eMERGE Network Steering Committee
January 23-24, 2014
Bethesda, MD

Attendance

Network Members in Attendance

CCHMC/BCH	Armand Antommaria
CCHMC/BCH	Beth Cobb
CCHMC/BCH	John Harley
CCHMC/BCH	Ingrid Holm
CCHMC/BCH	Zak Kohane
CCHMC/BCH	Todd Lingren
CCHMC/BCH	Melanie Myers
CCHMC/BCH	Bahram Namjou
CCHMC/BCH	Yizhao Ni
CCHMC/BCH	Cassandra Perry
CCHMC/BCH	Cindy Prows
CCHMC/BCH	Wendy Wolf
CHOP	Berta Almoguera
CHOP	John Connolly
CHOP	Hakon Hakonarson
CHOP	Michael Holmes
CHOP	Brendan Keating
CHOP	Frank Mentch
CHOP	Lyam Vazquez
Geisinger	David Carey
Geisinger	Helena Kuivaniemi
Geisinger/U. of Maryland	Casey Overby
Geisinger	Gerard Tromp
Geisinger	Janet Williams
Geisinger	Marc Williams
GH/U WA	Andrea Hartzler
GH/U WA	David Crosslin
GH/U WA	Gail Jarvik
Marsh/Essentia/PSU-CC	Gretta Armstrong
Marsh/Essentia/PSU	Murray Brilliant
Marsh/Essentia/PSU	Molly Hall
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	Chris Chute
Mayo	Iftikhar Kullo
Mayo	Jyoti Pathak
Mt. Sinai/Columbia	Erwin Bottinger
Mt. Sinai/Columbia	Wendy Chung
Mt. Sinai/Columbia	Steve Ellis
Mt. Sinai/Columbia	Alanna Gomez
Mt. Sinai/Columbia	Eimear Kenny
Mt. Sinai/Columbia	Ana Mejia
Mt. Sinai/Columbia	Aniwaa Owusu Obeng
Mt. Sinai/Columbia	Chunhua Weng
Mt. Sinai/Columbia	Saskia Sanderson
Northwestern	Rex Chisholm
Northwestern	Geoff Hayes
Northwestern	Abel Kho
Northwestern	Laura Rasmussen-Torvik
Northwestern	Maureen Smith
Northwestern	Justin Starren
NIH	Steven Benowitz
NIH	Adam Felsenfeld
NIH	Jean Jenkins
NIH	Rongling Li
NIH	Teri Manolio
NIH	Jackie Odgis
NIH	Laura Rodriguez
NIH	Murat Sincan
NIH	Simona Volpi
Vanderbilt-CC	Will Bush
Vanderbilt	Ellen Clayton
Vanderbilt-CC	Josh Denny
Vanderbilt	Nanibaa' Garrison
Vanderbilt	Jennifer Malinowski
Vanderbilt-CC	Brad Malin
Vanderbilt	Josh Peterson
Vanderbilt	Dan Roden
Vanderbilt-CC	Sarah Stallings
Vanderbilt	Sara Van Driest
CC	Melissa Basford
CC	Kyle Brothers
CC-Vanderbilt	Dana Crawford
CC	Paul Harris
CC	Lauren Melancon
CC	Martha Shrubsole
CC-PSU	John Wallace

Affiliate Members

Air Force	Ron Miller
Air Force	David Watson
Air Force	Catherine Witkop

Network Invitees and Guests

AAAS	Deborah Runkle
Case Western	Jonathan Haines
CIDR	Kim Doheny
CIDR	Elizabeth Pugh
CIDR	Jane Romm
U. of Minnesota	Susan Wolf

Thursday, January 23rd

Full Session

Welcome, Opening Remarks, General Updates –Rongling Li

Rongling welcomed members. Recent NHGRI staff changes were noted as was logistics of the January 21st NHGRI eMERGE Workshop – 16 attendees were able to attend in person, 70 remotely, online via GoToMeeting. The weather was only a small disruption and the Workshop succeeded in exploring the Network's future directions.

