated polygenic risk scores (PRS) for several complex diseases. 16 conditions are currently under consideration and undergoing validation.
		- Communicating genomic risk profiles and relevant clinical recommendations based on PRS, family history, and other clinical data
		- Recruiting and genotyping 25,000 individuals of diverse ancestry, and prospectively calculating their genomic risk for selected conditions & return risk estimates and management. A new standard of care will not be created, but it will be identified when someone would be moved to a “high-risk” recommendation area.
		- To assess uptake of risk-reduction recommendations and impact on related clinical outcomes.
		- The prospective recruitment study goal is: How does a GIRA impact the clinical actions taken by providers to manage risk, and the propensity of patient-participants to develop a disease?
			* The goal is to measure how adding the GIRA to usual care changes clinical actions and outcomes.
			* It was determined that the best way to return GIRA results is through a dichotomized return.
				+ Participants are determined to be high-risk by a threshold selected by the network would be ordered to implement an intervention.
			* Process outcomes & intermediate and health outcomes that can be measured within a specific time frame (1-2 years) after return will be considered.
			* The phenotypes selected for the GIRA return will have specific recommendations pertaining to the care of that patient-participant.
		- The retrospective validation goals are to validate the PRS for implementation in diverse cohorts.
		- The Network would like to establish and validate genome informed risk assessments that incorporate PRS and other elements into a returned result that said “This participant is at high-risk”, or “below study threshold for high-risk.” Summary sheets have been collected for all the conditions that are currently under consideration.
		- The eMERGE network gets most of its work done through workgroup processes.
			* There are currently 7 workgroups in the Network:
				+ PRS Validation & Evaluation; Genotyping; Risk Assessment & Return; Recruitment, Retention, IRB, & ELSI; EHR Workflow & Infrastructure; Phenotyping; Provider Uptake & Outcomes.
		- Goals of eMERGE Network:
			* To establish metrics for evaluation of PRS model validations.
			* To establish the what, how, and where data elements are integrated into the GIRA.
			* To establish what constitutes “high-risk”.
			* To establish pathways for data integration and return.
		- The GIRA will be a document that integrates the monogenic risk (when applicable), PRS, and Family Health History (when applicable).
			* One of the things that have been identified is that this needs to be done on a condition-by-condition basis because each condition has its own elements.
			* For conditions where Family History is used, a summary of the MeTree results will be included.
				+ The full MeTree reports will be available to download by participants.
			* Only the threshold cut off for a given “high risk” condition should be displayed in the methods section on the GIRA. For Tier 1 conditions, specific risk, such as 5-year or lifetime, will still be considered for return by the Co-leads. Quantitative risk assessment scores in the GIRA should only be returned to ‘high risk’ participants. The GIRA will use a “matrix-like” concept for the report. The columns on the GIRA report are not independent; The risks in one column possibly could affect the risk in another column.
		- For the PRS report for this prospective cohort, the lab reports will report risk as dichotomous (“high risk” and “under the study cut off for high risk”) for each of the conditions.
			* The threshold cutoffs are yet to be determined. The sites that are leading and co-leading each of the 16 conditions will decide what the threshold will be to determine what is “high risk”.
			* If the PRS z-score/percentiles value is needed for clinical purposes, the actual values/ scores can be included on the CLIA PRS report.
		- The Network would like feedback on the following items:
			* The overall study design, approach, and the IRB framework. In order to start recruiting participants in the summer, the IRB will need to be submitted early in 2021.
			* The PRS validation of conditions without an existing published PRS for underrepresented groups.
			* How to maximize recruitment for downstream study analysis.
			* The risk calculation & integration proposal. The GIRA has CLIA & non-CLIA components. The network would like feedback on how to integrate those reports into the EHR. Family History is a non-CLIA component.
			* The network wants to know the ESP’s proposed study outcomes, controls, and downstream analysis.
* **Retrospective validation**
	+ **PRS WG | Eimear Kenny (Mt. Sinai), Patrick Sleiman (CHOP)**
		- Workgroup Timeline & Goals
			* The goals of the group are primarily focused on year one and to retrospectively generate and validate polygenic risk scores, particularly in diverse populations working most closely with the phenotyping, genotyping, and CARE workgroups.
			* In addition to evaluating the scientific validity and performance of PRS, the group will be supporting the genotyping group and the generation of the GIRA report.
