Summary of SC Call: June 2021

June 11th, 2021

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- Announcements & Opening Remarks | **Rex Chisholm (SC Chair, NU)**
    - The goals of the meeting are to discuss and consider the eMERGE conditions and select which will move forward. The number one priority of the project is to be scientific and selecting conditions should consider that.
    - Conditions that do not make it into the prospective cohort can still be worked on and will be considered a developmental cohort.
    - Sites will vote for each condition and whether or not it will move forward. A few caveats include adding validation in Asian ancestry populations and adding analysis of age related onset of disease to support actionability guidelines.
    - A transancestry or ancestry adjusted PRS model should be validated and returnable across ancestry groups. The PRS should also add significant value to discrimination even when used in a larger model.
    - The rationale for the proposed high risk cut off should be scientifically valid and justified.
    - Validation sets should be appropriately sized and relevant.
        - Published polygenic risk scores are preferred to implement in the clinical pipeline (the Broad). Unpublished scores will need to provide additional information and documentation.
    - Additional work on PRS beyond today's decision can be conducted prior to transfer to the Broad.
        - For those conditions selected to move forward, the PRS should move to the Broad as soon as possible.

PRS Session 1:

- Asthma | **CCMHC & CHOP**

- Asthma is the most common chronic condition in children and is highly heterogeneous and highly polygenetic.
- Case definition was determined by using an NLP algorithm for asthma at CHOP and also using a second independent dataset determined by ≥2 ICD codes.
- There are almost 1 million SNPs after weighting of 2.1 million markers.
- Asthma prevalence in different ethnic groups are:
    - European 10%; African 14%; Hispanic 15%; Asian 10%
- UKBiobank, CAAPA, and Japanese discovery sets were considered for PRS but not used.
- Post-hoc adjustment at the Broad will not be necessary.
- Cases/Controls in validation cohort by ancestry
    - NLP algorithm is considered the gold standard for validating cohorts by ancestry when compared to the data set compiled using ICD 9 codes.
- The AUC for the full model shows good results ranging from 0.59 (African), 0.61 (European), 0.65 (Asian), and 0.70 (Hispanic) in the pediatric ethnic groups.
- High risk cut off table shows good performance in pediatric asthma in the various ethnic groups.
- In summary, Trans-national Asthma Genetic Consortium (TAGC) is recommended as a discovery set and the model uses a standard sites and weights only format.
- Return of the asthma PRS has minimal risk of harm with good outcomes expected since the return will be in the context of family history and environmental/clinical factors in the GIRA.
- Actionability would include anticipatory guidance.
- The PRS was developed and validated in-house.
- There was no overlap in samples comparing the two eMERGE populations (NLP vs. ICD9 codes).
- Interventions include environmental recommendations such as HEPA filters, pillow covers, avoiding outdoors during poor air quality days, recognizing symptoms, and when to see a provider.
- Other interventions can include chronic or control medications and determination to refer to a specialist or not.

- **Breast Cancer | Columbia & VUMC**
    - Breast Cancer prevalence across different ancestry groups:
        - European: 12.6%; African; 12.1%; LatinX: 9.5%; Asian: 9.8;
    - The PRS model used was a 313-SNP developed by the BCAC consortium.
        - The 313 PRS has been validated in other studies across different ancestry groups.
    - It has been proposed to return the GIRA based on the BOADICEA v5 calculation.
        - In older versions of the BOADICEA model, only the monogenic risk was included. In the latest version model, the PRS is also included.
    - This PRS will be restricted to females over 18 years old.
    - The 313 PRS was validated in the eMERGE III and BioMe Datasets.
    - The proposed threshold cutoff for breast cancer is the top 5%.
    - European Ancestry:
        - European ancestry has been validated in BCAC, UKBB, and eMERGE III, with odds ratio per standard deviation being 1.65, 1.59, and 1.37, respectively.
    - African Ancestry:
        - African ancestry has been validated by AABC, BioMe, and eMERGE III, with odds ratio per standard deviation being 1.27, 1.25, and 1.15, respectively.
    - LatinX Ancestry:

