emerge network
ELECTRONIC MEDICAL RECORDS & GENOMICS

External Scientific Panel

Background Materials

April 17, 2017

BCM Baylor College of Medicine
BROAD INSTITUTE
Cincinnati Children's Hospital Medical Center
The Children's Hospital of Philadelphia
COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
GEISINGER HEALTH SYSTEM
HARVARD UNIVERSITY
KAISER PERMANENTE
MAYO CLINIC
MEHARRY MEDICAL COLLEGE
Northwestern Medicine
PARTNERS HEALTHCARE
VANDERBILT UNIVERSITY MEDICAL CENTER
UW Medicine UNIVERSITY OF WASHINGTON MEDICAL CENTER

National Human Genome Research Institute

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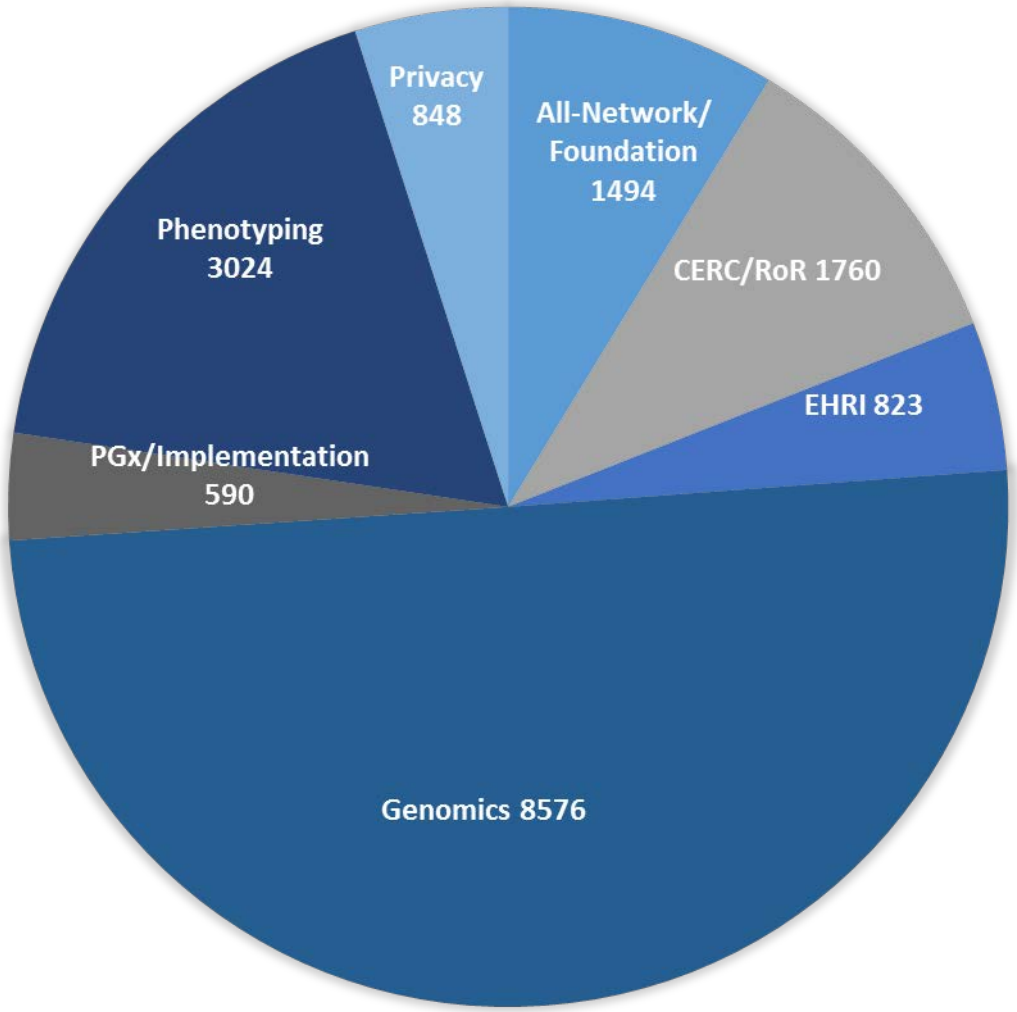
*e*MERGE CITATION ANAYLSIS

