**eMERGE Network Steering Committee Meeting**

June 29-30, 2015

New York, NY

Attendance

Network Members in Attendance

CCHMC/BCH Armand Antommaria

CCHMC/BCH Beth Cobb

CCHMC/BCH John Harley

CCHMC/BCH Ingrid Holm

CCHMC/BCH Todd Lingren

CCHMC/BCH Bahram Namjou

CCHMC/BCH Cassandra Perry

CHOP Berta Castillo

CHOP John Connolly

CHOP Joe Glessner

CHOP Hakon Hakonarson

CHOP Patrick Sleiman

Geisinger Kenneth Borthwick

Geisinger David Carey

Geisinger Les Kirchner

Geisinger David Ledbetter

Geisinger/U of Maryland Casey Overby

Geisinger Diane Smelser

Geisinger Janet Williams

Geisinger Marc Williams

GH/UW David Carrell

GH/UW David Crosslin

GH/UW Gail Jarvik

GH/UW Eric Larson

Marsh/Essentia/PSU Murray Brilliant

Marsh/Essentia/PSU Scott Hebbring

Marsh/Essentia/PSU Terrie Kitchner

Marsh/Essentia/PSU Cathy McCarty

Marsh/Essentia/PSU Peggy Peissig

Marsh/Essentia/PSU/CC Marylyn Ritchie

Marsh/Essentia/PSU/CC Shefali Setia

Mayo Mariza de Andrade

Mayo Suzette Bielinski

Mayo Sherry-Ann Brown

Mayo Pedro Caraballo

Mayo/JHU Chris Chute

Mayo Iftikhar Kullo

Mayo Jen McCormick

Mayo Jyoti Pathak

Mayo Carolyn Vitek

Mt. Sinai Noura Abul-Husn

Mt. Sinai Erwin Bottinger

Mt. Sinai Stephen Ellis

Mt. Sinai Genevieve Galarneau

Mt. Sinai Carol Horowitz

Mt. Sinai/Columbia George Hripcsak

Mt. Sinai Eimear Kenny

Mt. Sinai Ana Mejia

Mt. Sinai Girish Nadkarni

Mt. Sinai Aniwaa Owusu Obeng

Mt. Sinai Michelle Ramos

Mt. Sinai/Columbia Chunhua Weng

Northwestern Rex Chisholm

Northwestern Tim Herr

Northwestern Luke Rasmussen

Northwestern Laura Rasmussen-Torvik

Northwestern Maureen Smith

Northwestern Justin Starren

NHGRI Rongling Li

NHGRI Teri Manolio

NHGRI Ken Wiley

NHGRI Kira Wong

Vanderbilt/CC Josh Denny

Vanderbilt Todd Edwards

Vanderbilt Tracy McGregor

Vanderbilt Josh Peterson

Vanderbilt Dan Roden

Vanderbilt/CC Sarah Stallings

Vanderbilt Digna Velez-Edwards

CC Melissa Basford

CC Adam Hardebeck

CC Paul Harris

CC/Vanderbilt Bradley Malin

Network Invitees and Guests

Aurora Research Institute Michael Michalkiewicz

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| **eMERGE Network** ***Summary of the eMERGE Steering Committee*** June 29-30th, 2015; New York |
| The eMERGE Steering Committee Meeting was held on June 29-30th, 2015 in New York, New York. In order to ensure that the Network remains productive as we continue through our final year, please find highlights from the Steering Committee Meeting below.  Presentation slides are [available here](https://emerge.mc.vanderbilt.edu/?page_id=1500) (login required) and are also linked within the meeting summary below.  *Goals for the meeting:*   * Scientific Presentations and discussions * Network projects update   + PGx   + CERC Survey * Sites’ accomplishment reports * Workgroup achievement reports * Coordinating Center Report |
| **Day 1: Full-day Session** |
| Welcome, Opening Remarks, General Updates – *Rongling Li*   * There will be two Precision Medicine Initiative (PMI) events in July on Participant Engagement and Health Equity, and mHealth. * Take aways from this meeting include:   + Summarize network wide and site specific accomplishments as Phase II closes   + Identify unfinished tasks   + Setup timeline for completion of eMERGE phase II Projects   Announcements, Opening Remarks – *Rex Chisholm*   * The focus of the meeting will be on the science of the Network. * This is a chance to celebrate all that has been accomplished.   Presentations  Effect of Disclosure of Genetic Risk for Coronary Heart Disease on Psychosocial Domains, Information Seeking, and Information Sharing– Sherry-Ann Brown   * Dr. Brown reported on the importance of patient’s active engagement as participants in their healthcare and investigated whether knowledge of genetic risk influences information seeking and/or sharing. * Results indicated that Genetic Risk Score (GRS) patients are more likely than Conventional Risk Score (CRS) patients to seek information from baseline to 3 months after risk disclosure, and this trend continues 3-6 months after risk disclosure. At three months post risk disclosure GRS patients have a larger sharing radius than CRS patients, and this trend continues 3-6 months after risk disclosure.   [CERC](http://emerge.mc.vanderbilt.edu/qf/private/Appendicitis-Harley.pdf) Survey Update – *Ingrid Holm & Maureen Smith*   * The Survey workgroup reported that the survey is in its second wave of mailings. Deliverables have been on time, with the exception of reminder post cards due to Scantron issues. Final data will be available in September. The survey population demographics, sampling strategy rationale, experimental design, and response rates were discussed. Overall response rate is 12% with the expectation of an increase with the second wave to 15-16%. Preliminary results indicate that most people are interested and willing, and will allow their child to participate in a biobank, though they are a little more conservative about their children. The group discussed accepted and in-progress manuscripts. Analysis is expected to extend beyond the grant period, and a no cost extension has been granted for all sites until February 2016. * The overall Workgroup reported on the Infobutton project and the “For Health Professionals” section of MyHealthResults.org, which has experienced a significant level of usage. The group discussed overlap with the Return of Results workgroup and collaborations with other groups inside and outside of eMERGE (Including CSER and the pediatric workgroup). Challenges addressing regulation/regulatory environment were discussed, and ideas for future goals and efforts (such as online education) were developed.   Group Health / UW Site Report – *Gail Jarvik & Eric Larson*   * The site reported the results of their GWAS study of Varicella Zoster, in which recruitment for replication is in process. The group provided updates on the ongoing investigations into CAAD and C-diff phenotypes, copy number variations, and the PGx project. In addition, the site outlined the pilot study on hematological adverse drug events in the PGx cohort being conducted (which has been submitted as an abstract to ASHG). CERC highlights were provided- focus groups and stakeholder interviews, manuscripts in progress and published. * The group described their experience with Alzheimer disease studies, a phenotype ongoing from Phase I. Collaborating with the National Alzheimer’s Disease Consortium has been a positive and productive experience. Recently the site entered into a collaboration with a larger international consortium. * GH/UW conducted key informant interviews into appropriate and effective integration of genomic information into clinical care and the EMR, which illuminated interest in up-stream CDS processes. * The group has already returned the results of known pathogenic variants to 3 participants. The medical value of being able to study a family pedigree was discussed. * The site is on schedule to wrap up Phase II efforts on time. * The group discussed returning results and education efforts at different sites (including Mayo).   eMERGE PGx Plenary Session – *Dan Roden, Josh Denny, & Laura Rasmussen-Torvik*   * The group highlighted accomplishments (nearly completed with all goals, all goals expected to be completed by the end of the grant), reviewed work in progress (primarily Process Outcomes measures) and discussed moving forward (such as a one-time analysis of prescription based drug exposure data). Special attention was given to describing the cohort, and there was discussion on the differences between the variation found in the eMERGE cohort and that of other cohorts. The PGx set has significantly more variation than ExAC, for example, but we have more read depth. Variance is upstream, downstream, and intronic variance. Public data is only shared start to stop. Optimization of the sequencing platform is also a possible source of the discordance.   BCH / CCHMC Site Report - *Ingrid Holm and John Harley*   * The site reported their progress towards their aims. Results towards their first aim include creating a model for ensuring phenotypic standardization and national scalability (SHRINE). Aim 2 results include the indication of age dependence of the obesity phenotype, the identification of a subgroup of autistic patients that had seizures, and investigations into inversion/risk haplotype at BLK. * The group also described PGRNseq data (776 PGRNseq results were received and uploaded to SPHINX and dbGaP). Results towards aim 3 indicated parents and physicians used CYP2D6 results to care for the child, and parents were likely to share the CYP2D6 results with their child’s physician and pharmacist (but not with the child). Aim 4 results include providers placing importance on returning research results that could potentially improve their patients’ health outcomes (82% plan to enter CYP2D6 results in child’s EMR).   