			* The group’s biggest challenges are managing the rapidly evolving field that is PRS validation and evaluation and generating PRS for diverse populations.
			* In terms of timeline, the workgroup has done a deep dive into current literature and emerging studies. Currently, the group is developing validation strategies for tran ancestry approaches.
				+ The plan is to focus on a “bake-off” for determining the best strategies to generate trans-ancestry PRS and standardizing metrics. This will be in parallel to efforts at each site for optimizing and validating PRS.

**Action Item:** The results of the trans-ancestry method “bake-off” will be presented to the Steering Committee.

* + - * A subgroup has been developed for members with development expertise to discuss different ways to generate scores for multi ethnic populations.
			* In the spring, the group will establish how to move pipelines on to the AnVIL platform.
		- The group may need to address sites recruiting in New York where the CLIA guidelines (The Broad is awaiting certification) are slightly different.
	+ **Genotyping WG (GDA deliverables) | Meg Roy-Puckelwartz (NU), Niall Lennon (Broad)**
		- The Genotyping workgroup’s role in eMERGE includes:
			* Offering the technology for data generation, the validation of infrastructure for clinical testing, the validation of PRSs as they are chosen.
			* The Genotyping group also works closely with the PRS validation group.
			* The Genotyping workgroup will handle the logistics around sample and data transfer. Instructions have been sent to sites on what the group will need when they begin recruiting participants and collecting DNA from samples. The Broad will receive the clinical specimens and process them.
				+ The CC is also building a portal to store clinical information. An API interface will be built with the R4 portal and tubes will be sent to clinical sites.
				+ The sites will link the specimens in a manifest that goes to the R4 portal. The portal will be queried to accession the sample and run processed at the Broad. The PRS will be generated, and there will be another 2-way API PHI elements that need to be on the report.

The raw genotyping data will be submitted to AnVIL as research data, the clinical report will be pushed to the R4 portal for sites.

* + - * + The primary analysis will be to deliver VCFs.
				+ The secondary analysis will involve imputing the raw data. There has been discussion across workgroups on how the data be imputed (1000 Genomes or TOPMed), and how this would affect the PRS score.
				+ The tertiary analysis is to create the PRS, then generate reports and deliver them to sites.

Regarding the PRS CLIA lab report, there are discussions being had about how the report will be delivered in various settings and what components would be included.

The Consensus has been to report a categorical result of high/not high polygenic risk. Broad can use ‘Under threshold cut off for return’ instead of ‘study cut off’ since it is a CLIA report.

A new report will not be issued every time a new condition gets validated, rather it will be released in two batches.

* + - The technology chip that is being used is the Illumina Infinium Global Diversity Array (GDA).
			* This chip was chosen because it includes a lot of clinically relevant categories such as ACMG59, PGx, Clinvar, MHC, and HLA. This application works well because it has diverse population content.
			* Indels do not perform as well as SNPs, so InDels will only be used in specific instances. The same array is also being used in the All of Us research program.
		- The GDA has a number of markers across a broad range of disease categories (e.g. cancer, digestive system disorder, immune system disorder, metabolic disorder, etc.).
		- The PRS group validates the scores to be used for given conditions.
			* The genotyping group will work on a technical transfer to validate the pipeline into their group as part of the genotyping process.
			* There will then be a CLIA validation. Performance and limitations will need to be documented for a CLIA test as the formal validation for a CLIA report.
			* This will be a layered infrastructure; currently, there is the existing infrastructure to generate the genotyping data itself because the array chosen was the GDA. Work has been done to create a CLIA validated genotyping workflow for the array, so it is possible to create a CLIA report from it. This will be layered on top of the additional elements and will be validated as the group goes to support PRS validation.
		- The PRS workgroup validates the PRS scores which allows the Genotype workgroup to validate it clinically.
		- The TopMed Imputation server may not be desirable from a CLIA perspective due to not having control over the remote server, software versioning, or downtime.
		- The performance of the imputation can depend heavily on the reference panel that is used. The main reference panel that is currently used is the 1000 Genomes panel.
		- There has been discussion with the AnVIL and NHGRI regarding ways to build better reference panels within AnVIL using other NHGRI data. The raw data from the arrays will be in AnVIL for discovery.