        - LatinX ancestry has not been validated in public literature, however, it is validated by the eMERGE III datasets with an odds ratio per standard deviation being 1.27.
    - Asian Ancestry:
        - Asian ancestry has been validated by BCAC-Asian and eMERGE III, with odds ratio per standard deviation being 1.52 and 1.45, respectively.
    - Feasibility:
        - The phenotype is mainly based on ICD-codes.
            - PheKB: 1052
        - 311/313 (99.39) SNPs were covered by the GDA array.
            - 2 were excluded due to allele mismatches.
    - The crude AUCs that are listed on the breast cancer validation graph are based on PRS only.
    - The PPVs have been adjusted for ancestry specific prevalence.
    - The regression weights were brought over directly from public literature.
    - The estimation of model discrimination for non-genetic variants on the spreadsheet only include age and PCs.
        - The criteria of the PRS adding significant value to discrimination in a larger model should not be consider as a "go, no-go" rule. It should just be considered when deciding whether the PRS should be included in the study or not.
    - The interventions for breast cancer will be screening, HRT, MRI, and additional clinical exams.
- **Atrial Fibrillation | NU & VUMC**
    - The Atrial Fibrillation PRS model is adapted from the Nielsen et al. paper. The paper looked at two large GWAS studies with 1.6 million individuals (largely European ancestry).
    - Atrial Fibrillation is defined using ICD 9 and 10 codes and the age at first diagnosis has to be over or equal to 40 years old.
    - The PRS model has 166 SNPs and the population point prevalence is 3% keeping in mind that the population was restricted to over 40 years of age. The SNP based heritability is 22%.
        - The 3% is a cut off that captures a good number of people at risk for Atrial Fibrillation and results in nice odds ratios.
    - The PRS is not transancestry but does perform well across ancestries.
    - The eMERGE I-III cohort was used for validation by ancestry in addition to the VUMC African cohort.
    - Atrial Fibrillation increases with age and creates a high stroke risk.
        - Early identification of Atrial Fibrillation triggers anticoagulation management to reduce stroke. Screening strategies range from minimally invasive and escalate to more costly measures.
    - AUCs by ancestry range from 0.57 to 0.68.
    - The Broad has already run all SNPs and weights which perform well. It is currently being validated in the eMERGE I-III cohort.
- **Abdominal Aortic Aneurysm | VUMC & UAB**
    - GWAS from 2019 (Klarin et al) was entirely European ancestry + FinnGen was used to construct a PRS using PRS-CS + p-value thresholding.
    - The optimal PRS had p<5e-3 and had 12,314 SNPS.
    - True prevalence of AAA is 4-8% based on screening with a diagnosis prevalence around 1%.
        - Many AAAs are very small and not very dangerous.
        - Once discovered, the AAA will be monitored for progression.
    - The PRS was not built in a trans-ancestry context but the score has been validated in EA and AA populations.

- Phecodes defined the cases and were consistent with GWAS phenotype.
- The OR are statistically significant.
    - There are not enough cases in the eMERGE data for Hispanic and Asian ancestries.
    - BioVU data was used in these populations.
- The proposed high risk cut off is 5%.
    - European OR is 2.21 with a p-value <2e-16
    - African OR is 3.34 with a p-value 0.0033.
- All sites are on the GDA.
- Standard sites and weights was the only format model used.
    - Other covariates include smoking status and BMI.
    - The specific sites and weights have not been published but plans are to publish.
- AAA occurs most often in European ancestry groups compared to African groups.
- Timing of screening for AAA relies on smoking status.
    - Smoking has a significant effect on AAA risk but didn't have a smoking variable in the eMERGE data.
    - Clinical recommendations are not great at identifying high risk individuals with regard to who gets diagnosed with AAA.
    - Determining those who have existing AAA but not diagnosed is not well defined.
    - AUCs increased to 0.9 when smoking status was used in BioVU data.
- Due to low incidence in Asian and Hispanic populations, return of results in these groups might be difficult.
- The ORs at the tails are large but were not shown in this data.
- The proposed intervention for those determined to be at high risk would be an aortic ultrasound.