Citations of eMERGE Publications by Category

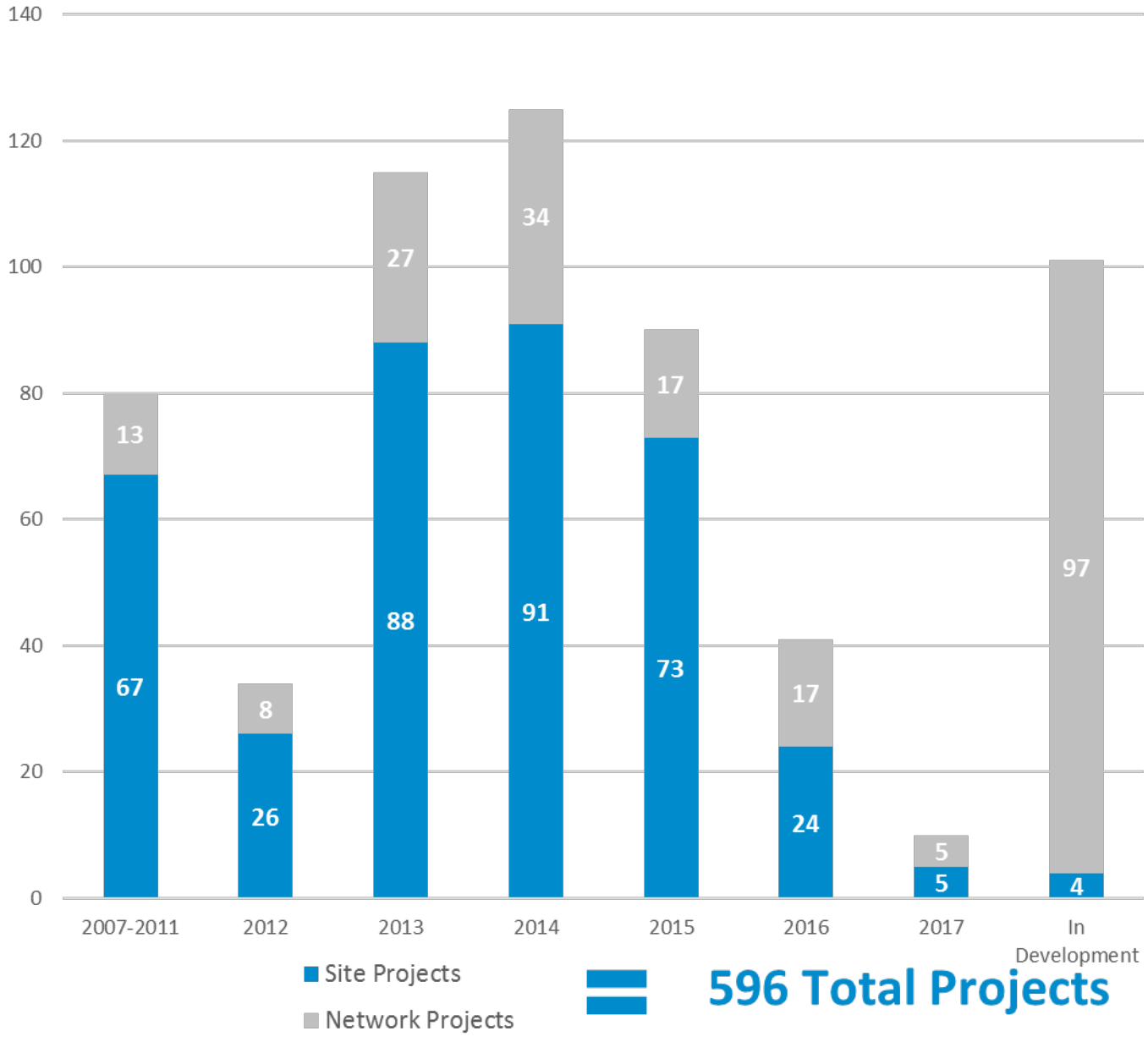


Cumulative Citation Count

2007 – March 2017: 17,115

*e*MERGE PUBLICATIONS

Number of Published Projects through March 2017



*e*MERGE PUBLICATIONS

from October 2016 – April 2017

Digital Reference Library Available Here

Published/Accepted and Submitted Network Manuscripts

1. Mosley J, Denny J, Roden D, Bastarache L, Van Driest S et al. Characterizing the individual and shared genetic components of pheWAS phenotypes. (Submitted)
2. Ritchie M, Holzinger E, Verma S, Farrall M, Drenos F et al. *Discovery and replication of genetic interactions for quantitative lipid traits.* (Submitted)
3. Peissig P, Schwei K, Kadolph C, Finamore J, McCarty C et al. *Development of a dynamic XML event-driven ophthalmologic data capture framework.* (Submitted)
4. Edwards T, Torstenson ES, Gilbertson J, Tsosie K, Giri A et al. *MVtest: a method to flexibly model the genetic determinants of trait variability* (Submitted)
5. Lingren T, Thaker V, Lingren T, Kennebeck S, Namjou B et al. *Pediatric Providers are Poor at Identifying Severe Obesity in Young Children at Two Tertiary Pediatric Medical Centers.* (Accepted)
6. Heit JA, Armasu SM, McCauley BM, Kullo IJ, Sicotte H, et al. *Identification of unique venous thromboembolism-susceptibility variants in African-Americans*. Thromb Haemost. 2017 Feb 16; PMID: 28203683
7. Sanderson SC, Brothers KB, Mercaldo ND, Clayton EW, Antommaria AHM, et al. *Public Attitudes toward Consent and Data Sharing in Biobank Research: A Large Multi-site Experimental Survey in the US*. Am J Hum Genet. 2017 Feb 4; PMID: 28190457
8. Wan Z, Vorobeychik Y, Xia W, Clayton EW, Kantarcioglu M, et al. *Expanding Access to Large-Scale Genomic Data While Promoting Privacy: A Game Theoretic Approach.* Am J Hum Genet. 2017 Jan 2; PMID: 28065469
9. Dumitrescu L, Ritchie MD, Denny JC, El Rouby NM, McDonough CW, et al. *Genome-wide study of resistant hypertension identified from electronic health records.* PLoS ONE. 2017;12(2):e0171745. PMID: 28222112
10. Jones GT, Tromp G, Kuivaniemi H, Gretarsdottir S, Baas AF, et al. *Meta-Analysis of Genome-Wide Association Studies for Abdominal Aortic Aneurysm Identifies Four New Disease-Specific Risk Loci.* Circ Res. 2016 Nov 29; PMID: 27899403
11. Schmidt AF, Swerdlow DI, Holmes MV, Patel RS, Fairhurst-Hunter Z, et al. *PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study*. Lancet Diabetes Endocrinol. 2016 Nov 28; PMID: 27908689
12. Smith ME, Sanderson SC, Brothers KB, Myers MF, McCormick J, et al. *Conducting a large, multi-site survey about patients' views on broad consent: challenges and solutions.* BMC Med Res Methodol. 2016 Nov 24;16(1):162. PMID: 27881091
13. Jackson KL, Mbagwu M, Pacheco JA, Baldridge AS, Viox DJ, et al. *Performance of an electronic health record-based phenotype algorithm to identify community associated methicillin-resistant Staphylococcus aureus cases and controls for genetic association studies.* BMC Infect Dis. 2016 Nov 17;16(1):684. PMID: 27855652
14. Mosley JD, Van Driest SL, Wells QS, Shaffer CM, Edwards TL, et al. *Defining a Contemporary Ischemic Heart Disease Genetic Risk Profile using Historical Data.* Circ Cardiovasc Genet. 2016 Oct 25; PMID: 27780847

In-Process Network Manuscripts

1. Characterizing the costs of implementing genomic clinical decision support. Lead Investigator: Patrick Mathias (UW/KPW)
2. The relative impact of environmental and genetic factors on phenotypic expression of disease. Lead Investigator: Kathryn Jackson (NU)
3. EHR Phenotyping of Atopic Dermatitis in Adults using more detailed data including from NLP. Lead Investigator: Erin Gustafson (NU)
4. Machine learning-based discovery of Atopic Dermatitis (AD) Sub-Populations in Adults. Lead Investigator: Alona Furmanchuk (NU)
5. Infobutton Genomic Medicine Initiatives Survey. Lead Investigator: Casey Overby (Geisinger/JHU)
6. A phenome-wide association study to discover pleiotropic effects of lipid metabolism genes (LDLR, APOB, PCSK9, and LPA). Lead Investigator: Maya Safarova (Mayo)
7. The Genetic Architecture of Auto-Inflammatory and Auto-Immune Diseases. Lead Investigator: Patrick Sleiman (CHOP)

8. Identifying relationship between obesity and post-operative complications through Mendelian randomization. Lead Investigator: Tom Mou (VUMC)
9. 22Q11.2 Deletion Syndrome, Leveraging Copy Number Variation to Examine Health Outcomes. Lead Investigation: Patrick Sleiman (CHOP)
10. New approaches to the genetic basis of developmental language disorder. Lead Investigator: Reyna Gordon (VUMC)
11. CNV Association of quantitative and discreet traits across eMERGE-II/III array and PGRNSeq datasets. Lead Investigator: Joseph Glessner (Harvard)
12. Outcomes in Asthma Patients Treated in Accordance with NHLBI Guidelines. Lead Investigator: Nikita Sood (CHOP)
13. Identifying clinical phenotypes associated with serum protein and metabolite levels. Lead Investigator: Jonathan Mosley (VUMC)
14. Decentralized and HIPPA Compliant Geocoding to Characterize Community and Environmental Exposures for Multi-Site Studies. Lead Investigator: Cole Brokamp
15. A genetic association study of benign prostatic hyperplasia (BPH) in the eMERGE network. Lead Investigator: Todd Edwards.
16. Incidental and secondary Findings (IFs) in 10,000 eMERGE participants. Lead Investigator: Adam Gordon (UW/KPW)
17. Genetic Determinants of Statin Response in African Americans. Lead Investigator: Qiping Feng (VUMC)
18. GWAS of MACE while on statin. Lead Investigator: Wei-Qi Wei (VUMC)
19. AutoImmuneMERGE - PheWAS for major Auto-Immune Diseases, whole genome sequencing. Lead Investigator: Rachel Knevel (Harvard)
20. Lipid distribution in Pediatric population. Lead Investigator: Agnes Sundaresan (Geisinger)
21. Pulm_eMERGE" Common and rare variant association of asthma using the network-wide eMERGE 3 cohort. Lead Investigator: Jessica Lasky-Su (Harvard)
22. NLP algorithm development and GWAS study for Eosinophilic Esophagitis (EoE) using eMERGE subjects. Lead Investigator: Bahram Namjou
23. A Machine Learning Approach to EHR Phenotyping of (Migraine & other) Headaches in Adults. Lead Investigator: Jennifer Pacheco (NU)
24. Applying a structured curation process to determine a minimal consensus set of actionable genes and variants for universal use on diverse biobank cohorts. Lead Investigator: Hana Zouk (Partners/Broad)
25. Linking biomarkers to clinical phenotypes based on underlying genetic risk. Lead Author: Jonathan Mosley (VUMC)
26. Common and rare variation associated with headache in eMERGE 3. Lead Investigator: Laura Rasmussen Torvik (NU)
27. Common and rare variation associated with valvular disease in eMERGE 3. Lead Investigator: Laura Rasmussen Torvik (NU)
28. MEdicine Gene Annotation (MEGA): A REDCap based tool to support consensus variant interpretation. Lead Investigator: Wayne Liang (GHC/UW)
29. PheWAS for functional variants in the complement system. Lead Investigator: Krzysztof Kiryluk (Columbia)
30. Genomics of structural kidney and urinary tract defects. Lead Investigator: Miguel Verbitsky (Columbia)
31. PsycheMERGE. Lead Investigator: Jordan Smoller (Harvard)
32. Establishing Electronic Genetic Report Flow Within the eMERGE Network to Enable Genomic Clinical Decision Support. Lead Investigator: Samuel Aronson (Partners/Broad)
33. Linking 25,000 eMERGE participants with highly-accurate imputed HLA regions to electronic health records. Lead Investigator: David Crosslin (GHC/UW)
34. PhEMA phenotyping authoring tool validation with eMERGE BPH case algorithm as use/test case. Lead Investigator: Jen Pacheco (NU)
35. Broad consent and data sharing in biobank research: An eMERGE Network Study of Parent Perspectives . Lead Investigator: Armand Antommaria (CCHMC)
36. A Phenome-wide Survey of the Phenotypic Effects of High- Frequency Human-Derived Alleles. Lead Investigator: Corrine Simonti (VUMC)and Tony Capra (VUMC)
37. Pharmacogenetic variation identified via targeted next-generation sequencing among 9000 eMERGE subjects. Lead Investigator: Adam Gordon (GHC/UW)
38. Comprehensive genetic association study of kidney traits across the EMERGE network. Lead Investigator: Krzysztof Kiryluk (Columbia)
39. Detection of copy number variants (CNVs) and their kidney disease associations across the EMERGE network. Lead Investigator: Miguel Verbitsky (Columbia)
40. Combined GWAS-PheWAS Approach to Serologic Markers of Autoimmunity & Inflammation. Lead Investigator: Krzysztof Kiryluk (Columbia)
41. Knowledge driven rare variant PheWAS in eMERGE to identify regions associated with disease using collapsing based approach. Lead Investigator: Anna O Basile (Geisinger)
42. GWAS study on non-alcoholic fatty liver disease (NAFLD) in pediatric and adult population: comparison of size effect between adult and children using participants of the eMERGE Network. Lead Author: Bahram Namjou (CCHMC)