		- A lot of the improvement that comes with using larger references panels comes from the rare allele bins. The differences are much smaller in the more common alleles that are likely to be used in PRS models across different groups.
		- There was a discussion about handling the performance of different PRSs in different ancestries.
			* There are multiple places where that can be considered:
		- The selection of the PRS and how it was first determined, and what cohorts were used to build it. The aim will be to find trans ancestry PRSs to start with so there is not a big influence on the validity or performance of the score based on ancestry.
		- The accuracy of the imputation can be different based on ancestry; that is a function of the reference panel used.
		- A model could be fit to say based on the genotyping data, you can essentially project individuals into the principal component space for ancestry and create a model to correct for that, then create an adjusted score to be more accurate across different ancestries.
		- The genotyping group worked on the coronary artery disease score and looked at validating the accuracy of the imputed risk percentile using deep genomic data as truth, and then they looked at the error that exists. Most errors in the imputed risk percentile occur in the center of the distribution.
		- To help the work of the PRS group, the Genotyping group has been providing example VCFs of genotyped and imputed variants to the PRS group so that they can determine what an imputed VCF from this pipeline will look like. The group will be able to do screening for a given model and say if it has been genotyped or imputed and determine what its likely performance will be.
		- Discussion:
			* Bi-weekly Co-Chair meetings were created to address cross-workgroup issues.
			* For this clinical pipeline, no individual variant data is being reported from these genotyping arrays. Only the PRS workflow will be run.
			* The phasing “high risk” or “not high risk” in the report may not be clear to participants.
			* This report is intended for the provider. It is not to be a consumer facing report.
			* There was discussion regarding the reporting standards from ClinGen and the group will adhere to those standards as much as possible with regards to the PRS validation.
			* This workgroup is deciphering which SNPs are imputed and which ones are on the chip for a PRS.
			* New laws state that the patient-participants will be able to access all of their medical reports when they become available.
				+ The sequence of return of reports will be important particularly for those whom a high risk has been identified. Careful thought on which order the reports are available should be made - PRS to the EHR first vs. GIRA to the participant first so study staff have the opportunity to provide counsel on the results.
	+ **Phenotyping WG| Chunhua Weng (Columbia), Wei-Qi Wei (VUMC)**
		- In previous eMERGE cycles, the phenotyping workgroup was responsible for developing, validating, and implementing phenotyping algorithms for genetic research.
		- In eMERGE IV, the phenotyping workgroup will work very closely with multiple workgroups to achieve the network’s overarching goal to promote the GIRA in clinical practice.
		- The group’s core function is to carry out phenotyping to facilitate the development of GIRA for clinical use. The group will also identify and bridge the gap between the existing phenotyping algorithms and need for GIRA practice. This will include identifying phenotypes and evaluating how phenotyping can be used to facilitate and reduce the manpower to capture clinical outcomes.
		- Within year one, the phenotyping workgroup plans to achieve three goals:
			* Identifying the gaps between existing algorithms and PRS validation requirements.
			* Modifying, validating, and sharing 16 PRS phenotype algorithms.
				+ Algorithms that do not currently exist will be developed and shared on PheKB.
			* Implementing the algorithms and delivering phenotype statuses to PRS leads.
		- So far, the group has identified the phenotyping lead for each phenotype, conducted a survey to identify the gaps between existing algorithms and PRS validation requirements, and proposed tentative timelines for each condition.
		- Many of the selected conditions have pre-existing algorithms. Those that do not include Type I diabetes and Prostate Cancer.
		- Conditions like Atrial Fibrillation and Colorectal Cancer will use external datasets for implementation. All algorithms will be shared via PheKB.
		- Most sites that are in charge of multiple conditions stated that they will be able to work on those at the same time. Exceptions include Type I Diabetes and Prostate Cancer since there are no existing algorithms.
		- Common data to be used for PRS validation for all 16 algorithms includes age, gender, race.
			* BMI will be used for seven algorithms and height/weight for three algorithms.
			* Smoking status will be used by three algorithms although this data quality may not be consistent since sites collect this differently and a lot of the data is incomplete. This may need to combine EHR data and survey results.
			* Labs used for four algorithms include lipids and blood pressure.
			* Medications for four algorithms include statins and antihypertensive drugs.
			* Additionally, encounters will be used for two algorithms.
		- Challenges
			* The group is currently deciding the best way to collect and harmonize information and whether that should be done through the workgroups or by each phenotype lead.