PRS Session 2:

- **Chronic Kidney Disease| Columbia & UAB**
    - Chronic Kidney Disease (CKD) disproportionately affects African Americans with prevalence being over 16%.
    - The study being used for validation is GWAS for eGFR (Wuttle et al. Nat Gen 2019).
        - The study has about 1 million participants across 121 different studies.
        - The ancestry breakdown of the study is as follows:
            - European: 75%; East Asian: 23%; African: 2%; Hispanic: <1%
    - There is good evidence for APOL1 risk variants being important in the determination of CKD in African Americans.
        - These variants used a recessive model.
        - The variants are present in about 10-15 % of African Americans, 0.5-2% in Hispanic ancestry, and almost nonexistent in European ancestry.
    - eMERGE III CKD phenotype is being used for validation.
        - Cases are defined by participants that have CKD 3 or above.
        - Age, Sex, diabetes, and PCs of ancestry are being used as the covariates.
    - Study Design
        - For the CKD PRS study design, summary statistics are first taken from the CKDGen GWAS for eGFR.
        - 1000G Reference panel is used for all populations.
        - The best GPS is selected by using UK Biobank for Europeans.
            - The best performing GPS is P+T (r2<0.2, P<0.03) + APOL1 risk genotype.

- An ancestry adjustment was applied for UKBB and eMERGE III datasets.
- European Ancestry:
  - European ancestry has been validated in UKBB, eMERGE III, and BioMe with OR at 2% being 3.46, 3.16, 3.39, respectively.
- African-American validation
  - There is some variability due to small sample size.
  - Odds ratio at 2% across all datasets is averaged to be 2.33.
- Asian validation
  - Odds ratio at 2% across all datasets is averaged to be 3.59.
- Hispanic validation
  - Odds ratio at 2% across all datasets is averaged to be 4.44. The metrics for the Hispanic ancestry group shows good performance even though a small case/control group was used.
- Being high risk for CKD based on family history is considered actionable and an indication for clinical screening.
- There is a 99.6 market overlap with the Broad-imputed blood and saliva-derived data.
- The CKD group believes that a threshold of 2% is reasonable and provides clinical actionability.
- Combining APOL1 and PRS together does not perform worse than APOL1 alone.
- If a participant has high PRS, the action will be to screen for CKD since the majority of people are unaware that they have it.

- **Coronary Heart Disease | Mayo & UW**
  - CHD prevalence ranges from 11 to 6 percent across ancestry groups in the US reported by National Health Interview Survey, CDC.
  - There is prior evaluation of the CHD PRS in 3 ancestry groups in the eMERGE III cohort. Additionally, the MVP transethnic GWAS for CHD includes 243,392 cases and a total of 1 million individuals.
  - A new transethnic score has been developed using the pruning and thresholding approach with 542,218 SNPs.
  - The validation cohorts included multiple studies with no overlap between validation and derivation/tuning cohorts.
  - All results from cohorts have been meta-analyzed into a single odds ratio.
  - Three models were used including PRS, age and sex, and PRS plus age and sex.
    - Including PRS plus age and sex yielded a rise in AUC
  - A small number of sites are not available in the imputed GDA set but no foreseeable issues are anticipated.
  - PRS model used a standard sites and weights only format (ie weighted sum of SNP coefficients).
  - For interventions, CHD could be used for combined risk. The PRS, because it has independent predictive value, will increase the value of risk prediction.
- **Type 2 Diabetes | UAB & MGB**
  - The prevalence for type 2 diabetes for European 7.6%, African 9.3%, Hispanic 7.8%, and Asian 7.3%.
  - The algorithm was validated in eIII and MGB Biobank
  - There are two published PRS studies but two GWAS studies were combined into a larger cohort, DIAMANTE, which was used for this analysis.
    - Ancestry-specific scores are being developed at this time.
  - A transancestry score was validated using the MGB Biobank.
  - The PRS-CSx method was used and trained in the ancestry groups in eMERGE.
  - The PRS-CSx model with a 2% threshold is recommended from this group.