43. The identification and reporting of actionable incidental genetic variants from large scale clinical sequencing of drug response genes. Lead Investigator Quinn Wells (VUMC)
44. Feasibility of using geocoded US Census/ACS variables as proxy for socioeconomic status in genotype-phenotype interaction studies of T2DM and obesity. Lead Investigator: Kathryn Jackson (NU)
45. A targeted sampling scheme utilizing both EHR and census information. Lead Investigator: Nate Mercaldo (VUMC)
46. The eMERGE Network: Healthcare provider education to support genomic medicine in practice. Lead Investigator: Carolyn Vitek (Mayo)
47. An investigation into the genetics of Intractable Epilepsy in the pediatric population. Lead Investigator: Berta Castillo (CHOP)
48. The identification of adverse events in the eMERGE PGx cohort using the electronic health record, and assessing association with genetic variation in the 84 pharmacogenes. Lead Investigator: David Crosslin (GHC/UW)
49. Agreement between research-grade sequencing and CLIA validation genotyping in eMERGE-PGx. Lead Investigator: Laura R Torvik (NU)
50. The eMERGE Network: The practice of patient education in the return of genomic medicine results. Lead Investigator: Cassandra Perry (CCHMC/BCH)
51. An investigation of somatic mutations in PGx-eMERGE dataset. Lead Investigator Kenneth Kaufman (CCHMC)
52. A phenome-wide association study to discover pleiotropic effects of PCSK9. Lead Investigator: Maya Saforova (Mayo)
53. Clinical Decision Support for Pharmacogenomics – Results from the eMERGE Network. Lead Investigator: Tim Herr
54. Multi-site IRB review – experience of the eMERGE Network. Lead Investigator: Jen McCormick (Mayo)
55. Quantitative and discreet trait analysis across eMERGE-II phenotypes. Lead Investigator: Joseph Glessner (Harvard)
56. Quantitative and discreet trait analysis across eMERGE-I phenotypes. Lead Investigator: Joseph Glessner (Harvard)
57. Investigation of CETP SNPs with LDL-C, BMI and risk of T2D. Lead Investigator: Brendan Keating (CHOP)
58. Cognitive Interviews associated with developing a national survey on consent across a national network of genomic medicine sites. Lead Investigator: Melanie Myers (CCHMC)
59. A Review of U.S. Individuals' Perspectives on Governance and Consent in Biobanking. Lead Investigator: Nanibaa' Garrison
60. A Highly Accurate Electronic Algorithm for the Classification of Asthma Severity in Children. Lead Investigator: Eric Hysinger (CHOP)
61. Exploring the genetic architecture of Age-Related Macular Degeneration (AMD) in the eMERGE network. Lead Investigator: Molly Hall (Marshfield/PSU)
62. Genome-wide Association Study of Gastroesophageal Reflux Disease (GERD) in Adult and Pediatric Populations. Lead Investigator: Patrick Sleiman (CHOP)
63. Genome-wide Association Study of Atopic Dermatitis in Adult and Pediatric Populations. Lead Investigator: Berta Almoguera (CHOP)
64. Genome-wide Association Study of Attention Deficit Hyperactivity Disorder (ADHD). Lead Investigator: Berta Almoguera (CHOP)
65. Locus-specific PheWas study: An investigation of size effect of IRF5 and STAT4 in various autoimmune diseases and other phenotypes in all available samples in eMERGE. Lead Investigator: Bahram Namjou (CCHMC)
66. Phenotype transportability across Electronic Health Records. Lead Investigator: Joshua Denny (VUMC)
67. The COGENT consortium meta-analysis of blood pressure African ancestry cohorts. Lead Investigator: Digna Velez Edwards (VUMC)
68. Using PheWAS to assess disease comorbidity and potential pleiotropy of genetic risk scores for rheumatoid arthritis. Lead Investigator: Robert Carroll (VUMC)
69. Association of Variation in 84 Pharmacogenes with Low-density Lipoprotein Cholesterol Levels in the eMERGE-PGx Project Lead Investigators: Daniel Kim (Michigan), Erin Austin (Mayo)
70. PGRNseq and GWAS predictors of Methylphenidate (MPH) response. Lead Investigator: Tanya Froelich (CCHMC)
71. Discovery, Replication and Clinical Associations of Pathway-Based Trans-eQTL. Lead Investigator: Laura Wiley (VUMC)
72. Multiscale Analysis Of Influenza Host-Pathogen Interactions: Fluomics. Lead Investigator: Ellie Sang Sukerman (NU)
73. Rare RYR1, CACNA1S variant annotation, exposure history, observed phenotypes in cases and controls. Lead Investigator: Senthilkumar Sadhasivam (CCHMC)
74. Examining gene variants in eMERGE samples for association with uterine fibroids. Lead Investigator: Todd Edwards (VUMC)
75. Association of APOL1 G1/G2 risk alleles with metabolic and cardiovascular traits. Lead Investigator: Girish Nadkarni (MSSM) & Miriam Udler (CCHMC/BCH)
76. Burden of structural variation and PheWAS. Lead Investigator: Adam Gordon(GHC/UW)
77. Chromosomal Anomalies that Affect Levels of White Blood Count (WBC) and its Differential. Lead Investigator: David Crosslin (GHC/UW)
78. Extracting the Quality of Prostate Cancer Care from Electronic Healthcare Records. Lead Investigator: Tina Hernandez Boussard (External)
79. Portable Applications for Implementing Multi-Site Clinical NLP Algorithms. Lead Investigator: David Carrell (GHC/UW)
80. Genetic Risk Factors for Development of Diverticulitis. Lead Investigator: Abel Kho (NU)

81. Colon Polyps. Lead Investigator: Abel Kho (NU)
82. Genetic Variants Associated with Response to Heart Failure Treatment: The Electronic Medical Records and Genomics (eMERGE) Network. Lead Investigator: Sue Bielinski (Mayo)
83. Genome-Wide Association of Risk of Heart Failure: The Electronic Medical Records and Genomics (eMERGE) Network. Lead Investigator: Sue Bielinski (Mayo)
84. Genetic variation that predicts susceptibility to Clostridium difficile. Lead Investigator: David Crosslin (GHC/UW)
85. Copy number variation burden analysis on a range of phenotypes in the eMERGE network. Lead Investiator: Marylyn Ritchie (Geisinger)

Site-Specific Manuscripts

CCHMC

1. Aberle T, Bourn RL, Munroe ME, Chen H, Roberts VC, et al. *Clinical and serological features distinguish patients with incomplete lupus classification from systemic lupus erythematosus patients and controls*. Arthritis Care Res (Hoboken). 2017 Jan 24; PMID: 28118528

2. Lu R, Munroe ME, Guthridge JM, Bean KM, Fife DA, et al. *Dysregulation of innate and adaptive serum mediators precedes systemic lupus erythematosus classification and improves prognostic accuracy of autoantibodies.* J Autoimmun. 2016 Nov;74:182–193. PMCID: PMC5079766

KPW/UW

1. Marouli E, Graff M, Medina-Gomez C, Lo KS, Wood AR, et al. *Rare and low-frequency coding variants alter human adult height.* Nature. 2017 Feb 1; PMID: 28146470

Mayo

1. Afzal N, Sohn S, Abram S, Scott CG, Chaudhry R, et al. *Mining peripheral arterial disease cases from narrative clinical notes using natural language processing.* J Vasc Surg. 2017 Feb 8; PMID: 28189359

2. Safarova MS, Klee EW, Baudhuin LM, Winkler EM, Kluge ML, et al. *Variability in assigning pathogenicity to incidental findings: insights from LDLR sequence linked to the electronic health record in 1013 individuals.* Eur J Hum Genet. 2017 Feb 1; PMID: 28145427

3. Brown S-A, Jouni H, Marroush TS, Kullo IJ. *Disclosing Genetic Risk for Coronary Heart Disease: Attitudes Toward Personal Information in Health Records.* Am J Prev Med. 2017 Jan 3; PMID: 28062272

4. Jouni H, Haddad RA, Marroush TS, Brown S-A, Kruisselbrink TM, et al. *Shared decision-making following disclosure of coronary heart disease genetic risk: results from a randomized clinical trial*. J Investig Med. 2016 Dec 19; PMID: 27993947

5. Safarova MS, Liu H, Kullo IJ. *Rapid identification of familial hypercholesterolemia from electronic health records: The SEARCH study.* J Clin Lipidol. 2016 Oct;10(5):1230–1239. PMID: 27678441

Vanderbilt (VUMC)

1. Schildcrout JS, Denny JC, Roden DM. *On the Potential of Preemptive Genotyping Towards Preventing Medication-Related Adverse Events: Results from the South Korean National Health Insurance Database*. Drug Saf. 2016 Nov 21; PMID: 27873192

2. Shekhar A, Lin X, Liu F-Y, Zhang J, Mo H, et al. *Transcription factor ETV1 is essential for rapid conduction in the heart.* J Clin Invest. 2016 Oct 24; PMID: 27775552