PGx CDS Process Outcomes – *Tim Herr*   * Dr. Herr discussed how PGx CDS alerts effect clinical action by inventorying alert scenarios across sites, gathering data on firing rate, and determining how physicians are interacting with the data. This report also expounded on previous discussions of when to initiate clinical decision support (at time of prescription or downstream), and how to initiate it (actively or passively). * Preliminary results of the study indicate that just because a physician ignored an alert doesn’t mean the alert wasn’t considered in the treatment plan. Passive alerts are potentially a useful way of disseminating information. Clopidogrel is the most common alert firing, and while on the whole physicians took no action, there was some change (23 followed the alert). One explanation is that the alert can be viewed and acted on at any time after firing, and they may see the alert at a time when they aren’t making a prescribing decision yet. Also, there are differences in recommendation acceptance of different DGIs (Simvastatin recommendations were accepted more often than those for Warfarin). * Follow up interviews to gather qualitative information are in process. The group discussed legal precedence and implications of CDS, including where liability lies and standard of care.   Phenotyping Workgroup Update *– Josh Denny & Peggy Peissig*   * The workgroup completed a total of 56 phenotyping algorithms throughout eMERGE I & II. The phenotypes had ~98% PPV overall. * Working with Brad Malin, the group developed meta-analysis tools (SecureMA), as was able to do a systematic review of re-identification attacks (findings showed only 1 paper using modern de-identification methods on healthcare data, and had a success rate of .013%). * During Phase II, PheKB.org was expanded to include validation tools. * Portable NLP was explored during Phase II. * The KNIME workflow engine was utilized for phenotyping at a minimum of 2 sites for 4 phenotypes. This engine was shown to reduce implementation burden at other sites, although the group noted that a common data model would help more sites be able to utilize.   + “A Prototype for Executable and Portable Electronic Clinical Quality Measures Using the KNIME Analytic Platform” - Winner of ‘Best Paper Award’ at 2015 AMIA CRI * The workgroup published 91 papers, with an additional 19 in progress.   Next Generation Phenotyping Using Interoperable Big Data – *George Hripcsak & Chunhua Weng*   * An overview of OHDSI was provided. Observational Health Data Sciences and Informatics (OHDSI) is a network of researchers and health databases with a central coordinating center at Columbia. Their mission is to provide a large-scale analysis of observational health databases for population-level estimation and patient-level predictions. The vision for OHDSI is for patients and clinicians to use the tool to access evidence based on a 1 billion patient cohort. OHDSI is currently comprised of >120 collaborators from 11 different countries.   + Takes 3 months for collaborators to convert data to the common data model.   eMERGE Coordinating Center Report – *Paul Harris , Marylyn Ritchie, Josh Denny, & Brad Malin*   * The CC assisted the network in:   + Accelerating phenotype development/sharing:     - PheKB, Data Dictionary/Data Validation Tool, PheWAS Catalog, and the eMERGE Record Counter were all given as examples of tools developed by the CC.   + Expanding genomic data integration:     - 55,028 total samples were genotyped during Phases I & II. The merged imputed dataset was released to dbGaP.     - The CC developed a variant calling pipeline for eMERGE-PGx w/ the Genomics workgroup. CC also performed variant calling for all eMERGE-PGx samples.     - The CC led a special issue to Frontiers in Genetics (currently over 41,000 views online)   + Enhancing methods to determine re-identification & privacy risks   + The CC also provided logistical support to the network by way of tool development, updated website, reporting, meeting management, and project management for workgroups.   Large-scale phenome-wide scan in twins using electronic health records – *Scott Hebbring*   * This scan sought to prove that EHR-linked twin cohorts can be used for phenome-wide studies to identify diseases with genetic etiologies. The study used 28,888 twins found in the Marshfield (~16,000) and Mayo (~12,000) twin cohorts. * The study concluded that:   + most diseases are not random events in twins. 