- The PRS will be transethnic and will not require post-hoc adjustment.
- Datasets from eMERGE 3, the MGB Biobank, and the UAB cohorts differ:
  - The eMERGE dataset is adjusted for the site and includes children and adults.
  - The MGB Biobank only included individuals over 18 years old and are European.
  - The UAB cohort were individuals under 18 and included mostly self-reported AA ancestry.
- The eMERGE training set showed the highest R^2 in the European ancestry with the lowest in the African cohort.
  - The AUC including covariates range from 0.79-0.89.
- African cohorts have a higher AUC with covariates + AUC across the literature, ranging from 0.597-0.738
- The European model also shows a higher AUC with covariate + PRS at 0.76.
- The eMERGE model using the PRS-CSx transethnic method has an OR at the top 2% ranging from 1.81-4.36.
  - The adjusted NPV range from 0.91-0.93 across the different ethnicities.
- This condition is validated across four ancestries in eMERGE with a transferability of 99% of all sites that are genotyped/imputed on the GDA array.
- Interventions include PCP perform A1C, fasting glucose, lifestyle changes.
  - The American Diabetes Association has approved guidelines to treat pre-diabetes with metformin but unsure how prevalent this recommendation is followed.
- A proposal has been made to return this to children 12 years and above.
- Other conditions (obesity, hypercholesterolemia) will have similar interventions as type 2 diabetes.
- Basic metrics can be collected through the EHR while other metrics can be collected in the surveys.

- **Hypercholesterolemia | Mt. Sinai & Mayo**
  - Prevalence of Hypercholesterolemia is estimated to be about 7% in adults.
  - The current estimate for LDL SNP-based heritability is 12.7%.
  - Severe Hypercholesterolemia cases were defined by statin-adjusted max LDL-c greater than or equal to 190 mg/dL. Controls were defined by participants with statin-adjusted max LDL-c less than or equal to 160 mg/dL.
  - A trans-ethnic LDL-c PRS is being used from the Global Lipids Genetics Consortium (GLGC).
    - The GLGC has published multiple public blood-lipid GWAS.
  - A trans-ancestry PRS was created by P+T, which contains 9009 SNPs.
  - Individuals of African, Asian, European, and Hispanic ancestry were included in all three stages of PRS development: discovery, training, and validation.
  - The Mount Sinai BioMe dataset is being used for validation.
  - The Hypercholesterolemia model used PRS, age, sex, chip, and top 10 PCs.
  - The study was restricted to individuals who are over the age of 18.
  - The odds ratio per PRS standard deviation is about 2.0 across all ancestry groups.
  - Discrimination measures:
    - The AUC is approximately around 0.66 across all ancestry groups.
    - The chip covariant will not be included in Broad implementation.
  - The threshold decided was the top 3% since this threshold performed the best across metrics.
    - Odds ratios for each ancestry:
      - European: 4.98; African: 2.99; Hispanic: 3.96; Asian: 1.40
  - Feasibility:
    - 99.9% (8996/9009) of sites on the Broad imputed Global Diversity Array.
    - The model uses a standard sites and weights format.

        - There is expected to be validation in Asian populations by the end of June 2021.
    - Discussion:
        - Overlap of Hypercholesterolemia and CHD
            - CHD PRS measuring differs from Hypercholesterolemia. It is predicted that there will be some overlap.
        - Currently, Hypercholesterolemia is only focused on adults, but will be useful to test in children in the future.

PRS Session 3:

- **Prostate Cancer | NU**
    - Northwestern is proposing to use a published score for Prostate Cancer that was developed in a large GWAS with 105K cases across the 4 different ancestry groups. The plan is to return the top 10% of men.
    - Lifetime risk for Prostate Cancer was calculated using SEER 2016 data.
    - In looking at the eMERGE I-II data, there are about 40 sites that are missing from validation data. These sites are in the GDA but when looking at the validations highest effect variants are missing.
    - Covariates included age, eMERGE site, and PC 1-10. Age is by far the best predictor of Prostate Cancer.
    - NU proposed a high risk cut off of the top 10% of men. The top versus bottom percent was comparable to having one first degree family member with Prostate Cancer would be (top 2-3 percent).
    - Regarding feasibility in the pipeline, 264/269 of the variants are imputed and/or genotyped on the GDA with 5 missing low-effect chrX variants.
    - NU has proposed returning to men ages 35 and above.
- **Colorectal Cancer | UW & Mt. Sinai**
    - Currently, a trans-ancestry PRS manuscript is under preparation.
    - Several approaches were attempted before settling on an independent Genetic Epidemiology Research on Aging (GERA) cohort and an eMERGE cohort to validate the PRS.
    - Colorectal cancer cases were defined by ICD codes only including European and East Asian ancestry with a heritability of approximately 7%.
    - GERA and eMERGE 1-3 were used for validation.
        - There are low cohort numbers for all ancestries except for Non-Hispanic whites (n = 1884).
            - Asians n = 99
            - Hispanic = 78
            - African = 98
    - AUC and OR for each cohorts PRS
        - AUC range 0.57-0.63, OR 1.13-1.72 for all ancestries in the GERA cohort.
        - AUC 0.60-0.65, OR 1.4-1.64 (African and European ancestries only) in the eMERGE cohort.
    - The PPV for African and European at 2% at the top 7% cut-off.
    - There are 99.7% of SNPs in the GDA, either as genotyped or imputed.
    - The model presented uses the standard sites and weights format and the SNP sites and weight information has been shared with The Broad.
    - A transancestral PRS still under development by continuing to include GWAS data for African, Hispanic and Asian cohorts.
    - Clinical applications include earlier screening approaches to possibly detect cancer at an earlier stage.
    - PRS not used as a diagnostic test but should prioritize early screening (similar to positive family history).
    - A small validation set was used with the GWAS being from East Asian and European.
        - The original publication was in a European population.
        - Three of the four populations have under 100 cases each in the GERA and e1-3 cohorts.