OVERVIEW *of e*MERGE TOOLS

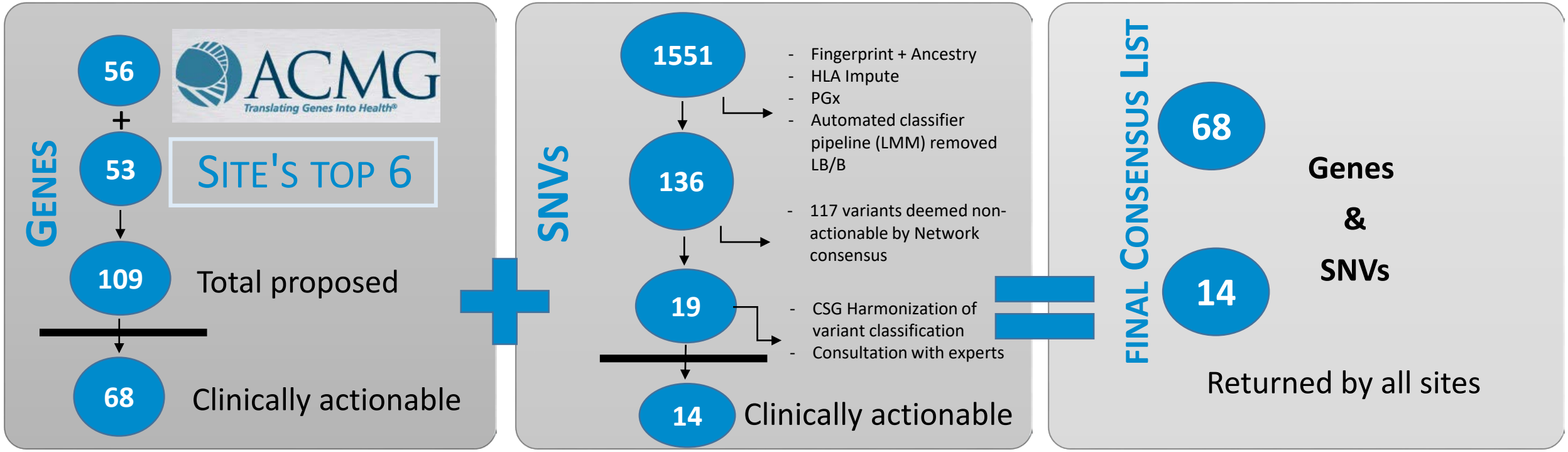
Main resources and tools produced and supported *(click on blue links):*

- CDS KB: A repository of clinical decision support knowledge designed to support clinical processes from diagnosis and investigation through treatment and long-term care.
- eleMAP: A tool that allows researchers to harmonize their local phenotype data dictionaries to existing metadata and terminology standards such as the caDSR (Cancer Data Standards Registry and Repository), NCIT (NCI Thesaurus) and SNOMED-CT (Systematized Nomenclature of Medicine-Clinical Terms).
- eMERGE Infobutton Project: A template containing important content topics for genomic medicine.
- eMERGE Record Counter: A web-based research tool that provides exploratory data figures for research planning purposes and feasibility assessment.
- Model consent language: A publication representing the compiled work of eMERGE I investigators and consultants on consent language for the collection and storage of human biospecimens and data for future research, particularly those collections that have an electronic medical records component.
- MyResults.org: A website to educate providers and patients about genetic test results and the related medications.
- PheKB: An online collaborative environment for building and validating electronic algorithms to identify characteristics of patients within health data.
- PheWAS Catalog: A catalog that contains the PheWAS results for 3,144 single-nucleotide polymorphisms (SNPs) present in the NHGRI GWAS Catalog.
- SPHINX: A data exploring tool for genetics related drug response hypothesis generation.
- Synthesis-View, PheWAS-View and Phenogram: Visualization tools for genome & phenome-wide data.
- IMAGene: An educational website including both English and Spanish about the use of personalized medicine to improve health care for everyone.
- Learning Genetics: Learn about exome sequencing and secondary findings.

*e*MERGE PHASE III PHENOTYPES

Primary Site	Phenotype
CCHMC	Pediatric Migraine
	Fatty Liver condition = (NAFLD/NASH-Alcoholic)
	Pediatric Pain = including post surgical pain/pain sensitivity
CHOP	Epilepsy
	Intellectual disability
	AID - Autoimmune disease
Columbia	Chronic Kidney Disease (eGFR, proteinuria)
	Autoimmunity
	Breast cancer
Geisinger	Pediatric FH
GH/UW	Colorectal Cancer (CRC)
	Endometrial and Ovarian Cancer
	Depression
Harvard	Rheumatoid arthritis
	Hyperlipidemia
	Bipolar disorder
Mayo	Adult familial hypercholesterolemia (PGx)
	Contrast Induced nephropathy (PGx)
	Peripheral arterial disease
	Metformin response (PGx)
	Response HF medication (PGx)
NU	Chronic Rhinosinusitis
	Atopic Dermatitis
	Valvular Heart Disease
	Adult Headaches, esp. Migraine
VU	Hearing Loss
	Arrhythmias
	Pneumonia

CLINICAL REPORTING: Overview *of* Consensus Lists *for* *e*MERGE III



Comprehensive List of Genes and SNVs on Next Two Slides

CLINICAL REPORTING: Gene Consensus List *for* *e*MERGE III

Consensus List *for which* **Pathogenic** *or* **Likely Pathogenic Variants** *will be* **Returned**

Phenotype	Gene‡
Cancer susceptibility and tumor diseases	*APC, BMPR1A, BRCA1, BRCA2, MEN1, MLH1, MSH2, MSH6, MUTYH[#], NF2, PALB2, PMS2, POLD1, POLE, PTEN, RB1, RET, SDHAF2, SDHB, SDHC, SDHD, SMAD4, STK11, TSC1, TSC2, TP53, VHL, WT1*
Cardiac Diseases	*ACTA2, ACTC1, COL3A1, COL5A1, DSC2, DSG2, DSP, FBN1, GLA[+], KCNE1[§], KCNH2, KCNJ2, KCNQ1, LMNA, MYBPC3, MYH7, MYH11, MYL2, MYL3, MYLK, PKP2, PRKAG2, RYR2, SCN5A, SMAD3, TGFBR1, TGFBR2, TMEM43, TNNI3, TNNT2, TPM1*
Hypercholesterolemia	*APOB*, LDLR*, PCSK9*
Diabetes & Kidney Disease	*HNF1A, HNF1B*
Ehlers-Danlos Syndrome	*COL3A1, COL5A1*
Neuromuscular Diseases	*CACNA1A, CACNA1S, RYR1*
Ornithine Transcarbamylase (OTC) Deficiency	*OTC[+]*

‡ Site TOP-6 genes are indicated in blue

*semi (incomplete) dominant, [+]x-linked, [#]recessive, [§] dominant or recessive

CLINICAL REPORTING: SNV Consensus List *for* eMERGE III

Consensus List *of* Actionable Pathogenic *or* Likely Pathogenic Variants *to be* Returned*

rs#	Gene	Molecular Consequence	Associated Disease	Mode *of* Inheritance	Disease Category
rs77931234	*ACADM*	c.985A>C (p.Lys329Gln)	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	AR	Inborn error of metabolism
rs387906225	*ALDOB*	c.360_363delCAAA (p.Asn120Lysfs)	Hereditary fructose intolerance	AR	Inborn error of metabolism
rs386834233	*BCKDHB*	c.832G>A (p.Gly278Ser)	Maple syrup urine disease	AR	Inborn error of metabolism
rs79761867	*BCKDHB*	c.548G>C (p.Arg183Pro)	Maple syrup urine disease	AR	Inborn error of metabolism
rs80338898	*FAH*	c.782C>T (p.Pro261Leu)	Tyrosinemia type I	AR	Inborn error of metabolism
rs1801175	*G6PC*	c.247C>T (p.Arg83Cys)	Glycogen storage disease type I	AR	Inborn error of metabolism
rs397509431	*CPT2*	c.1239_1240delGA (p.Lys414Thrfs)	Carnitine palmitoyltransferase II (CPT II) deficiency	AR	Inborn error of metabolism
rs113993962	*BLM*	c.2207_2212delATCTGAinsTAG ATTC (p.Tyr736Leufs)	Bloom Syndrome	AR	Cancer susceptibility
rs193922376	*MSH2*	c.942+3A>T	Lynch syndrome	AD	Cancer susceptibility
rs6467	*CYP21A2*	c.293-13C>G	21-hydroxylase deficiency	AR	Inherited disorder of steroid synthesis
rs6025	*F5*	c.1601G>A (p.Arg534Gln)	Factor V Leiden thrombophilia	Complex	Clotting disorder
rs1800562	*HFE*	c.845G>A (p.Cys282Tyr)	Hereditary hemochromatosis	AR	Iron storage
rs28940579	*MEFV*	c.2177T>C (p.Val726Ala)	Familial Mediterranean fever	AR	Hereditary auto-inflammatory disease
rs61752717	*MEFV*	c.2080A>G (p.Met694Val)	Familial Mediterranean fever	AR	Hereditary auto-inflammatory disease

*** AR and risk variants: Only bi-allelic (homozygous, or if applicable compound heterozygous) variants will be returned**