			* The group is also deciding how to make the data collection process more efficient and the best way to expand common data variables.
			* **Action Item:** The Phenotyping workgroup will determine what additional variables will be required for the next “common variable data” refresh and initiate that refresh in January 2021.
		- Currently, the plan is to collect family history on all study participants through the MeTree tool.
* **Prospective study design**
	+ **CARE WG– GIRA report & integration | Gail Jarvik (UW), Iftikhar Kullo (Mayo), Cindy Prows (CCHMC)**
		- The goal of the CARE Workgroup is to operationalize the integration of genomic information into clinical risk assessment so that it is easily understood and acted on by healthcare providers and patients.
		- Genome Informed Risk Assessment (GIRA) concept is to improve the accuracy of current risk tools using genomic risk information.
			* The elements are monogenic risk for Tier 1 conditions, polygenic risk score (PRS), and family health history from MeTree. Family history will only be on high risk GIRA and those conditions have yet to be finalized.
		- All of the GIRA information has to be contextualized in the clinical risk for the condition to ensure clinicians understand risk information and act on it.
		- The CARE Workgroup will be working with other groups to operationalize the PRS estimate and return GIRAs.
			* The major decision process includes taking the CLIA PRS report from the Broad placed in EHR.
				+ GIRA is an addendum to the PRS. GIRA is an interpretation of elements appended to the CLIA report and added to EHR. The group is working with the EHR workgroup to link GIRA to decision support.
		- The proposed study population for adults is 18-75 and pediatric 0-18.
		- The assembly of the GIRA will take place in the R4 Portal where the PRS report, family history, and clinical risk variables will be assembled in a way that clinicians understand.
		- Phenotype leads will be responsible for developing algorithms/pseudocode to assemble reports from elements.
		- There will be return customization by ancestry, age, and prior diagnosis.
			* Ancestry is being worked on by the PRS workgroup. There may be certain ancestry groups the Network is not confident to return due to lack of validation.
				+ Individuals with multi ancestry is another challenge and the group hopes to develop a trans ancestry method to return PRS to these participants.
			* Age will have certain conditions not actionable in childhood and will not be returned.
				+ In adults there may be certain conditions not applicable in certain age ranges and not returned.
			* Those with prior diagnosis may not receive a high PRS result and Medelian negatives may be useful for family members especially for Tier 1 disorders.
		- Due to logistical and budgeting constraints, return will be given in-person for high risk of 16 conditions or have pathogenic variants for Tier 1 conditions.
			* This estimate is based on using the top 2 percentile as a threshold, so if 15 conditions are in the top 2 percentile then 25% of the cohort may qualify. 25% may not be feasible for in-person return, the group will n4eed to decide who will qualify for high risk.
			* It is predicted that approximately 0.8-1% of the general population will have pathogenic variants for Tier 1 conditions.
			* Individuals that do not fit any high risk criteria in the GIRA will receive a report by mail and EHR.
				+ Education materials will be included in the letter and FAQs on the website for participants will receive additional information.
				+ Letter will include language that makes it easier to understand risk estimates and the need to consider patients’ socioeconomic status and education.
				+ Healthcare providers will be notified by EHR and/or letter that the result is available for view.
				+ Participants may be able to schedule an appointment with a PCP or specialist for follow up.
		- Participants will be able to withdraw at any time but there will be a certain point where return of results cannot be stopped.
			* Digna Velez-Edwards clarified that everyone has to agree in consent to have results returned. They can always withdraw from the site.
			* It may be worth adding in the consent that the report cannot be removed from the EHR once added.
		- Since GIRA is an addendum, there may be more flexibility to add “does not meet the threshold for high risk” compared to what is noted in the CLIA report.
	+ **EHRI WG– data integration/flow | Luke Rasmussen (NU), Bob Freimuth (Mayo)**
		- This workgroup is primarily looking to operationalize the data flow through the clinical sites.
			* Not all data will necessarily get to the EHR. This group is working to answer how the monogenic, PRS, family history, GIRA flow in and clinical data flow out.
		- Semantics should be harmonized in order to optimize workflow in the clinical sites.
		- This group is currently investigating site capabilities and logistical aspects at each site.
		- Data standards are key for this project to work as smoothly as possible.
		- Identifying the different human roles in the study will help optimize workflow, access, and use.