        - UW is currently adding more samples for the African ancestry group to aid in prediction and model development.
    - Better validation is needed for tail discrimination at the top 7% cut-off.
    - False positives could cause someone to get screening that may not be needed with the current data presented.
- **Obesity/BMI | CHOP & CCHMC**
    - The PRS was developed based on BMI, using the EMR-derived measures. A cleaning algorithm was developed to point out potential outliers in the data.
    - For this study, BMI greater than or equal to 27.5 kg/m2 for Asians, and BMI greater than or equal to 30 kg/m2 for non-Asians will be used.
    - Based on a study by NHANES 2017-2018, the prevalence of obesity based on ancestry is as follows:
        - Hispanic: 45.2%; Non-Hispanic White: 41.5%; Non-Hispanic Black: 50.6%; Non-Hispanic Asian: 36.1%
    - The SNP-based heritability of BMI is estimated at 22.4%, which is based on a study from the GIANT consortium.
    - The PRS used will be based on meta-analysis from the GIANT consortium.
        - This is a trans-ancestry study with a total of over 1.6 million participants. The breakdown of ancestry is as follows:
            - South Asian: 2%; Hispanic: 4%; African: 6.4%; East Asian: 16%; European: 71.6%.
    - The PRS was developed using PRS-CS-auto using 1000G data. Approximately 1.2 million SNPs are included in the final score.
    - This PRS has been validated in all 4 ancestry groups.
    - Odds ratio per standard deviation by ancestry:
        - European: 2.05; African: 1.49; Hispanic: 1.87; East/South-East Asian: 2.18; South Asian: 2.09.
        - The mean value across all ancestry groups was 1.94, and the standard deviation across all ancestry groups was 0.274.
    - In pediatric data, the results are similar to the results reported by the Khera et al paper (PMID: 310002795). The study found that the PRS score is more strongly associated with BMI, rather than a child's birth weight.
    - The covariates that are being used for analyzation are age, sex, and the top 4 PCs.
        - The results are primarily driven by PRS.
    - The threshold cutoff will be the top 3%. Below are the odds ratios for the top 3% adjusted for prevalence of obesity for the different ancestry groups:
        - European: 4.08; African: 2.54; Hispanic: 2.33; East/South-East Asian: 5.73; South Asian: 4.19.
        - PPvs and NPVs have been adjusted for prevalence of obesity based on ancestry.
    - There are not any foreseeable issues in regards to implementation.
    - The model being used only includes standard sites and weights format.
    - The age range for this PRS is 3-40 years.
    - The NPV is lower than usual since obesity has a high prevalence.
    - The Network will need to decide what would be the recommendation for adults who have a high polygenic risk for obesity and are already obese.
- **Type 1 Diabetes | CHOP & CCHMC**
    - The Type I Diabetes phenotype was defined using eMERGE T1DM algorithm, electronic phenotyping, ICD codes, and medication prescriptions.