Partners Broad Site Reporting Preferences

Actionable genes on consensus list	SOURCE	SITE 1: UW	SITE 2: GEISINGER	SITE 3: CCHMC adolescent cohort	SITE 3: CCHMC biobank cohort	SITE 4: HARVARD
BMPR1A	TOP6	X**		X	X	X
CACNA1A	TOP6	X		X		X
COL5A1	TOP6	X		X		X
HNF1A	TOP6	X	X	X		X
HNF1B	TOP6	X		X		X
KCNE1	TOP6	X	X	X		X
KCNJ2	TOP6	X	X	X	X	X
OTC	TOP6	X	X	X*		X
PALB2	TOP6	X		X		X
POLD1	TOP6	X**		X		X
POLE	TOP6	X**		X		X
SMAD4	TOP6	X**	X	X	X	X
ACTA2	ACMG56	X	X	X	X	X
ACTC1	ACMG56	X	X	X	X	X
APC	ACMG56	X**	X	X	X	X
APOB	ACMG56	X	X	X	X	X
BRCA1	ACMG56	X	X	X		X
BRCA2	ACMG56	X	X	X		X
CACNA1S	ACMG56	X	X	X	X	X
COL3A1	ACMG56	X	X	X	X	X
DSC2	ACMG56	X	X	X	X	X
DSG2	ACMG56	X	X	X	X	X
DSP	ACMG56	X	X	X	X	X
FBN1	ACMG56	X	X	X	X	X
GLA	ACMG56	X	X	X*	X	X

KCNH2	ACMG56	X	X	X	X	X
KCNQ1	ACMG56	X	X	X	X	X
LDLR	ACMG56	X	X	X	X	X
LMNA	ACMG56	X	X	X	X	X
MEN1	ACMG56	X	X	X	X	X
MLH1	ACMG56	X**	X	X		X
MSH2	ACMG56	X**	X	X		X
MSH6	ACMG56	X**	X	X		X
MUTYH[#]	ACMG56	X**	X	X	X	X
MYBPC3	ACMG56	X	X	X	X	X
MYH11	ACMG56	X	X	X	X	X
MYH7	ACMG56	X	X	X	X	X
MYL2	ACMG56	X	X	X	X	X
MYL3	ACMG56	X	X	X	X	X
MYLK	ACMG56	X	X	X	X	X
NF2	ACMG56	X	X	X	X	X
PCSK9	ACMG56	X	X	X	X	X
PKP2	ACMG56	X	X	X	X	X
PMS2	ACMG56	X**	X	X		X
PRKAG2	ACMG56	X	X	X	X	X
PTEN	ACMG56	X**	X	X	X	X
RB1	ACMG56	X	X	X	X	X
RET	ACMG56	X	X	X	X	X
RYR1	ACMG56	X	X	X	X	X
RYR2	ACMG56	X	X	X	X	X
SCN5A	ACMG56	X	X	X	X	X
SDHAF2	ACMG56	X	X	X	X	X
SDHB	ACMG56	X	X	X	X	X
SDHC	ACMG56	X	X	X	X	X

Additional Non-consensus genes	SOURCE	SITE 1: UW	SITE 2: GEISINGER	SITE 3: CCHMC Adolescent	SITE 3: CCHMC Biobank	SITE 4: HARVARD
SDHD	ACMG56	X	X	X	X	X
SMAD3	ACMG56	X	X	X	X	X
STK11	ACMG56	X**	X	X	X	X
TGFBR1	ACMG56	X	X	X	X	X
TGFBR2	ACMG56	X	X	X	X	X
TMEM43	ACMG56	X	X	X	X	X
TNNI3	ACMG56	X	X	X	X	X
TNNT2	ACMG56	X	X	X	X	X
TP53	ACMG56	X**	X	X	X	X
TPM1	ACMG56	X	X	X	X	X
TSC1	ACMG56	X	X	X	X	X
TSC2	ACMG56	X	X	X	X	X
VHL	ACMG56	X	X	X	X	X
WT1	ACMG56	X	X	X	X	X
CACNA1C	TOP6		X			
SERPINA1	TOP6			X*		
CHEK2	TOP6			X		
CFTR	TOP6			X*		
TYK2	TOP6			X*		
BMPR2	TOP6			X		
TCIRG1	TOP6			X*		

Only bi-allelic (homozygous, compound heterozygous) variants will be returned

* carrier status will be returned

** VUS's will be returned for 13 colorectal cancer genes in this site

Gene	rs #	Molecular consequence	SITE 1: UW	SITE 2: GEISINGER	SITE 3: CCHMC Adolescent	SITE 3: CCHMC biobank	SITE 4: HARVARD
ACADM	rs77931234	c.985A>C (p.Lys329Gln)	X		X*		X
ALDOB	rs387906225	c.360_363delCAAA (p.Asn120Lysfs)	X		X*		X
BCKDHB	rs386834233	c.832G>A (p.Gly278Ser)	X		X*		X
BCKDHB	rs79761867	c.548G>C (p.Arg183Pro)	X		X*		X
FAH	rs80338898	c.782C>T (p.Pro261Leu)	X		X*		X
G6PC	rs1801175	c.247C>T (p.Arg83Cys)	X		X*		X
CPT2	rs397509431	c.1239_1240delGA (p.Lys414Thrfs)	X		X*		X
BLM	rs113993962	c.2207_2212delATCTGAinsTAGATTC (p.Tyr736Leufs)	X		X*		X
MSH2	rs193922376	c.942+3A>T	X		X		X
CYP21A2	rs6467	c.293-13C>G	X		X*		X
F5	rs6025	c.1601G>A (p.Arg534Gln)	X		X		X
HFE	rs1800562	c.845G>A (p.Cys282Tyr)	X	X	X		X
MEFV	rs28940579	c.2177T>C (p.Val726Ala)	X		X*		X
MEFV	rs61752717	c.2080A>G (p.Met694Val)	X		X*		X

Only bi-allelic (homozygous, or if applicable compound heterozygous) variants will be returned unless otherwise noted, except MSH2 due to AD mode of inheritance

* carrier status will be returned

Baylor Site Reporting Preferences

Actionable genes on consensus list	SOURCE	SITE 1: Northwestern	SITE 2: Mayo	SITE 3: CHOP	SITE 4: Columbia	SITE 5: Vanderbilt
BMPR1A	TOP6	X	X	X	X	X
CACNA1A	TOP6	X	X	X	X	X
COL5A1	TOP6	X	X	X	X	X
HNF1A	TOP6	X	X	X	X	X
HNF1B	TOP6	X	X	X	X	X
KCNE1	TOP6	X	X	X	X	X
KCNJ2	TOP6	X	X	X	X	X
OTC	TOP6	X	X	X	X	X
PALB2	TOP6	X	X	X	X	X
POLD1	TOP6	X	X	X	X	X
POLE	TOP6	X	X	X	X	X
SMAD4	TOP6	X	X	X	X	X
ACTA2	ACMG56	X	X	X	X	X
ACTC1	ACMG56	X	X	X	X	X
APC	ACMG56	X	X	X	X	X
APOB	ACMG56	X	X	X	X	X
BRCA1	ACMG56	X	X	X	X	X
BRCA2	ACMG56	X	X	X	X	X
CACNA1S	ACMG56	X	X	X	X	X
COL3A1	ACMG56	X	X	X	X	X
DSC2	ACMG56	X	X	X	X	X
DSG2	ACMG56	X	X	X	X	X
DSP	ACMG56	X	X	X	X	X
FBN1	ACMG56	X	X	X	X	X
GLA	ACMG56	X	X	X	X	X
KCNH2	ACMG56	X	X	X	X	X
KCNQ1	ACMG56	X	X	X	X	X
LDLR	ACMG56	X	X	X	X	X
LMNA	ACMG56	X	X	X	X	X
MEN1	ACMG56	X	X	X	X	X
MLH1	ACMG56	X	X	X	X	X
MSH2	ACMG56	X	X	X	X	X
MSH6	ACMG56	X	X	X	X	X
MUTYH*	ACMG56	X	X	X	X	X
MYBPC3	ACMG56	X	X	X	X	X
MYH11	ACMG56	X	X	X	X	X