			* From a patient standpoint, the patient may be able to see their chart/info when it is uploaded and before the clinician can contact him/her.
		- The PRS would be returned to the EHR and is the GIRA an addendum to the PRS report. It is unclear if return would happen one time or two to each participant.
		- Implementation of effective clinical decision support (CDS) is desirable. CDS is not just a pop up alert and all CDS pathways need to be considered, including Info buttons.
		- Decision support may not be limited to the clinical context. The research workflow or return of results provide an opportunity to support decisions and information needs.
		- A lot of what this workgroup has done to date is trying to identify and mitigate risk.
		- Integration is probably the most important component of this workgroup and includes definition of data at rest, data in motion, and maintaining robust standards so data can be meaningful.
		- Integration across the network involves several aspects.
			* Technical Integration includes the data exchange across AnVIL, R4 Portal, sequencing centers, and the standards that support that exchange.
			* Clinical integration with workflows, software limitations, use of data for research, and clinical decision support.
		- Discussion:
			* Most systems (lab systems, EHR) are not set up to send discrete genetic data or these risk reports.
				+ The standards are not yet mature but progress is ongoing.
				+ There are a variety of ways that sites have developed to capture the risk reports including general lab observations, and capturing some of the information that is natively supported in EHRs like a PRS appearing as a flow sheet.
			* The Network discussed when CDS and other elements might be available.
				+ Within the current year, this group is looking at site-specific capabilities but this also depends on final decisions being made on study design.
				+ There will be at least one CLIA report per participant. This group can determine how these CLIA reports will get integrated into the clinical site systems.
* Fragmented EHR systems within a health system may be problematic in sharing the results within the health system as a whole. Trying to find balance between making data accessible and usable are large issues this group grappling with.
	+ **Provider Uptake and** **Outcomes WG| Noura Abul-Husn (Mt. Sinai), Nita Limdi (UAB)**
		- The mission of the Provider Uptake and Outcomes workgroup is to establish a network-wide plan for the analysis and interpretation of outcomes from implementing genome informed risk assessments.
		- The Year 1 timeline and goals include collaborating with other workgroups in overall study design to define research questions and develop an analysis plan, developing harmonized participant baseline and outcomes surveys, and establishing a framework to evaluate outcomes.
		- The workgroup has primary and secondary research questions.
			* The primary research questions are (1) are patient-participants with high PRS/GIRA more likely to follow recommendations for risk-reducing clinical interventions compared to the control group and (2) are providers more likely to recommend risk-reducing interventions for patient-participants with high PRS/GIRA compared to the control group.
			* The secondary research questions are (1) are clinical outcomes improved in patient-participants with high PRS/GIRA compared to the control group and (2) are behavioral/lifestyle factors improved in patient-participants with high PRS/GIRA compared to the control group.
			* Additional research question is what provider and patient-participant characteristics are associated with providing or following recommendations based on PRS/GIRA?
		- The group has identified 11 survey domains and are identifying which belong in the baseline survey, pre-ROR survey, or post-ROR survey.
			* The survey domains are demographics, socioeconomic, lifestyle and environment, psychosocial, health related, knowledge and understanding, genetics (pre-ROR, patients), genetics (pre-ROR, provider), genetics (post-ROR), pediatric measures, and phenotype specific measures.
			* The Baseline survey will include demographics, socioeconomic, psychosocial, health related, knowledge and understanding domains.
		- The draft conceptual model for outcomes was presented.
			* The model flows through patient characteristics, patient belief system, provider characteristics, disease characteristics, PRS/GIRA education return of results, medial recommendations, patient perceived utility and feelings about genomic testing, intent to change health behavior, uptake of risk reducing interventions, family communication, lifestyle modifications, and ends with clinical outcomes and health-related quality of life.
			* The control group would be considered standardized. The intervention would be PRS/GIRA cut-point which may be disease-specific. Regression discontinuity design analysis will enable isolation of the effect of PRS/GIRA.
		- The group envisions the study being done on patients seen in primary care as a prospective cohort study.
			* The Network aims to recruit 25,000 participants. A baseline survey will be completed at recruitment.
			* Once the PRS is generated, it is estimated that about 7,500 will be at high risk due to all elements (polygenic, monogenic, family history) and disease specific. The GIRA and intervention will be presented to these participants.