- A chart review was performed at CHOP with a sensitivity of 0.988. The MGB site reviewed charts as well and got similar results in adults.
- An increase of 20% in African and Hispanic children in the last decade with an approximate 14% increase in European children.
- The PRS was based on the GRS2 score published in 2019. The score was originally published to add non-HLA T1D associated loci to the GRS to better discriminate diabetes subtypes and to predict T1D in newborn screening studies. The GRS2 includes 67 SNPs (32 non-HLA).
- The discovery set was 6,670 cases and 9,414 controls, validated in the UK Biobank cohort. AUC was 0.96 for early onset cases.
- The validation cohort was all pediatric CHOP samples. The odds ratios per SD for Europeans was 3.79 and for Africans 3.48.
- The high risk cut off is set at the top 3% based on sensitivity values in Europeans.
    - Sensitivity of the GRS at the proposed cutoff is 13% for European ancestry and 18% for African ancestry.
- For individuals ages 3-21, CHOP recommends urine analysis with a dip stick every 3 months to test for glucose and ketones (low cost and can occur at home) in addition to annual antibody testing for insulin and islet cell autoantibodies with fasting blood glucose.
- All sites are present in the imputed GDA.
- The model requires a standard SNPs and weights file and SNP2HLA imputation of the HLA region.

- **Final Condition Selection & SC Committee Vote | Leadership**
    - A consensus on the majority of the conditions appears to have been reached.
        - Breast cancer, CKD, CHD, type 2 diabetes, and prostate cancer were unanimously voted to be included in the clinical pathway.
        - Hypercholesterolemia, obesity/BMI, type 1 diabetes, and asthma received a majority vote to be included in the clinical pathway
        - Atrial fibrillation received a tie vote for inclusion into the clinical pathway.
        - AAA and colorectal cancer received a majority of votes to be placed in the developmental pathway.
    - Atrial Fibrillation
        - This condition will be included due to no justified concerns as to why a site voted against the inclusion were provided during the discussion.
        - The sites that voted against inclusion provided their reasoning.
            - Many of the sites that voted against inclusion had divided opinions in the sites and the decision to vote against inclusion was not unanimous.
            - There is a low prevalence in the African ancestry population.
            - There was a cost concern for the prevention recommendation of wearing a smartwatch as an atrial fibrillation monitor.
                - The study could purchase the smartwatches for the participants.
                - There are less expensive smartwatches currently on the market.
            - This condition does not have a trans-ancestry score, and the confidence intervals around African and Asian ancestry populations are broad.
        - There were other concerns that this condition is more common in European ancestry and in older adults, and could lead to unnecessary monitoring in younger populations.
        - The sites that voted for inclusion provided their reasoning.
            - The stroke prevention outcome led sites to vote to include the condition.

        - The interventions are easy to implement.
        - Measuring outcomes is straightforward.
        - It is a very relevant condition, and understanding the genetic components would be useful.
    - Increasing the threshold to the top 2% is an option to improve the PPV.
    - The odds ratio in European ancestry was 2.46, and 2.19 in African ancestry in the Vanderbilt cohort.
    - The language on the GIRA must be carefully considered since it will remain in a participant's EHR.
    - This is a research study and participants should be fully educated on the risks and implications of the PRS return before consenting.
    - Currently, the actionable age of return is 40+. The sites were asked to consider raising the actionable age of return to 50.
    - Northwestern and VUMC will continue to seek other cohorts that can be used to increase the validation.
        - Many atrial fibrillation cases are in GWAS.
        - Raising the age to 50 could increase validation in different ancestry populations.
        - UAB can provide data from REGARDS to strengthen the African ancestry validation.
    - UAB switched their vote to include atrial fibrillation in the clinical pipeline.
    - Based on this, atrial fibrillation will be included in the prospective cohort.
- Abdominal Aortic Aneurysm
    - The sites that voted against inclusion provided their reasoning.
        - There was inadequate validation in minority populations.
            - A rebuttal to this was that the African ancestry population is at a significantly reduced risk than the other ancestry groups.
            - Returning results in populations other than European ancestry could be problematic with the lack of robust validation in non-European ancestry.
        - In comparison to the other conditions' data sets, there was not enough data in the AAA set.
    - The PRS was developed using multiple independent data sets and was validated in independent data sets by the sites. These data sets were of majority European ancestry.
    - The sites that voted for including AAA in the clinical pipeline provided their reasoning.
        - This is one of the leading causes of death in men.
        - There are already guidelines in place for screening over the age of 60.
            - There is a relatively inexpensive test for AAA if an individual has a family history of the condition.
            - The PRS assessment may be able to be integrated into these guidelines.
        - This disease is often not detected.
        - The PRS alone has a better predictive value than the current guidelines.
        - There is a high medical actionability.
    - Smoking data is lacking. Smoking is the strongest risk factor for AAA.
    - The PRS has a stronger predictive value when the variable of smoking is included.
    - Clinically, this is an important phenotype based on mortality - mostly a silent killer.
        - A strong consideration should be made due to this and the case that this may save lives where the other conditions are chronic and may only have an earlier diagnosis.