MYH7	ACMG56	X	X	X	X	X
MYL2	ACMG56	X	X	X	X	X
MYL3	ACMG56	X	X	X	X	X
MYLK	ACMG56	X	X	X	X	X
NF2	ACMG56	X	X	X	X	X
PCSK9	ACMG56	X	X	X	X	X
PKP2	ACMG56	X	X	X	X	X
PMS2	ACMG56	X	X	X	X	X
PRKAG2	ACMG56	X	X	X	X	X
PTEN	ACMG56	X	X	X	X	X
RB1	ACMG56	X	X	X	X	X
RET	ACMG56	X	X	X	X	X
RYR1	ACMG56	X	X	X	X	X
RYR2	ACMG56	X	X	X	X	X
SCN5A	ACMG56	X	X	X	X	X
SDHAF2	ACMG56	X	X	X	X	X
SDHB	ACMG56	X	X	X	X	X
SDHC	ACMG56	X	X	X	X	X
SDHD	ACMG56	X	X	X	X	X
SMAD3	ACMG56	X	X	X	X	X
STK11	ACMG56	X	X	X	X	X
TGFBR1	ACMG56	X	X	X	X	X
TGFBR2	ACMG56	X	X	X	X	X
TMEM43	ACMG56	X	X	X	X	X
TNNI3	ACMG56	X	X	X	X	X
TNNT2	ACMG56	X	X	X	X	X
TP53	ACMG56	X	X	X	X	X
TPM1	ACMG56	X	X	X	X	X
TSC1	ACMG56	X	X	X	X	X
TSC2	ACMG56	X	X	X	X	X
VHL	ACMG56	X	X	X	X	X
WT1	ACMG56	X	X	X	X	X
Additional non-consensus genes	**SOURCE**	**SITE 1: Northwestern**	**SITE 2: Mayo**	**SITE 3: CHOP**	**SITE 4: Columbia**	**SITE 5: Vanderbilt**
ANK2	TOP6	X				X
ATM	TOP6	X				X
ATP1A2	TOP6	X				
BMPR2	TOP6	X				X
CACNA1C	TOP6	X				X
CFH	TOP6	X				

CFTR	TOP6	X				
CHEK2	TOP6	X				X
FLG	TOP6	X				
MC4R	TOP6	X				
*MTHFR**	TOP6	X				
*NTRK1**	TOP6	X				
SCN1A	TOP6	X				
SCN9A	TOP6	X				
*SERPINA1 **	TOP6	X				
*SLC2A10 **	TOP6	X				
TCF4	TOP6	X				
*TCIRG1**	TOP6	X				
TTR	TOP6	X				X
*TYK2**	TOP6	X				
UMOD	TOP6	X				
*VDR**	TOP6	X				

* Only biallelic or homozygous variants will be returned for disorders with AR inheritance

Gene	rs #	Molecular consequence	SITE 1: Northwestern	SITE 2: Mayo	SITE 3: CHOP	SITE 4: Columbia	SITE 5: Vanderbilt
ACADM*	rs77931234	c.985A>C (p.Lys329Gln)	X	X	X	X	X
ALDOB*	rs387906225	c.360_363delCAAA (p.Asn120Lysfs)	X	X	X	X	X
BCKDHB*	rs386834233	c.832G>A (p.Gly278Ser)	X	X	X	X	X
BCKDHB*	rs79761867	c.548G>C (p.Arg183Pro)	X	X	X	X	X
FAH*	rs80338898	c.782C>T (p.Pro261Leu)	X	X	X	X	X
G6PC*	rs1801175	c.247C>T (p.Arg83Cys)	X	X	X	X	X
CPT2*	rs397509431	c.1239_1240delGA (p.Lys414Thrfs)	X	X	X	X	X
BLM*	rs113993962	c.2207_2212delATCTGAinsTAGATTC (p.Tyr736Leufs)	X	X	X	X	X
MSH2	rs193922376	c.942+3A>T	X	X	X	X	X
CYP21A2*	rs6467	c.293-13C>G	X	X	X	X	X

F5*	rs6025	c.1601G>A (p.Arg534Gln)	X	X	X	X	X
HFE*	rs1800562	c.845G>A (p.Cys282Tyr)	X	X	X	X	X
MEFV*	rs28940579	c.2177T>C (p.Val726Ala)	X	X	X	X	X
MEFV*	rs61752717	c.2080A>G (p.Met694Val)	X	X	X	X	X

* Only biallelic or homozygous variants will be returned for disorders with AR inheritance

Additional non-consensus SNPs	rs #	Molecular consequence	SITE 1: Northwestern	SITE 2: Mayo	SITE 3: CHOP	SITE 4: Columbia	SITE 5: Vanderbilt
ABCC8*	rs151344623	c.3989-9G>A (p.?)	X				
ATP7B*	rs76151636	c.3207C>A (p.His1069Gln)	X				
CLRN1*	rs111033258	c.144T>G (p.Asn48Lys)	X				
COL5A2	rs786205104	c.2031+1G>T (p.?)	X				
COL5A2	rs786205103	c.1924-2_1928del (p.?)	X				
DHDDS*	rs147394623	c.124A>G (p.Lys42Glu)	X				
DLD*	rs121964990	c.685G>T (p.Gly229Cys)	X				
F11*	rs121965064	c.901T>C (p.Phe301Leu)	X				
F11*	rs121965063	c.403G>T (p.Glu135*)	X				
FANCC*	rs104886456	c.456+4A>T (p.?)	X				
HPS3*	rs201227603	c.1163+1G>A (p.?)	X				
KCNE2	rs74315447	c.161T>C (p.Met54Thr)	X				
SPG7*	rs61755320	c.1529C>T (p.Ala510Val)	X				
TOR1A	rs724159981	c.907_909del (p.Glu303del)	X				
JAK2	rs77375493	c.1849G>T (p.Val617Phe)					X

KCNE1**	rs1805128	c.253G>A (p.Asp85Asn)					X

* Only biallelic or homozygous variants will be returned for disorders with AR inheritance

** KCNE1 on the gene list and considered a risk allele

Additional non-consensus SNPs returned for all Mayo patients	rs #	Molecular consequence	SITE 1: Northwestern	SITE 2: Mayo	SITE 3: CHOP	SITE 4: Columbia	SITE 5: Vanderbilt
PCSK9	rs2479409	N/A		X			
CELRS2	rs629301	N/A		X			
APOB	rs1367117	N/A		X			
ABCG8	rs4299376	N/A		X			
SLC22A1	rs1564348	N/A		X			
HFE	rs1800562	N/A		X			
MYLIP	rs3757354	N/A		X			
ST3GAL4	rs11220462	N/A		X			
NYNRIN	rs8017377	N/A		X			
LDLR	rs6511720	N/A		X			
APOE	rs429358	N/A		X			
APOE	rs7412	N/A		X			

no clinical interpretation will be provided for these variants.

eMERGE Network: Summary of the eMERGE Steering Committee

October 6-7, 2016 in Rockville, MD

The first year two, Phase III eMERGE Steering Committee and ESP Meeting was held on October 6th and 7th, 2016 in Rockville, MD. In order to ensure that the Network continues on a productive note as we begin our second year, please find highlights from the Meeting below.

Presentation slides are available here (login required).

Day 1: Full-Day Session

Welcome, Opening Remarks, General Updates – *Rongling Li*

- Supplement Request Update
  - Network Supplements: The Geocoding and Impact of Return of Genomic Results on Health Care Providers supplements have been funded.
  - Site Specific Supplements: The Cascade Screening for Severe Hypercholesterolemia (Mayo) and Family network approach to assess the trickle-down effect of genetic testing (GHC/UW) supplements have been funded.
- Overall Program update:
  - The group reviewed expected race/ethnicity distribution of the data, program timeline, and dbGaP submission details.
- Goals for the meeting:
  - Update on genomic sequencing status and dataflow
  - Propose approaches of fully using the eMERGE resources
  - Share results of ongoing scientific projects
  - Report of workgroups activities, timelines, and results/products
  - Respond to the ESP recommendations
- Prospective New Affiliate Member: Meharry Medical College
  - 500 samples from Meharry with African American ancestry and early stage cancer phenotype will be sequenced by Baylor. The recruitment and sequencing timelines are being developed.

ACTION ITEM: Members are encouraged to investigate other funding mechanisms for supplements that were not funded.
ACTION ITEM: The Phenotyping Workgroup will develop an overall timeline for completion of all 42 eMERGE phenotypes.

Announcements, Opening Remarks – *Rex Chisholm*

- The workgroup co-chairs and leadership team will meet at 5:15 pm to discuss the Workgroups and Network processes.

The eMERGE sequencing panel: CSG updates on performance, content curation and sequencing progress – *Richard Gibbs (BCM), Niall Lennon (Partners/Broad), Birgit Funke (Partners/Broad), and Larry Babb (GeneInsight/Sunquest)*

- Sequencing has begun at both centers and they are now in the data generation/variant calling/annotation filtration stage of the pipeline. The panel is unique in that it includes discovery genes and SNVs in a clinical reporting setting.
- Sequencing Timeline:
  - Both sequencing centers are committed to finishing sequencing by the end of year 3 (April 2018). Reporting will be complete as outlined in the pipeline documentation.
  - The exact sequencing timeline is an evolving document. Sequencing centers will communicate with sites directly to coordinate sample shipment, sequencing start dates, and any timeline changes that may arise.
  - Sequencing centers will create a Network-wide progress dashboard that will be updated monthly (provided through DNAnexus). Investigators will be able to query data through this tool.