Goals for the Winter 2014 Steering Committee meeting are to:

- Provide updates on Network and Site-Specific achievements and projects
- Identify current obstacles and devise a plan to overcome them
- Summarize and discuss NHGRI Workshop feedback

Take aways from the meeting are to:

- Provide evidence to support an eMERGE renewal
- Refine the Network's future directions
- Update plans for disseminating lessons learned and research results

NHGRI/eMERGE Workshop Summary –Teri Manolio

Teri summarized the January 21st NHGRI eMERGE Workshop discussions and received feedback from the group.

Panel 1: Discovery vs Implementation – Participants agreed that the strengths of the Network lend themselves well to research, clinical implementation, and research *on* clinical implementation, but felt that the following expertise is still needed: quality improvement, clinical workflow, disseminating/implementing science. eMERGE is uniquely positioned to address penetrance, heritability and pathogenicity.

- Steering Committee members agree that there is ample opportunity to explore penetrance, heritability, and pathogenicity within both adult and pediatric populations.

Panel 2: EMR and Clinical Phenotyping –Participants discussed ideas for leveraging the unique nature of the EMR and methods for better convening with clinical leadership to find common ground for genomic medicine research. Participants also agreed that "modular" phenotypes (re-use of algorithm subcomponents) may speed up develop and facilitate transportability, although that field is immature. The principal of having comparable and standard components provides a framework to leverage modularity.

- Phenotyping is still an extremely important aspect of eMERGE; the data, especially from longitudinal phenotypes, allow the Network to forge ahead with discovery opportunities that do not exist in other consortia. eMERGE may also be positioned to measure genuine reproducibility of electronic phenotype/cohort identification. EHRs are also capturing more (patient reported outcomes, for example) which will allow for more opportunities for electronic phenotyping.

Panel 3: EMR and Genomic Discovery – eMERGE is well positioned to address the importance of rare, but collectively common variants and that the Network should consider developing an eMERGE-specific chip focused on loss of function variants. Alternative designs for discovery and ideas for expanding data collection processes were also discussed.

- Members commented that non-genetics consortia groups are adopting completed eMERGE phenotypes; tracking this type of adoption would be useful. The group agrees that future sequencing projects, particularly those involving rare variants, would incorporate both discovery and implementation components. In terms of choosing future projects, the Network needs to prioritize and choose areas of science to focus on (*e.g.* rare variants, copy number variants, etc.) and then secure the matching technologies needed.

Panel 4: Genomic Testing –Discussions focused on CLIA issues, standards for clinical lab reporting, consent for EMR deposit, and the process of re-interpretation and approach to re-contacting as potential research questions.

Panel 5: Consent, Education, and Governance – Participants discussed integrating family history into the EMR, assessing the impact of POC education, and facilitating interactions regarding ELSI research across multiple networks. Participants also agree that policy development may be needed for effective implementation of eMERGE findings and that the lifetime "persistence" of genomic data has unique policy implications.

- Members commented that there is an opportunity in eMERGE to address questions regarding access to and sharing of family history information that is collected in the EMR.

Panel 6: Return of Genomic Results –Participants felt that return of results is a key topic in relation to eMERGE's integrated infrastructure for empirical ELSI research. Future directions could include investigating highly penetrant variants, addressing the implications of return of results with regards to sequencing, examining the impact of return of results on relatives, and studying the impact of patients having access to genomic information.

- Members commented that the work of eMERGE I & II has not been guided by patient preferences. It would be useful to engage the patient community when determining future research questions, particularly in terms of return of results. eMERGE is positioned to contribute to determining and defining actionability, particularly regarding patient perspectives.

Panel 7: EMR Integration – Participants stressed the long-term value of returning results to patients. Discussions also focused on clinical decision support (CDS) education, versioning, and transportability. Clinical practice leaders should be included in discussions to ensure CDS integrates in their specific clinical workflows.

- Members commented that eMERGE is well-positioned to potentially collaborate with ClinGen on CDS versioning and transportability.

Panel 8: Genomic Medicine and Pediatrics –Discussions focused on the challenges of creating adult/pediatric phenotypes; adult sites should be encouraged to further adopt pediatric phenotypes. Participants pointed out that pediatrics is under-represented in genomics; the Network should consider more gene-environment (GxE) data collection in pediatrics.