1,406/5,598 (25%) of phenotypes are statistically enriched in pairs of twins. ~1% of phenotypes have RRs. (<1.0); and   + family data may be efficiently captured in EHR and may be used to predict, prevent, and treat human disease for the advancement of precision medicine.   EHRI Workgroup Update – *Justin Starren & Marc Williams*   * Collaborations include:   + HL7 Clinical Genomics Workgroup, IOM Roundtable on Translating Genomic-based Research for Health, G2MC, CSER, ClinGen, IGNITE, Precision Medicine Initiative, CPIC Implementation Consortium, PGRN PGx Guideline Repository, IOM DIGITizE * Four recently- accepted publications were noted:   + AMIA 2015 Panel: *Public Implementation Resources for Genomic Medicine* – Josh Peterson, Marc Williams, Casey Overby, Robert Freimuth, Iftikhar Kullo   + *A Conceptual Model for Omic Data* – Tim Herr et al; accepted with revisions to Journal of Pathology Informatics   + *Practical Considerations in Genomic Decision Support: The eMERGE Experience* – Tim Herr et al; accepted JPI   + *CSER and eMERGE: Current and Potential State of the Display of Genetic Information in the EHR* – Brian Shirts et al; accepted to JAMIA * An overview of CDS KB was provided. The site is now live, and currently includes 31 artifacts from 9 institutions.   DANGER: Understand Your Data, Save Yourself – *Marylyn Ritchie*   * While running pediatric null variant PheWAS analyses, Marylyn’s lab was unable to replicate known findings. Specifically, some phenotypes were present in only discovery or replication analyses, but not both. The major issue was that regression models were not converging. * Variables in the model will have a p-value, but that p-value may not actually be valid. Additionally, some software doesn’t notify you that the model didn’t converge. * Comparisons of this issue between genomic analysis software were shown. * Suggestions to alleviate these issues:   + Adjust the models for site, platform, sex, and PCs. Having only cases and controls in some strata leads to non-convergence.   + Drop any rows from the table where zeros are present.   + Use firth regression. * It is critical to carefully look at regression results to confirm convergence while running analyses.   Vanderbilt Site Report – *Josh Denny & Dan Roden*   * Since Sept. 2010, 14,734 Vanderbilt patients have had PREDICT testing. Additionally, the PREDICT provider survey is complete and had a 56% response rate. Findings: 92% of clinicians favor immediate, active notification when significant drug-genome interaction is present. * Vanderbilt’s contribution to eMERGE II Phenotypes was also reviewed. VU led 4 phenotype algorithm validations (ACE-I Cough, MACE-Statins, BPH, and fibroids), and also provided secondary validation for 7 additional phenotypes. * The large scale replication of GWAS association results using PheWAS was reviewed. 3,000 SNPS were mapped. 751 phenotype associations were tested, 210 were replicated, 66% were adequately powered. Also discovered 63 new associations (mostly w/ skin phenotypes). * Results of the Neanderthal PheWAS found that 1.5% of the genome of non-African individuals is inherited from admixture with Neanderthals. Neanderthal alleles are identified in the eMERGE imputed set.   Geisinger Site Report – *David Carey & Marc Williams*   * Geisinger presented their site report as a ‘lessons learned,’ since their participation in eMERGE contributed to fundamental changes in their initial research approach. Two high level recommendations are:   + Adopt a concept of an enterprise wide Learning Health System.   + Embrace engagementengagement of and partnership with Geisinger patients. * Integrated health leveraged as platform for genomics research. This has caused Geisinger to think more aggressively about how to accelerate the return of information back to patients/providers to improve clinical care. * IT governance has changed, reorganization of informatics structure due to eMERGE processes.   Comprehensive Review of Infobutton Project Project – *John Connolly, Casey Overby, & Luke Rasmussen*   * The project aimed to develop new information resources based on eMERGE II and PGx scenarios, as well as implementing infobuttons within EHRs at eMERGE institutions. * A simulation study of 22 physicians using 3 prescribing scenarios from UW was provided. The resources were utilized by physicians: lab reviews were accessed 98 times, while the medication order entry context was accessed 74 times. * eMERGE sites are considering similar PGx scenarios (clopidogrel, warfarin, simvastatin). * Practical considerations were reviewed. Major considerations include ‘how content is developed,’ ‘where content is hosted’ (locally hosted content is preferred), ‘a mix of site-specific and general content is required.’ * Myresults.org was reviewed. An end-user evaluation is under way to gather perceptions of eMERGE-developed content. 18 surveys have been submitted at this point from eMERGE sites and collaborating institutions. * The project will continue developing during eMERGE Phase III.   Marshfield/Essentia/PSU Site Report – *Murray Brilliant, Catherine McCarty, & Marylyn Ritchie*   * Site phenotype work was presented. Algorithms were developed and validated for Ocular Hypertension, Glaucoma, and AMD. They also assisted in the validation of 32 network algorithms (16 being the primary or secondary validator).   + A machine learning phenotyping article was published in the *Journal of Biomedical Informatics* (‘Relational Machine Learning for Electronic Health Record-driven Phenotyping’) * The site leveraged GWAS data available for ~6,000 research subjects at Marshfield and ~23,000 additional subjects across eMERGE to undertake discoveries for ophthalmic conditions and pharmacogenetics. 10,538 samples were available after QC.   + ‘Biology-driven Gene-Gene Interaction Analysis of Age-Related Cataract in the eMERGE Network’ was published in *Genetic Epidemiology*.   eMERGE-PCORnet Discussion - *Group*   * NHGRI asked the group to identify avenues for collaboration with PCORI. * There is real opportunity in leveraging patient-reported data along with EHR data to improve association analyses and understand population effects. Also to use this data combination to study intervention effectiveness. * eMERGE would focus on incorporating more on patient-reported data, not so much comparative effectiveness analysis. * Comparative analysis is slippery slope. We don’t know enough about whole genome vs. targeted yet to make that kind of comparison. An uninformed trial could damage the field. * PCORI funds methodology development, so eMERGE could perhaps co-fund a methodology development project through PCORI.   Central Phenotype Dataset Discussion - *Group*   * NHGRI inquired with the group as to whether there was utility in having a phenotype dataset for the Network. A large dbGaP set including the main study is already available, but only includes case/control status. The phenotype association study data would likely be needed as well, but it’s being submitted in a secondary round, and kept separately. * The CC will draft a dataset proposal to circulate to PIs for feedback.   **ACTION ITEM: The CC will draft a central phenotype dataset proposal to circulate to PIs.** |
| **Day 2: Half-day Session** |
| Return of Results Update – *Gail Jarvik & Iftikhar Kullo*   * The workgroup cites their work on GRS/variants for complex disease risk, phenotypic correlates of Variants of Unknown Significance, HFE variants, pathogenicity, penetrance, and actionability as accomplishments. Additionally, return of results linkage to CDS, interactions & collaborations with other groups (CERC, CSER, AIG), along with 13 eMERGE RoR abstracts presented at ASHG in 2014 and the CSER collaboration paper reflect the group’s productivity. * Reflecting eMERGE II’s emphasis on implementation, the flagship genomic medicine projects, ranging from genetic risk scores, SNPs, WGS, and to PGx have proved successful. * The process of returning actionable variants is not trivial. Both MyResults.org portal and the recently created return of results web resource have allowed for standardized collection across sites. CDS at point of care has also led to collaborations within eMERGE through discussions and tools. * The workgroup actively discussed the FDA regulation of genomic tests. Many eMERGE members endorsed comments submitted by Barbara Evans and Gail Jarvik. * In closing out eMERGE II, the workgroup has discussed two Network papers: 1. Site specific response to the high penetrance response and 2. Return of PGx variants across the Network. The workgroup also plans to complete Network wide projects (HFE penetrance, RoR in eMERGE PGx), leverage the EHR for variant annotation, link EHR-based RoR to CDS, assist ClinVar pathogenicity submissions, follow and respond to FDA regulation of genomic testing, and continue collaborations across NHGRI and other genomic programs, including interactions with CSER, INGNITE, and CLINGEN.   **ACTION ITEM: Members interested in leading the two proposed Network proposed RoR papers should contact Gail Jarvik & Iftikhar Kullo.**  Northwestern Site Update – *Rex Chisholm & Maureen Smith*   * Northwestern’s phenotype analysis focused on a lower GI case & control study flow, focusing on cases with colon polyps, diverticulitis, or diverticulosis. A natural language processing pipeline was developed and allowed generation of clinical quality metrics. * A chart review validation tool was created that allows data capture in a structured way, which eases the creation of training and validation data sets. Two other eMERGE sites are also using this tool and the related KNIME workflow. * A GWAS of diverticulosis showed near genome wide significance, using nearly 5,000 European American cases. A GWAS comparing African American diverticulosis v. diverticulitis was completed and shows an odds ratio of .36, which NU will follow up. NU colon polyp research found a 94% PPV for cases, 98% PPV for controls, looking at over 10,000 colonoscopies across 6 eMERGE sites. NU tried to find “gold” and “silver” standard caMRSA definitions in the EHR, but such proved difficult. The numbers were small, but the GWAS finding shows significant hits in the HLA region. * Fluomics project looks to return exomes to the eMERGE sites. The next step is sequence the remaining samples. * NU physicians decided they wanted all results and NU has worked closely with the physicians through an advisory committee. A patient advisory committee was also created to ease communication between the patient and physician. Genetic results are implemented into the EHR through an Ancillary Genomic System and there is a patient portal as well, so both groups are interacting with the data. * Return of Results: Genomic Medicine Project: 29 NU patients have received results (7 carriers – 6 HH, 1 PT) and all the results are in the EHR with BPA firing. They then compared CLIA results with GWAS for 19 participants and found a discordance for 2 participants who are heterozygous for PT mutation. PGx: 750 NU patients enrolled, pre & post studies were sent to all the patients, and so far, 450 patients received results. Results will continue to be returned over the next 5 weeks. * A shortened consent v. standard length consent study showed no statistical differences in objective or subjective comprehension.   Homozygous Deletions in eMERGE – *Joseph Glessner*   * A pipeline was established for copy number variant (CNV) calling, sample QC, association analysis, and further CNVR QC. * CNV calls were identified by PennCNV, which implements a hidden Markov model algorithm. Associations between CNVs and diseases/traits were identified by ParseCNV and PLINK. * A total of 560 homozygous deletion regions were identified, which may affect the gene structure. Of those, 146 were found in multiple individuals and 57 were significantly enriched for a broad category of phenotypes including autoimmune, cancers, cardiovascular, healthy and neurological diseases. * Harvey Weinberg Equilibrium and large CNV filtering are crucial extra quality controls for this data. Discussion after the presentation suggested using age as a co-variant.   Mount Sinai Site Report – *Erwin Bottinger*   * BioMe, Mount Sinai’s biobank, is ancestrally diverse. Notably, 40% of the white population is Ashkenazi Jewish, and the majority of Hispanic population is Caribbean. BioMe has allowed participation in nearly all major genetic consortia. Ashkenazi Jews in the biobank have the highest level of genome sharing, at 3%. Three different rare variants have been linked with the EHR. * CLIPMERGE platform interacts with EMR bio-directional and in real time, providing CDS to the physicians. * Mount Sinai has contributed over 40,000 cases and controls to eMERGE phenotype data. Mount Sinai phenotypes focused on kidney and liver (Columbia) diseases. * CKD: validated by Columbia and Marshfield. Combined reduced kidney function & CKD yielded over 20,000 instances. Analysis is underway using a population control instead of the standard case control. The development and validation of the CKD algorithm won the 2014 AMIA distinguished paper award. AKI: preparing algorithm development paper, but unable to do genetic analyses. * Mount Sinai has developed machine learning tools for advanced phenotyping to cluster longitudinal kidney data. They have also incorporated temporal EHR data in predictive models for risk stratification of renal function. * Return of Results: Genomic Medicine Projects: 3,700 patients enrolled in longitudinal protocols (including 663 eMERGE PGx). 