				+ The EHR workgroup is working on integrating the result in EHR.
			* A pre-ROR survey will be completed before report integration.
				+ Diet, alcohol, and sleeping are at pre-ROR instead of baseline to account for possible changes in lifestyle to capture close to ROR. The post-ROR survey will include these domains to see if any changes were made.
				+ **Action Item:** This workgroup will determine the timing of all planned surveys prior to the sIRB protocol being submitted in January 2021.
			* Provider has to accept intervention and give to participants who then have to accept and complete intervention.
				+ A post-ROR survey will be completed to capture lifestyle and behavior changes.
				+ The group will assess those with high risk who accept intervention and who do not.
		- The group has decided on a regression discontinuity design analysis plan for disease agnostic.
	+ **sIRB protocol | Digna Velez-Edwards (VUMC)**
	+ This subgroup was created to generate a common recruitment pipeline across the network and to prepare the draft sIRB protocol.
	+ Approach to harmonize protocols: Sites were surveyed on multiple topics related to population, study design, recruitment strategy, retention, biospecimen collection approach, and return of results approach.
	+ Inclusion and Exclusion Criteria have been developed.
		- Inclusion criteria for participation includes the ability to consent in English or Spanish, be able to provide a healthcare provider, intent to stay in the area, and be willing to accept at least one GIRA score.
		- Exclusion criteria include the inability to consent, transplant (solid organ or bone marrow) or transfusion within two weeks of consent, research staff and investigators in eMERGE, being unable to provide a healthcare provider to receive results, and not a patient at a parent institution.
	+ The target population is representative of a general clinical population.
	+ The pediatric age range survey shows that most sites are comfortable recruiting 12-17 year old’s.
	+ The underserved definition used for eMERGE is the NIH definition for harmonization across sites.
	+ A recruitment pipeline/timeline has been harmonized for the network.
		- A preliminary timeline for surveys has also been proposed.
	+ There are some unharmonized components to recruitment.
		- There will be a central set of recruitment and consent documents.
		- Sites have some fluidity on recruitment mechanisms as long as the target population is met.
	+ Compensation schedule:
	+ Amounts for fair compensation may be more or less depending on geography and site budget.
	+ The sIRB allows for differing amounts as long as the protocol is written in such a way to allow it.
		- How results are returned to participants:
			* Most sites indicated the use of email/mail and the EHR portal on how results will be returned.
			* There needs to be a high risk/low risk mechanism in returns. High risk should be done by personal contact, preferably prior to the participant receiving the results. Low risk would not require the personal contact component.
		- Who returns results: most sites indicated a genetic counselor and/or a physician to return the results.
		- Biospecimen pipeline: An unharmonized approach is acceptable but the sites have to process the sample for DNA. The Broad will not extract DNA.
	+ The sIRB subgroup is still awaiting decisions that need broader feedback before the sIRB can be submitted in late January 2020 as proposed. These decisions include finalizing decisions on the target pediatric populations and consent considerations including newborns and pregnant moms, how to return of results to ‘high’ and ‘non high’ risk GIRA participants, return of results process for adolescent age groups, participant compensation, and harmonizing recruitment approaches (apps and paid advertising).
	+ This group has a [draft](https://docs.google.com/document/d/1UhzbUAhxwzMXn82MWugvQ5CW0lS_thPoX5sNRzMEeLw/edit) of the sIRB document completed.
		- The sIRB document does not need a lot of detail in the different sections but decisions on the topics above are still needed.
	+ Discussion:
		- **Action Item:** The PI group will make a final decision on the pediatric target population age range by mid-January 2021.
			* All sites do not have to recruit all ages, however a limited number of sites recruiting specific age ranges might not be scientifically sound. There are several sites that believe recruiting pediatrics is not scientifically justified. Further discussion about this topic will continue on the next PI call.
			* The Network had a discussion on sample sizes and estimates needed taking into account the prevalence of Type 1 diabetes, Type 2 diabetes, obesity and asthma, particularly in the 0-11 age ranges.
			* Pediatric diseases may have a different genetic profile than the adult form so a validated PRS in a childhood onset disease is available before applying it to children.
			* The selected conditions can be considered to be on a continuum so the same genes would be present in children and adults.
* **Input/Feedback from the ESP, general discussion**
	+ The ESP feels that the network is on a great track and that a tremendous amount of progress has been made within the first six months of eMERGE.