Site Update: Mount Sinai – Erwin Bottinger

Erwin briefly reviewed demographics and statistics for Mount Sinai's CAP accredited biorepository (BioME) before providing an update on eMERGE projects. Phase II phenotypes include Drug-induced Liver Injury (DILI) and Diabetes/Hypertension-Associated Chronic Kidney Disease (CKD). They are also studying Longitudinal CKD Outcomes (*e.g.* CKD progression, CVD events). Of 300 PGx subjects with samples sequenced at CIDR, 192 biobank participants with potentially actionable variants have been re-contacted. Clinical sequencing for an additional 100 samples is underway. NYS CLIA validation is complete for CYP2C19, CYP2C9/VKORC1, and SLCO1B1 and the site has been compliant with all data requests by the Network.

Patient and physician interviews have been conducted for the APOL1 study. Patients were interviewed during the consenting process, return of results, and 30 days after results were returned. The interviewing process and summarized results for all three interviews were reviewed. Results from physician interviews show that most physicians were not familiar with genetic testing, but would feel comfortable ordering tests if they had adequate information about the benefits. Attitudes toward APOL1 testing were mixed – some were excited, others felt that the time commitment outweighs any benefits. Draft CDS scenarios for APOL1 and identified novel associations were reviewed. The conclusions from the study show a significant association between the APOL1 homozygous risk genotype and elevated blood pressure independent of eGFR and other cofounding variables. This was the first study to show an association between APOL1 and non-renal traits. Erwin proposed that the group consider implementing a Network-wide APOL1 program. The objectives and plans for the proposed study were reviewed.

GWAS of Venous Thromboembolism (VTE) in African-Americans from the eMERGE Network – Mariza de Andrade, Mayo Clinic

The objective of the study was to identify novel SNPs associated with VTE in African Americans using an EMR-driven phenotype algorithm that leverages both structured (ICD-9-CM codes) and unstructured (clinical notes) data. The study included 39,200 eMERGE samples with Affymetrix or Illumina genome-wide SNP data from across the adult sites; to maximize sample size and power, an imputation pipeline for merging the data across the different platforms was developed. In terms of analyses, associations between each SNP and VTE were tested using unconditional logistic regression. Mariza briefly reviewed the results of the study, including the genome-wide significant SNPs. The study concluded that unique genetic variation is associated with VTE in African Americans.

eMERGE PGx Plenary Session – Laura Rasmussen-Torvik, Justin Starren, Marylyn Ritchie, Josh Denny & Will Bush

As of January 2014, all sites are approved to enroll patients for return of results; enrollment should be complete by September 2015. All sites will deliver CDS to primary care physicians; some will also deliver to specialists, pharmacists, nurses, nurse practitioners and physician assistants. The majority of CDS events will be triggered by the system, rather than initiated by the clinician. Throughout the Network, 63% of CDS events will be activated within the medication entry section of the EMR, 11% within the patient summary/review. CDS intervention types will vary–the range includes: point of care alerts, order sets, specific dosing recommendations, references/educational guides, and patient-specific data displays. EHR integration for PGx is either complete or in process at all sites. Each site's current plan for discordant variants was reviewed.

A demonstration of the SPHINX website was presented. Participant demographic characteristics were reviewed. 31.2% of subjects in SPHINX have a medication listed in their record that is also listed in the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling; top medications are clopidogrel, warfarin, simvastatin, azathioprin, mercaptopurine, tacrolimus, and codeine. SPHINX contains data for variants associated with six ACMG genes. In terms of data QC, concordance checks will be performed on the 32 HapMap trios; each site running PGRN-seq will submit the trios to the CC. Concordance checks will be performed between research and clinical variant calling pipelines for sites that have both. In terms of analyses, PheWAS and MedWAS will be performed for common and binned rare variants by March 2014. Security considerations were also discussed. Based on a review led by Will Bush and Brad Malin at the CC, subjects in SPHINX's public variant repository are at a minimal risk and threat of re-identification. Possible, but extremely unlikely, attacks include 1) identifying a person's race given their DNA and 2) determining if an individual participated in the study given a highly penetrant, extremely rare phenotype involving one of the genes sequenced. Brad will continue to consult with SPHINX developers to maintain privacy protections for future versions of the public data.