- Individuals who smoke are currently encouraged to be screened for AAA. The PRS screening will address the non-smokers who are at risk for AAA who are not included in the standard guidelines.
- There was no change to the votes following the discussion. AAA will be moved to the developmental pathway.

- Colorectal Cancer
  - The sites that voted against inclusion provided their reasoning.
    - The validation data is lacking in non-European ancestries.
      - The small number of cases in the data presented for the other ancestry groups was the biggest concern about moving forward.
      - The confidence intervals in African ancestry populations were concerning.
      - All validation data sets in non-European ancestries have less than 100 cases.
    - The Network recognizes the screening guidelines are currently being lowered to age 45 from age 50, but due to lack of data still do not want to include CRC in the clinical pipeline.
  - The sites that voted for inclusion in the clinical pipeline provided their reasoning
    - There is substantial data in Asian and European ancestries.
      - Many conditions in the clinical pipeline lack validation data in Asian ancestries.
      - The full Asian ancestry data set was not presented today.
    - There is a plan to validate new data in African ancestry in the next six to eight weeks. The plan also includes altering the model to improve performance in African ancestry. UW would withdraw the condition if it did not perform well in African ancestry.
    - Most individuals do not follow the screening recommendations.
    - There is widely available, safe screening intervention that can prevent the disease, and not just diagnose the disease.
    - Colorectal cancer is the second leading cancer cause of death in the US.
    - Individuals with a known family history of CRC have an increased rate of screening.
  - The power differential between the current European ancestry population and the proposed addition of 5000 individuals with African ancestry is too large to be made comparable before implementation in the study.
    - A rebuttal was that the condition leads would perform fine-mapping to support the African ancestry model.
      - There is concern regarding the timeline of fine-mapping.
  - Following adjustments for age and sex, the PRS does not seem to have a significant effect on the phenotype in African Americans.
  - The PRS working group asked conditions to provide: full model, non-genetic covariate predictors, and genetic predictors
    - Looking to estimate how well the PRS model is predicting phenotype.
  - UW can provide more Asian data than was shown in the presentation.
  - The study infrastructure cannot support different reporting or separate pipelines based on ancestries.
    - Selecting to return to populations only with strong validations would affect recruitment as well.
  - CRC genes are included in the CDC Tier 1 condition. The Tier 1 genes are classified due to their health impact and actionability.

        - eMERGE is a polygenic study not focused on monogenic results.
        - CRC genes include Lynch Syndrome genes, which have overlap with other conditions.
- There is a concern regarding returning PRS results to participants with Hispanic and African ancestry due to the PRS validation in Hispanic and African populations being nonsignificant.
- UW is requesting time to demonstrate validation in African ancestry groups, and Mt. Sinai will provide additional Hispanic ancestry data.
- Asthma, AAA, and Type 1 Diabetes have a reasonable data set size in only European ancestry and African ancestry.
- The only phenotypes that have a reasonable data set size in all ancestry groups are breast cancer and CKD.
- The developmental pathway would allow for gathering more data but would not allow observing if behavior changes.
- CCHMC supported UW and Mt. Sinai having time to improve their data sets and models, and confidence in the condition leads' ability to remove CRC from the clinical pipeline if the data was meeting standards.
    - The Steering Committee does not want to provide CRC with additional time.
- The Steering Committee decided to provide sites with additional discussion time to vote on CRC and AAA.
    - A REDCap survey will be distributed to the sites to vote on the inclusion of CRC and AAA in the clinical pipeline. There will be one vote allowed per site, and the vote will be due by 5 pm EST, Monday, June 14th.