	+ The ESP encourages the Network to be willing to make decisions sooner rather than later, primarily related to the Network's major decisions as there is an aggressive time.
	+ **ACTION ITEM:** The Network should aim to reach conclusions for major sIRB decisions in the next month to ensure submission by February 2021.
	+ Specific Questions for the ESP
		- The Network would like feedback on our approach and proposals to:
			* The overall study design, approach, and IRB framework
			* PRS validation of conditions without an existing published PRS for underrepresented groups.
				+ When thinking about the implementation of the PRS, the ESP recommends having a strong evidence base.
			* Maximizing recruitment for Downstream study analysis.
				+ The ESP recommends making decisions sooner rather than later to ensure that the Network has time to achieve all their goals.
			* Risk calculation and integration proposal
				+ There is still much work to be done on determining what the exact methods that are going to be used to validate conditions.
			* Integration of unsigned / non-CLIA reports into EHR and CDS implications.
				+ The ESP likes the idea of returning the report to the participant first before going to the provider.
				+ It needs to be considered how the immediate release of results to patients through the EHR would impact the study.
				+ The ESP recommends studying what happens when patient-participants view their results before their provider has a chance to communicate it to them.
			* Proposed study outcomes, controls, and downstream analysis
				+ One concern regarding study outcomes is how to define recommendations clearly.
	+ **ACTION ITEM:** The Network will determine for which conditions in which Family History is considered relevant.
	+ Due to the overlap with the *All of Us* research, the ESP would like to know what plans have been made to see common research questions between the two. The Network will provide the ESP with information regarding the link between the common research questions in the *All of Us* program an eMERGE.
	+ The Network needs to consider the timeline in evaluating changes due to interventions as behavioral changes are difficult to achieve.
	+ Based on the work group's primary focus, the group recommends pathways to the network for consideration. Once the workgroup makes a recommendation, it goes to the co-chairs and Steering Committee for final approval. The Co-Chair call was put in place to help with decisions that need input from other workgroups.
	+ The Network has determined that using trans-ancestry PRS will perform better for the underrepresented population as well as some additional populations.
	+ In the ELSI workgroup, there is a discussion about using focus groups, primarily consisting of LatinX and African-American communities, about making the reports easily readable and communicable to participants.
	+ The consent is drafted, and it incorporates the components that change fluidly with changing discussions.
		- The plan is to finalize in early January so it can be reviewed.
		- The Education group will need to think about ways to engage with participants to make sure that they understand all components of the consent.

**Action Items**

* **Network**
	+ Asthma will be added as a condition in pediatrics.
	+ The Network should aim to reach conclusions for major sIRB decisions in the next month to ensure submission by February 2021.
	+ The PI group will make a final decision on the pediatric target population age range by mid-January 2021.
	+ Determine the feasibility of returning the GIRA report twice to participants to accommodate PRS validation later in the project.
* **CARE workgroup**
	+ A GIRA report subgroup will be formed to develop and finalize the GIRA format.
	+ The Network will determine for which conditions in which Family History is considered relevant.
* **PRS workgroup**
	+ Likelihood of utilizing trans-ancestry PRS for the conditions of interest should be confirmed and reported out by the February 2021 steering committee meeting.
	+ The results of the trans-ancestry method “bake-off” will be presented to the Steering Committee.
* **Phenotyping Workgroup**
	+ The Phenotyping workgroup will determine what additional variables will be required for the next “common variable data” refresh and initiate that refresh in January 2021.
* **Provider Uptake and Outcomes Workgroup**
	+ This workgroup will determine the timing of all planned surveys prior to the sIRB protocol being submitted in January 2021.

**Decisions**

* **Pediatric Condition Recommendations**
	+ Atopic dermatitis will not be added to the conditions list.
	+ Only Type 1 and Type 2 diabetes and obesity will be considered for pediatric return.
* **Condition Age Ranges: Actionability & Returnability**
	+ The group reviewed an early draft GIRA report and will initiate a subgroup to finalize a GIRA template.
	+ Trans-ancestry PRS should be prioritized and validated when possible.
	+ One report will be returned and participants cannot opt in or out of a particular condition, it will only be customizable by age grouping.
	+ Educational materials will be provided to participants that already have a condition but the PRS/GIRA indicates that they “do not meet study criteria for high risk.”