Site Update: Marshfield/Essentia/Penn State – Murray Brilliant, Cathy McCarty & Marylyn Ritchie

Cathy reviewed the aims, methods, and preliminary results for the AMD pilot study at Essentia. Invitation letters were sent to 151 individuals – 101 have enrolled, 17 refused and 33 could not be reached. Participants have expressed overwhelming support for the project. The majority have a family history of AMD and most, even those with a low genetic risk, have made lifestyles changes upon receiving results.

Murray reviewed the group's progress implementing pharmacogenomics at Marshfield by detailing the PGx workflow system in place, from recruitment and enrollment to sequencing, return of results and EHR integration. The site's drug-gene pairs are: Simvastatin and SLCO1B1; Clopidogrel and CYP2C19; and Warfarin and CYP2C9, VKORC1.

Marylyn provided an update for gene-gene (GxG) and gene-environment (GxE) interactions. GxG analysis for cataracts was completed at Marshfield, replicated in eMERGE, and presented at ASHG in 2013. A concept sheet for GxG analysis in lipid traits and BMI will soon circulate. GxE analysis for cataracts was completed last year. GxE analyses for other phenotypes are in process, a new pipeline is under evaluation, and two GxE articles have recently been published.

Novel Population Genetic Approaches for Discovery in eMERGE – Eimear Kenney

Eimear outlined ways in which population genetics is useful. Population genetics can help to:

- Model neutral genetic forces
- Understand pre-historical demography
- Facilitate selection scans
- Interpret rare variant distribution
- Inform variant discovery for biomedical genetics and genomic medicine

The population structure of Mt. Sinai's biobank and lessons learned from large-scale sequencing studies were discussed:

- The vast majority of human genetic variation is rare.
- The rarer the variant, the more likely it is to be population and/or geographically restricted; globally rare variants can be common locally.
- Ascertainment of diverse populations and application of population genetics methods are needed.

Population genetic approaches for disease risk and loci discovery include leveraging local ancestry inference (LAI) and cryptic relatedness. LAI is computationally feasible and can be incorporated into an integrated framework for the next-generation of population aware GWAS. With finer resolution reference panels, better methods and data, sub-continental LAI should be possible. Identity by Descent (IBD), tuned to detect locally common and/or genetically drifted alleles, can capture recently arisen functional variation and reduce sequence and samples search space for fine mapping.

In conclusion, population genetic approaches for discovery represent a class of methods that exploit the 'genomic context' of variants. To effectively identify niches for discovery, these types of approaches should be coupled with genomic medicine expertise.

Friday, January 24th

Full Session

Air Force, Affiliate Site Update – Lt. Col. Catherine Witkop

An update on the Air Force's ongoing AFMS Personalized Medicine Program was provided. The vision of this program is to deliver state of the art evidence based on personalized medical care that incorporates emerging genomic data and the program mission is to develop a platform for the clinical implementation of genomic medicine across the AFMS. Anticipated impact includes:

- Development of clinical practice guidelines for the integration of genomics into patient care
- Improved patient outcomes and reduced heathcare costs
- Establishment of genomic education curricula
- Continued research to address knowledge gaps
- Creation and integration of clinical decision support tools
- Transition of a personalized health solution to the Defense Health Agency (DHA)

As the Air Force moves through its three planned phases of its Personalized Medicine Program, the emphasis on clinical implementation will increase, but they plan to always keep an aspect of their program focused on research. The Air Force has active partnerships with many different institutions who aid with the goal of managing and supporting research activities designed to facilitate the clinical integration of genomic-based medicine across the Air Force. Some of these institutions include: Johns Hopkins, the Coriell Institute, Duke University, USUHS, NHGRI, & eMERGE. Phase I (complete) and Phase II (in process) were discussed. Highlights from Phase I include:

- Collaboration with the Coriell Institute
- Recruited 2100 AFMS personnel from 19 military treatment facilities across the country for student enrollment
- To date, 1253 participants have activated an account and have been genotyped

Phase II will begin in FY 2014 with the plan to recruit 4000+ individuals with the hope of expanding the cohort to include beneficiaries and all Active Duty. Recruitment will be based around disease and the Air Force sees a possible collaboration with eMERGE beginning in Phase II.