- Current reagent status: Partners/Broad version 2 of the assay captures the underperforming areas from version 1. All variants that remain uncovered (for both sequencing centers) have been identified as not clinically significant.
- Next Steps:
    - Develop near real-time synchronization of variant curation.
    - Complete the addition of CNV calls to reports.
    - Complete DNANexus data schema and tools (Baylor).
- Sequencing centers have collaborated to create a de-identified case repository, GeneInsight, that is now live and ready to be populated with data from the sequencing centers' clinical reports. Partners/Broad knowledgebase data for the genes/variants on the eMERGE-Seq panel is already available. An SFTP site has been developed for Partners/Broad contributing sites to receive identified clinical reports. Baylor contributing sites will receive their identified clinical reports from DNAnexus.
- How sites incorporate, interpret, and further report lab clinical reports will be captured in a manuscript led by the Clinical Annotation workgroup. Labs are limited as they do not have complete phenotype and clinical data. The group discussed the role of clinical experts in returning results and the possibility of setting up a list of experts for eMERGE phenotypes for which ClinGen does not already have a framework.

Prevalence and Clinical Implications of Genetic Variants Associated with Familial Hypercholesterolemia in a Large Clinical Population – *Marc Williams (Geisinger)*

- Geisinger investigators concluded, per preliminary internal review of MyCode™ data, that familial hypercholesterolemia (FH) is underdiagnosed and undertreated. In order to close the care-gap, a Geisinger pharmacy fellow is looking at an innovative patient-centered, multidisciplinary approach for the delivery of genomic sequencing results and pharmacist-led lipid management to patients with FH. The FH Care Team for patient and family members is comprised of a pharmacist, PCP, clinical genomics, cardiology, OB/GYN and dietician. The FH Clinic Flow was reviewed is as follows: identification of pathogenic variant, pre-visit contact to return result, initial visit with genetic counselor or PCP for baseline assessment, risk stratification and determination of treatment goals, regular follow-up care, and specialty care as needed. Geisinger investigators are assessing process metrics and intermediate outcomes in pursuit of reducing the incidence of cardiovascular disease events.
- A PRIMUS algorithm was used to impute pedigrees with Geisinger MyCode™ data. Researchers found that there is much relatedness within their MyCode™ community health initiative, particularly at the second and third generation level. With this algorithm, researchers were able to identify an *LDLR* mutation (exon 13-17 duplication) in FH cases, and subsequent correlation to ischemic heart disease (IHD). It was noted that *LDLR* elevation in the case study pedigree was modest – not typical for someone with FH, but clearly associated with IHD. In addition, Geisinger researchers identified potential modifying effect of *PCSK9* variant in the "n" of the aforementioned pedigree. Investigators inferred that If you carry both variants, you might have an intermediate phenotype and basis for *PCSK9* inhibitor treatment.
- In conclusion, it was suggested that investigators may want to consider potentially returning results for protective alleles in clinical practice.

Variability in Assigning Pathogenicity to Incidental Findings: Insights from *LDLR* Sequence Linked to the Electronic Health Record in 1013 Individuals – *Maya Safarova (Mayo)*

- The aims of this pilot project were:
    - To assess discordance in assigning variant pathogenicity between databases/submitters and expert reviewers
    - Describe a framework to assign pathogenicity to incidental findings from *LDLR* sequencing.
- Mayo investigators leveraged data available from the eMERGE PGx project. A detailed overview was provided of variant selection (resulting in 25 LDLR variants), clinical characteristic criteria (n=124), reviewer criteria, prediction tools used and phenotyping criteria.
- Conclusions from the pilot study:
    - Out of 178 variants, 25 putatively disruptive low-frequency and rare variants in the LDLR sequences of 1013 biobank participants

    - In ClinVar, 26% of LDLR variants were reported to have discordant interpretation at the level of clinical actionability
    - Among two independent interpreters (laboratorian and cardiologist), the discordance rate was 40% (five-tier classification)
    - Based on independent review, two LDLR variants were deemed likely pathogenic, clinically actionable and returnable (disease prevalence of 1:507; 0.20%).
- The group acknowledged limitations to their pilot study: 1) Missing data: family members' information, knowledge of additional genetic and environmental factors, and assays for LDL receptor functional activity; 2) Limited sample size and number of interpreters; 3) Test data contain restricted number of variables; 4) Limited ethnic diversity – approximately 90% Caucasian.
- Next steps were identified:
    - Conduct a network-wide comparison of variant classification of FH-causing genes (*LDLR, APOB, PCSK9*) in 25,000 individuals
    - Compare laboratory expertise vs clinical expertise
    - Integrate phenotypic elements such as LDL-C levels and implement FH phenotyping eAlgorithm
    - For VUS's, utilize an *LDLR* functional assay (ongoing work at Mayo)
- Preliminary data is being worked on via a quantitative approach: a standardized approach built on cumulative estimation of strength of each predefined criterion in the contact of specific genes and syndromes to yield more consistency in variant classification.

PMI Network Update – *Josh Denny (Vanderbilt)*

- President Obama announced the PMI Cohort Program on January 20, 2015. The PMI Working Group Report met March-September 2015, with awards announced in February 2016 and July 2016.
    - PMI Cohort Program Pilot OTA (**Vanderbilt**/Verily/Michigan/**Broad**)
    - Communications OTA (Wondros)
    - Data and Research Support Center (**Vanderbilt**/Verily/**Broad**/**Columbia**/UM/UT Houston/**Northwestern**)
    - Biobank (**Mayo**)
    - Participant Technologies Center (PTC- Scripps, Vibrent, Sage + others)
    - HPOs (Regional Medical Centers; Community Health Centers; Veterans Affairs Medical Centers)
        - Regional Medical Centers: California Precision Medicine Consortium; Columbia University Medical Center; Geisinger Health System; Illinois Precision Medicine Consortium; New England Precision Medicine Consortium; Trans-American Consortium for the Health Care Systems Research Network; University of Arizona-Tucson; University of Pittsburgh at Pittsburgh
        - Health Center Pilot Sites: Cherokee Health Systems, Knoxville, TN; Community Health Center, Inc, Middletown, CT; Eau Claire Cooperative Health Center, Columbia, SC; HRHCare, Peekskill, NY; Jackson-Hinds Comprehensive Health Center, Jackson, MS; San Ysidro Health Center, San Tsidro, CA
- Josh provided a status report of the PMI Network. He reviewed the PMI Cohort Program timeline and awards to date, highlighted important elements of the PMI Working Group Report (September 17, 2015) and discussed the "expression of interest" web portal and Patient Provided Information (PPI) development. Josh notes that PMI is initially targeting ages 18+, but the goal is to eventually include children. Thus far, the program has recruited ~5,000 people around the US to assist in designing and testing features of the program.
- Expression of Interest (EOL) Web Portal: Built an "expression of interest" web portal as a gateway for testing to determine types of questions to ask. The group conducted community engagement studios that targeted 16 priority populations in an effort to optimize diversity and inclusivity.
    - Concerns: Trust, security, how data would be used
    - Return of value varies greatly (not one-size fits all)
- Participant Provided Information (PPI) Development: First versions of survey will be finalized soon (English/Spanish). Question domains selected for PMI cohort enrollment that will be included in the PPI modules at launch: sociodemographic data, personal habits, family health history, personal medical history, medications.

- Healthcare access and utilization, diet, physical activity, sleep, anthropometry, occupational history, oral health, and pain will be completed through this year.
- The program is building a variety of tools to support web-based GWAS for simple and common analyses.
  - Individual level data – require process of requesting access and going through an IRB. Access policies are still in development.
  - Computation environments can take this data and export to a manipulatable environment.

EHRI Infobutton Subgroup: DocUBuild Platform – *Luke Rasmussen (Northwestern)*

- The EHRI Workgroup's Infobutton subgroup is currently developing the DocUBuild Platform, an authoring platform that promotes sharing and reuse of content. The purpose of DocUBuild is to support unique institutional needs by: 1) making content accessible via multiple modes of delivery; and 2) making content discoverable and targeted in an infobutton context.
- The consortium is invited to provide feedback, specifically what is practical and pragmatic at your institutions and within your workflows.
- DocUBuild is temporarily located at: http://bit.ly/docubuild_tmp
  - Login email: demo@emerge.com
  - Login password: emerge
- Next steps: planning some evaluations and publications in this area
  - Infobutton context elements in existing information resources (led by ClinGen)
  - Utility of prospective vs retrospective context annotation
  - Usability of a tool to annotate infobutton context
  - The DocUBuild Platform

ACTION ITEM: Review the DocUBuild Platform, and provide feedback to Luke Rasmussen regarding what is practical and pragmatic at your respective institutions and within your workflow. Login email: demo@emerge.com; Login password: emerge

Estimate of disease heritability using 4.7 million familial relationships inferred from electronic health records – *Nicholas Tatonetti (Columbia)*

- Emergency contact data is a more reliable indicator of risk of disease than self-reported demographics and problem lists, which is can be noisy and missing in EHR data.
- Relationships can be inferred by matching emergency contacts to other patients in the medical system's EHR. Roughly 3.1 Million relationships were provided/inferred in Columbia's EHR using this method. The method yielded approximately 1.5 million relationship defined in Cornell's EHR, indicating the generalizability of the method. The method has been validated against genetic data.
- Heritability studies conducted with this more accurate relationship and clinical phenotypes will have uncontrolled ascertainment bias that will be highly variable. This can be controlled by repeated subsampling. Heritability using this method of relationship inference is sensitive to noise and robust to missing data. An overall study found significant heritability for 328 traits.
- The group discussed a clinician's responsibility to inform a patient's relatives about heritable conditions that may put the relative at risk of harm, vs HIPPA privacy requirements.
- The group discussed how to account for environment and therapeutic effect in heritability studies (ex: by matching case/controls).