512 total providers are enrolled, educated, and surveyed. GUARDD: 579 enrolled so far (out of 2,050 goal). GUARDD CDS activity is approaching 1,000 alerts. PGx: Close to 900 sequenced, 660 returned results, study is completed as of November 2015. There is a 74.4% acceptance rate of PGx projects at Mount Sinai. Incidental findings from PGRNSeq: Out of 663 individuals, 4 were found with known or likely pathogenic variants in ACMG genes. * Mount Sinai looks to continue their community and provider engagement through the building of large cohorts. They will continue genotyping sequencing Illumina MEGA array for all BioMe participants and look to whole genome sequence approximately 5,000 participants with two partners. The genomic medicine research in primary care and medical subspecialties will also continue.   Evolving Ancestry: The Shift in Individual Ancestry Composition over Time – *Tracy McGregor*   * The group evaluated ancestry informative markers and estimated proportions of racial ancestry with categorical race in a cohort of approximately 35,000 from BioVU, as recorded in the electronic health record. * In individuals born from 1905 – 2010, there is increasing admixture in the Hispanic-Latino, Asian, and White populations. Older Black populations were more admixed and now the population is slowly admixing again. * Individuals identified as White in the electronic health record have become more genetically admixed over time. The mean fractions of European ancestry have decreased from over 98% for all cohorts by decade of birth through the 1980’s to 95.7% and 90.0% for the cohorts born in the 2000’s and 2010’s, respectively. * Data indicate that younger cohorts of individuals exhibit higher levels of heterogeneity than older cohorts, particularly within those identified as White. There was also increasing heterozygosity over time, with more rapid increases in younger subjects, implying increasing rates of migration of alleles between racial groups over time.   Genomics Workgroup Update – *David Crosslin & Patrick Sleiman*   * The special issue of *Frontiers in Genetics* now has over 42,000 views. * The workgroup ongoing structural variation discovery projects include: RBC indices (Mayo), Global burden (Penn State), PheWAS (VU,GH/UW), PheWAS Pediatrics (CCHMC/BCH), WBC and differential (GH/UW), and Homozygous deletions (CHOP). * The following GWAS are completed: BMI-Obesity, Autism, Billrubin-LFT, Asthma, GERD, Atopic Dermatitis, Extreme Obesity, Ocular HTN, AMD, Glaucoma, VTE, Apolipoprotein L1 and HTN, Diabetic Hypertensive CKD, Diverticular disease, Shingles, ACE-I Cough, Statins for MACE * The workgroup is still trying to establish a concept sheet with ENCODE collaboration. The workgroup is also collaborating with Exome Chip project, which includes Geisinger, Mayo, and Group Health. * The workgroup is changing their focus from discovery to implementation as it looks to eMERGE III.   CHOP Site Report – *Hakon Hakonarson*   * All major pediatric and adult diseases are represented in the Center for Applied Genomics (CAG) biobank, including rare diseases; there are more than 70,000 children and 12,000+ adults. All participants consent to prospective genetic analyses. Children are re-consented when 18 years (>90% success). * Five phenotype algorithms were led at CHOP and CHOP has participated in multiple validations. Asthma severity was validated and near ready for publication. * 1,606 total PheWAS codes were translated in the phenotype table. Demographically, the numbers are comparable between European Americans and African Americans, with several years of follow up. * PheWAS on rs6967330: cases were defined as subjects with multiple hospitalizations for asthma exacerbations within 6 months between ages of 2–6. rs6967330 encodes an amino acid change in the CDHR3 protein. A recent study showed that the disease associated with a variant of the CDHR3 protein enhanced infection rates of rhinovirus C, which leads to asthma exacerbation. * Two genome wide significant loci were found in Asthma. There is a genome wide signal in African Americans with GERD, and CHOP is still pursuing this replication. Four genes replicated from the pediatric Atopic dermatitis dataset. Three SNPs reached genome wide significance in ADHD and have been replicated. * PGx: recruitment is completed with 1,650 children from CAG’s biorepository with well-documented drug related severe adverse events and EHR-based drug response profiles. Significant p-values were found in both analyses of African Americans and European Americans comparing severe asthma v. not severe. * Return of Results: 440 results were returned as of 6/26 and a projected 1,500 will be returned by 8/1/2015. Myresults.org was integrated into the EHR.   