Important components of the program were established in Phase I of the project that will aide with Phase II and the creation of the PC2 Digital Biobank. The objective of creating this biobank is to create a digital repository to store genomic and clinical information. While starting with the Air Force, the goal is to include all services. The digital biobank will: provide a resource for genomic researchers in the Air Force and their collaborators, save costs, and provide the Air Force with an initial test bed for methodologies and protocols for the security, storage and integration of genomic data. The Air Force continues to seek out collaborators to augment and provide external expertise, especially in the areas of transition to clinical implementation, clinical utility cohorts, and genomic discovery.

EHRI Workgroup Report – Justin Starren & Marc Williams

The EHRI workgroup updated the Steering Committee on site progress; almost all sites have completed their EHR Integration. One main project of the EHRI group is the Infobutton project. All sites are engaged in this project to some degree and the primary objectives are:

- To develop a new information resource based on eMERGE II & PGx scenarios. To date, scenarios include: carbamazepine, clopidogrel, simvastatin, thiopurine, & warfarin
- Implement infobuttons within EHRs at eMERGE sites

Progress is being made on both of these objectives and a concept sheet, targeted for AMIA submission, on "Establishing a genomic medicine content collection process: progress with the eMERGE Network" is being created and will be circulated shortly.

The EHRI workgroup has multiple ongoing collaborations, the most notable being the CSER/EHRI collaboration. These two groups are currently working to create a white paper, "What goes where", that will categorize different types/uses of genomic data for incorporation into the EHR, survey current practices, and provide recommendations for future consistent placement. The groups are jointly working on a list of candidate categories and candidate axes that will be refined as the process continues.

In response to the NHGRI eMERGE Workshop, the workgroup discussed how EHR implementation would take form in an eMERGE Phase III. Clayton's Implementation stages were reviewed and the group was reminded that most sites were in the very early stages of implementation. EMR integration for eMERGE Phase III could look like the following:

- Providing CDS education using Open InfoButton standards permits implementation in "any" EMR
- Genomic CDS requires reinterpretation, revision and maintenance of both variants and clinical actions, distinguished it from non-genomic CDS
- Promote and assess CDS scalability and transportability
- Bring clinical practice leaders into fold to ensure CDS integrates in their specific clinical workflows

Return of Results Workgroup Report – Gail Jarvik & Iftikhar Kullo

A manuscript is being written jointly with eMERGE and CSER that will address the topic of findings that should be returned in research, "Research RoR of genomic findings". This manuscript was motivated by the increase of genomics in research and by the recent ACMG clinical recommendations. This manuscript will outline research ROR principles, research ROR recommendations, and remaining controversies/opportunities for research.

The group continues to work on Hemochromatosis Penetrance. The chart abstraction form has been applied and most data has been sent to the University of Washington. The next steps are finalizing the database and cleaning the submitted data. HFE genotype counts after imputation were shared with the group and the number of actionable, pathogenic incidental findings in 6500 people's exomes include:

- African Ancestry – 2,203
- European Ancestry – 4,113
- Ashkenazi Jewish Ancestry – 187

Individuals were screened for variants in a list of 120 genes associated with medically actionable genetic conditions which may be undiagnosed in adults. A paper will be written upon the completion of the project and data will be submitted to Clinvar.

In response to the NHGRI workshop future directions were discussed. The group believed that many of the suggestions for eMERGE Phase III were achievable and provided examples of how each element would be addressed. In addition to the items outlined at the workshop the group suggested the following as possible future efforts:

- Patient portals and return of results

- Consent in the setting of EMR
- Return of Results as it impacts family members
- Location of information in the EMR
- Persistence of genetic data
- Choice of patients
- Stakeholder input

Presidential Commission Report on Incidental Findings Panel– Susan Wolf, Gail Jarvik, Ellen Clayton, & Ingrid Holm

Susan Wolf provided the group with a general overview of the report that was issued on December 5th, 2013. The Presidential Commission for the Study of Bioethical Issues was composed of 11 members and provided 17 recommendations: general recommendations, clinical, research, and DTC. Susan continued by defining some of the commission's taxonomy and reviewing recommendations of interest/items that left room for discussion. Considerations for eMERGE:

- Recommendations are dichotomized – don't address translational process between research & clinical care
- Don't address what goes in the EHR
- Don't systematically analyze of role of biorepositories
- Do consolidate the importance of the debate on return of results /incidental findings
- Do offer a different analysis than ACMG 2013 on Ifs
- Do urge more funded research & scholarship

Ethical Issues in Anticipate and Communicate – Ellen Clayton

Ellen believed that some recommendations from the commission were correct, including:

- It is critical to inform patients and research participants about what findings to expect and not to expect
- It is important to consider the downstream impact of reporting additional findings in assessing value
- No duty to hunt

Even though the topics listed above were well addressed by the commission, other topics were not as well addressed or caused concern. Most errors in the process had to do with the rights and responsibilities of professional organizations. Another area that is concerning is that a patient's wishes concerning their results do not have to be heeded. If patients do not want additional testing, "the clinician can ethically perform the testing but refrain from disclosure to the patient" and "within certain limitations, clinicians could, on ethical ground, decline to perform the test and elect to refer the patient elsewhere." These two statements, along with others, give physicians broad discretion to decide what tests to do and which results to report. Researchers & Investigators have also been given the ability to override participants' wishes. In conclusion, the commission bowed in the direction of patient and participant choice, but undermined it with too much vague deference to professionals without justification.

A Medical Perspective on the Presidential Commission Study: ANTICIPATE and COMMUNICATE Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts – Gail Jarvik

Gail highlighted some of the main points of contention with the report and commented on specific recommendations. Conversations with patients concerning their test results are time consuming and the question as to if doctors are truly qualified to inform patients is cause for concern. Recommendations 2 and 17 address professional groups but many professional groups have

inadequate expertise and have processes that are closed, affected by politics, and are driven by a few individuals. Professional groups are also not funded to set guidelines on matters of diagnostic modality. Recommendation 6 addresses the issue of incidental and secondary findings. Gail suggested the following in response to alerting patients of incidental findings:

- Clinicians should alert patients to the possibility of discovering incidental findings, and any secondary findings that will be actively sought, *before* testing occurs so that patients have the opportunity to express preferences regarding their disclosure and subsequent management.
- Clinicians should give patients enough information so that they comprehend their options, and should also protect patients from unnecessary anxiety produced by misunderstood communication of risk.

Malpractice as it is associated with incidental findings and respect for persons was also addressed. A recent study concluded that it is possible that clinicians could face liability for failure to identify or appreciate the significance of an incidental finding, if the recognition and disclosure would have prevented or altered the course of future disease but it is also stated that the autonomous patient also has the right not to know selected information and should be able to exercise this right. In response – within certain limitations, clinicians could, on ethical grounds, decline to perform the test and elect to refer the patient elsewhere. Alternatively, clinicians can ethically agree to perform the test but not return any incidental findings or secondary findings. The commission misses the option for the lab to not run the test, and ignores patient portals. Clinicians should clearly convey possible outcomes to patients and payment systems should not disincentivize clinicians from taking sufficient time with patients. CLIA was brought up as there is currently a disagreement about whether research findings discovered in non-CLIA-certified labs can be returned.

Presidential Commission Report on Incidental Findings: What did they say about incidental findings in minors? – Ingrid Holm

Minors were not specifically addressed in the report. The words "pediatric", "child" "children", or "minor" do not appear in the body of the document, however, "family", is addressed in one paragraph. The primary controversies in pediatrics with regard to incidental/secondary findings are: genes associated with adult-onset diseases, non-actionable findings, and revisiting return of results at age of maturity. In pediatrics there is also the ever evolving capacity, of the patient, to make decisions. With respect to the phases "respect a patient's preference not to know" and "participants might opt out of receiving certain types of findings", pediatrics have limitations on what a parent has the right to know and not know about their child. Parents are not able to infringe on a child's future right to decide to know or not. Also, the best interests of the child overrides the parents autonomy to not know, parents refusing to received results of life threatening treatable conditions is considered child abuse or neglects, and it is the clinician/researcher's duty to act in the best interest of the child. The report lacks guidance on how to balance the best interest of the child and parental autonomy.

Pediatric Workgroup Report – John Harley & Hakon Hakonarson

The workgroup discussed their thoughts on the role of pediatrics in an eMERGE Phase III. The main notes from the workshop were discussed and the group highlighted a few topics of interest.

- Incongruity in pediatric vs adult phenotypes
    - There are hundreds of traits that are longitudinal and apply to both pediatric and adult related medical traits, including: disease traits, hematologic/chem panel traits, neurocognitive/psychiatric traits, quantitative traits
    - In contrast there are unique traits for both pediatric and adults. An example being Alzheimer's vs. language/motor development

    - The group agrees that it would be beneficial for adult and pediatric sites to collaborate
- Is eMERGE's pediatric component large enough?
    - "Nothing is ever large enough"
    - Two approaches were suggested to increase the pediatric component:
        - Induct additional pediatric sites into the Network
        - Do additional work at current pediatric sites and activate more adults sites
- Encourage adult sites to come even more towards pediatrics
    - Some adult sites have a large number of pediatric samples that could be genotyped and included
    - A custom-based GWAS chip has previously been discussed and may be attractive for the group
- Children with adult diseases early in life likely have high genetic load and vice versa
    - This has been seen across multiple pediatric diseases that affect both children and adults
- Pediatrics under-represented in genomics, consider more Gene x Environment data collection in children
    - This is important to consider but power is needed. GeoCoding and capturing environmental information could be done at existing pediatric sites
- Relate eMERGE and Newborn Screening projects
    - Kansas, Boston, Duke, UCSF and others can be contacted to collaborate on this. There are also opportunities to integrate with Rare Disease programs and RoR.
- Targeting conditions for genomic analysis with early clinical utility in children is already an active focus at pediatric sites but could be expanded.

The pediatric workgroup plans to continue to discuss these topics on their monthly pediatric workgroup calls to assign various tasks to pediatric members for implementation.

Consent, Education, Regulation, & Consultation (CERC) Workgroup Report – Ingrid Holm & Maureen Smith

The group reviewed their ongoing efforts, including:

- Patient Website – myresults.org
- Pediatric Biobank Consent
- PGx Consent Paper

In addition to the projects listed, the group is working on the CERC survey supplement. Tasks for the supplement have been divided among workgroups and all timelines are moving forward on schedule. The primary objective of this study is: *To better understand the factors that influence patients' willingness to give broad consent for their samples and information to be stored in biobanks and used for multiple types of research.* The group anticipates that their findings will be valuable to researchers designing biobanks in the future. The group shared their thoughts on defining influencers, questions, and domains that will ultimately lead to a primary outcome – the willingness to give broad consent. Future actions include:

- Assess impact of POC education
- Integrate PGx into the EMR
- Study local differences across IRBs including differences in knowledge, approaches to remedy
- Facilitate interactions of ELSI research components across multiple networks
- Little work in legal (CLIA, HIPPA, liability, regulatory) or economic issues, engaging payers as stakeholders

- Policy development may be needed for effective implementation of eMERGE findings
- Potential lifetime "persistence" of genomic data has unique policy implications
- Pragmatic consent – brochures, short forms, web based
- ELSI issues relevant to changing EMR infrastructures

The CERC and RoR workgroup continue their collaboration with a bi-monthly workgroup call.

Environment-Wide Association Study (EWAS) for Type 2 Diabetes in the Marshfield Personalized Research Project Biobank – Molly Hall

The EWAS approach tests a variety of environmental variables in a high-throughput manner for association with phenotypes. These environmental variables can range from diet to smoking to UV exposure. The PhenX Toolkit, the Dietary History Questionnaire, and the Baecke Activity Index were all used to create a logistic regression that expressed 314 exposures and T2D. The PLATO (Platform for the Analysis, Translation, and Organization of large-scale data) was utilized to identify the top EWAS results for Type 2 Diabetes. These top results fell into the following categories: alcohol use, smoking exposure, diet, activity, residence, mental health, and UV exposure. The next step was to seek replication for variables in NHANES that fell into the listed categories. Numerous associations previously found in the literature between T2D status and decreased monthly alcohol use, increased smoking exposure, and decreased activity level replicated. The replication of these results demonstrates the utility of this method to identify environmental factors associated with disease in a high-throughput manner using survey data. Molly explained that future work will include incorporating exposure-exposure interaction analysis to the EWAS method in multiple phenotypes to identify novel exposures related to disease. It is believed that these methods can be applied to a diverse set of phenotypes, which will help elucidate complex mechanisms of common traits and can be used to identify putative exposures for novel gene-environment interactions.