Early-onset, severe forms of ‘essential’ hypertension and major cardiovascular complications of hypertension are associated with Apolipoprotein L1 (APOL1) renal risk alleles in African Americans - *Girish N Nadkarni & Geneviève Galarneau*   * APOL1 gene variants associate with increased ranges of blood pressure (both systolic and diastolic) in younger African Americans (under age 40) independent of estimated glomerular filtration rate. * The combined cohort of 9,203 participants across eMERGE led to 1345/14.6% with *APOL1* risk status. * APOL1 risk allele is associated with 2.4 Years earlier diagnosis of hypertension. Higher blood pressures were found in 20-39 years. * 2 APOL1 risk alleles were also associated with a higher rate of left ventricular hypertrophy and hemorrhagic stroke, complications of hypertension. After preforming a logistic regression that adjusted for age, sex and BMI, there were significant odds ratios of 1.52 and 2.66 respectively. * The results may warrant a paradigm shift from a kidney-intrinsic to systemic vascular pathomechanism(s) for APOL1 risk alleles. The results may also have considerable public health implications for BP screening in young AA carrying APOL1 risk alleles.   Mayo Site Update – *Iftikhar Kullo*   * Mayo has implemented eight phenotypes and lists the following as phenotype highlights: harmonized phenotype data dictionaries across the consortium, aligned eMERGE with PhenX, and developed the eleMAP tool, open-source NLP resource cTAKES, and PhEMA. * Genomics: Performed the QC for the network wide high-density genotype dataset for dbGaP submission, completing the GWAS of VTE, HF, and CRF, activity in genetic risk score research, structural and null variant projects, PheWAS projects, and the ENCODE collaboration. Mayo looks to replicate findings in the African American VTE cohort, CF, and HF. * Return of Results: Mayo’s primary return of results work focused on the MIGENES clinical trial. The site was also involved in MyResults.org, the RoR instruments repository, manuscripts describing RoR activities in the Network, the PGx consent form, the RoR template for PGx actionable events, and larger contributions to Network wide projects, such as HFE. * The MIGENES trial illustrates the feasibility of incorporating genomic risk information for common disease into the EHR. A risk report was placed in the EHR and a decision aid tool was also embedded into the EHR. Disclosing of CHD led to lower LDL cholesterol levels and increased information seeking and sharing amongst the physicians and patients. * Mayo has participated in several CERC and CERC Survey committees, including co-chairing the IRB committee in CERC Survey. eMERGE members at Mayo have also led the patient and provider PGx education surveys and participated in CERC/CSER and CERC/RoR papers. * EHRI: Mayo shared their EHR-based genomic decision aid to facilitate shared decision making after the disclosure of CHD. They contributed to the development of the InfoButton resource for PGx CDS and shared their CDS logic for simvastatin, clopidogrel, and warfarin. * PGx: Mayo had rapid and efficient recruitment, their PGx consent form was widely adopted, and they sequenced 84 pharmacogenes in addition to conventional genotyping for CYP2D6 which enabled direct deposit of variants in the EHR with linkage to CDS. Mayo received a 10K project expansion. * CDS: From January 2013 – May 2015, 3,353 drug order alerts fired. The CDS is linked to education at Mayo in a service called AskMayoExpert.   Closing Remarks – *Rex Chisholm*   * Thanks to the Mount Sinai group and eMERGE Coordinating Center for their organizing efforts. * The work heard at the Steering Committee meeting reflects the amount of work and collegiality of eMERGE II. |
| **Summary of Action Items:**   1. The CC will draft a central phenotype dataset proposal to circulate to PIs. 2. Junior faculty interested in leading the two proposed Network proposed RoR papers should contact Gail Jarvik & Iftikhar Kullo. |
| **Next Meeting: September 17-18th, 2015; Bethesda, MD** |
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