Phenotyping Workgroup Report – Josh Denny & Peggy Peissig

The workgroup began by updating the steering committee on phenotype progress to date. Thirteen phenotypes have been completed by the group, 9 are anticipated to be complete in the 1st quarter of 2014 and 5 are in development. Most phenotypes have been performing well across the network.

The phenotyping workgroup addressed the future directions of phenotyping as discussed during the eMERGE Workshop. The phenotype workgroup agreed that the following three items listed at the workshop were foci that could be further explored by the phenotyping group:

- "Modular" phenotypes
- A focus on methods, standards, and ability to scale
- Leverage unique nature of EMR: phenomic approaches; longitudinal, rare, detailed, PGx phenotypes; pleiotrophy

Other areas the group believes would be beneficial to a future eMERGE Phenotyping efforts include:

- Additional phenotypes focusing on evaluating subjects that are at risk earlier than the general population
- Still focus on common phenotypes; ex. BPH, appendicitis
- Test eMERGE phenotypes at other health care entities to determine appropriate use cases
- Explore a federated data model

The group gave a brief update on the Record Counter and SPHINX. Three phenotyping workgroup members (Jyoti Pathak, Abel Kho, & Josh Denny) served as editors for a recent JAMIA Special Phenotyping Issue that included about 20 articles. Next steps for the phenotyping workgroup

include working to extend PheKB to become a data repository with data validation tools and computable data dictionaries. The group continues to work on resistant hypertension and reviewed the most recent case report with PPVs. Some sites are manually curating their results due to algorithm implementation issues while others have had trouble extracting the necessary components from the EMR.

Genomics Workgroup Report – Dana Crawford, David Crosslin, & Marylyn Ritchie

The workgroup is working on a variety of projects, those highlighted include:

- Null Variants
- PGx Analysis
- Structural Variation
- Frontiers in Genetics

The Null Variants Project is being led by Dana Crawford and Gerard Tromp. The eMERGE I/II merged sample size is large and the number of null variants is expected to have low MAF. The group still has many questions concerning how many null variants will be identified but is taking a brute force approach to annotation in an effort of identify "all" null variants in the eMERGE dataset. The data has already been run on SnpEff and the group plans to run additional platforms in the coming weeks including: ANNOVAR, SeattleSeq, GEMINI, HGMD.

The group shared a list of genes from Clinical Pharmacogenetic Implementation Consortium that the Network may want to consider incorporating in SPHINX.

David Crosslin at the University of Washington has been looking at structural variation in the eMERGE I dataset and presented his current findings. This is an effort that could be run on Phase II & potential Phase III data.

Most manuscripts have been submitted for the Frontiers in Genetics special issue. The last few pending papers should be finalized and submitted shortly.

Coordinating Center Update – Dana Crawford & Paul Harris

Dana Crawford and Paul Harris were introduced as the new eMERGE Coordinating Center PIs. Paul, who is new to the Network, has a background in clinical research and biomedical informatics. His interests are systems design and implementation, measurement and analysis, evaluation, technology dissemination models, and consortium organization and operations. The mission of the Coordinating Center is to 1) support the ongoing goals and Network projects related to eMERGE II and 2) assist the Network in evolving to meet the goals and projects outlined for eMERGE III. Keeping to this mission, examples of possible new Coordinating Center initiatives were proposed. These include:

- A Global Asset Review to identify dissemination and connection opportunities outside of eMERGE. The focus will be to maximize awareness and impact of eMERGE science and tools.
- Leveraging Vanderbilt's relevant efforts and increasing engagement with the CDSC to identify collaborative opportunities between the CDSC and eMERGE.
- Increasing the capacity of REDCap to best serve the needs of eMERGE investigators.

Along with these examples of possible new initiatives, several Vanderbilt-related resources were also reviewed, including ResearchMatch and IRBShare.