Adolescent and Parent Choices about Return of Genomics Research Results: Development of Tools to Facilitate Decision Making – *Melanie Myers (CCHMC)*

- CCHMC conducted focus groups to fill the knowledge gap around adolescent perspective on return of genetic results in two phases:
  - Design and evaluate supplemental messaging for return of genomic research results from the eMERGE-Seq panel. Participants were presented with a mock eMERGE report, an online video, and paper copies of existing materials from My46.

    - Develop and refine preference models facilitate both parent's and adolescent's choices about return of results. The current version of the tool allows choices based on preventability, treatability, and age of onset with two exclusion criteria (adult onset conditions with no actionability in childhood, and carrier status).
- Lessons learned:
    - Supplemental information is needed before testing, not just when results are available.
    - Interpretation of positive/negative results varied with context.
- All groups strongly agreed that adolescent participation should depend on age, maturity level, and personality of the individual. Adolescents wanted a third party (their pediatrician) present to moderate decision making.

Evidence of hybrid vigor in a human population from PheWAS – *Todd Edwards (Vanderbilt)*

- Vanderbilt biobank and Tennessee State/US Census evidence suggests recent and ongoing admixture in US population race/ethnicity with an increase in heterozygosity.
- Increased heterozygosity is associated with an overall decreased burden of disease, specifically protection from reproductive disease (ex: menstrual disorders).
- Increased heterozygosity is also associated with increased risk for autoimmune and fibroproliferative disease (chronic asthma exacerbation).

Facilitating Investigator-Initiated Grant Applications in Genomic Medicine – *Teri Manolio (NIH/NHGRI)*

- As the Genomic Medicine field matures, the opportunity for Investigator-Initiated (as opposed to Institute-Initiated) research increases.
- Currently, the NHGRI receives few Investigator-Initiated applications in the Genomic Medicine field. The group discussed the known reasons for this (concern that NHGRI is not willing to fund, no clear home for peer review) and provided additional insight (acceptance rate of discovery vs implementation projects, partnerships with other Institutes needed). Teri shared feedback from the study sections on why Genomic Medicine applications tend to review poorly (too vague, not innovative).
- The group discussed targeting NHGRI study sections other than SEIR (DIRH, HSOD), how to work with CSR (use the language of the study section you are targeting in your application's specific aims, interact with CSR when then call you to discuss your project), and open Investigator-Initiated funding opportunities. Investigators are encouraged to apply for funding if they have ideas.

Day 2: External Scientific Panel Session

Opening Remarks – *Teri Manolio (NIH/NHGRI) & Rongling Li (NIH/NHGRI)*

- Welcome and thank you to the ESP for their expertise and contributions to the Network.

Comments from ESP Interim Chair – *Eta Berner (UAB)*

- Eta Introduced ESP members Geraldo Heiss (UNC), Stan Huff (Intermountain Healthcare), Lisa Parker (U Pittsburg), and Kim Doheny (Johns Hopkins).
- ESP will ask clarifying questions after each presentation if needed and hold in-depth comments and recommendations for the end of the day.

eMERGE Network Overview: Priorities and Goals; Review of Progress of Prior ESP Recommendations & Best Practices Topics – *Rex Chisholm (SC Chair, Northwestern)*

- Rex reviewed the Network specific aims, publication status, and responded to the recommendations made by the ESP in February of 2016: Network wide project being developed to study social and ethical issues, all variants are being provided to sites for their review.

The eMERGE sequencing panel: CSG updates on performance, content curation and sequencing progress – *Richard Gibbs (BCM), Birgit Funke (Partners/Broad) and Sandy Aronson (Partners/Harvard)*

- The CSGs provided an overview of the pipeline, the sequencing panel, the capture design, and the timeline. They also provided current progress and initial results, and outlined next steps.
- Sandy provided an update on the flow and integration of data between the two CSGs. eMERGE Network efforts show that it is possible for two discreet labs to have clinical data flow into a single shared repository (GeneInsight Knowledgebase), with the data harmonized and useable (able to be queried).
- The group discussed and clarified what data would be on which platform. Sites will have access to both raw genetic data and clinical interpretation results. VCF files will be available via DNANexus for all contributing sites. Structured results will be available as XML files via DNANexus (for Baylor sites) and Partners sFTP site (for LMM/Broad sites), and Query & Download (XLS) files will be available via GeneInsight (for LMM/Broad sites). De-identified data will be available via DNANexus (XML) and via GeneInsight (XLS) for all sites. "De-identified" in the context of the case repository is data stripped of PHI such as name, and date of birth.
- Richard clarified the status and function of the Dashboard on DNAnexus and how it will be used in the eMERGE Network to track progress and run simple queries.

ACTION ITEM: CSGs will work to develop near real-time synchronization of variant curation.
ACTION ITEM: CSGs will complete the addition of CNV calls to reports.
ACTION ITEM: Baylor will complete the DNANexus dashboard and tool development.

CERC Survey Project Update & Discussion – *Ingrid Holm (BCH) & Maureen Smith (Northwestern)*

- During Phase II, the eMERGE Network conducted a survey designed to help policymakers understand how underrepresented populations thought about biobank research (including: benefits, concerns, information needs and wiliness to participate). The hope is that the findings will be of value to those involved in biobank governance and the development of educational materials for individuals considering taking part in biobank research.
- Results:
    - The study found little evidence that type of consent and data use affected willingness to participate in a biobank.
    - The group identifies demographic characteristics and attitudes that may help target efforts to increase wiliness to participate in biobank research.
    - Only 75% of parents willing to participate in a biobank would agree to let their child participate
    - Parents perceived fewer benefits and greater concerns for their child participating in biobank research compared to themselves.
- Next steps are to determine demographic, SES, trust and privacy issues that explain differences in parent/child willingness to participate.

Clinical Annotation Workgroup Report –*Gail Jarvik (GHC/UW)*

- Workgroup accomplishments include applying the ClinGen approach to Gene-Disease validity to develop a consensus list of genes and variants that will be returned Network-wide. A manuscript describing this process and the outcome (the variants to be returned), is in development. The group also harmonized interpretation discrepancies of previously reported variants in the eMERGE-Seq panel.
- Next steps:
    - Review the update to the updated ACMG 56 gene list to be released this winter.
    - Compile a list of Network experts on the genes/SNVs on the eMERGE-Seq panel for rapid feedback as the group considers lower penetrance/impact variants (focusing on molecular experts and care experts).
    - Develop an additional (incidental/secondary) findings manuscript.
    - Review lower penetrant risk variants. This includes defining "low penetrant" and deciding if they should be returned.
    - Ancillary study of CNVs.

ACTION ITEM: The Clinical Annotation Workgroup will develop a list of experts to support variant interpretation.
ACTION ITEM: The Clinical Annotation Workgroup will work with CSER to plan the joint meeting scheduled for February 2017.

Genomics Workgroup Report – *Megan Roy-Puckelwartz (Northwestern), Patrick Sleiman (CHOP), & David Crosslin (GHC/UW/CC)*

- The group discussed the aims of the Geocoding supplement (to enrich phenotypic data from the EHR with environmental variables to enable gene-environment interaction analysis (including SES, and food desert data). The group discussed expertise available and working with the Phenotyping Workgroup.
- Workgroup accomplishments include development of an analysis pipeline, identifying tools needed in DNAnexus, completing an in-person DNAnexus training, and outlining SPHINX updates.
- The CC is imputing and merging pre-e3 data, developing a coordinated phenotyping dataset, and recalling/annotating the PGRNSeq data.
- A subgroup has been created, focusing on the imputation and sequence alignment of the HLA region. The goal of the subgroup is to generate highly accurate HLA calls and link this to phenotype data.

ACTION ITEM: CC will make all documentation around imputed/merged dataset available to the Network.
ACTION ITEM: CC will make a coordinated phenotyping dataset available to the Network.
ACTION ITEM: CC will complete Q/C and make all documentation around the PGRNSeq data available to the Network.

Phenotyping Workgroup Report-Out – *Josh Denny (Vanderbilt) & George Hripcsak (Columbia)*

- Workgroup accomplishments to date include:
  - The first four prioritized Phase I and II Phenotypes have been (re)implemented. The group will continue to pursue (re)implementation of the remaining phenotypes. Lead authors of Phase I and II phenotype manuscripts will be provided a status summary.
  - Development/implementation of Phase III phenotypes is in progress and expected to be complete by February of 2018.
  - The Network definition of "Consistent Care" is mature. Next steps include defining and validating the definition clinically and adding it to PheKB.
- Next Steps/Discussions:
  - Phase III Phenotype development/Validation: Does the number of case/controls need to be increased? Does training/test environment need to be noted?
  - The group expressed concern over the large list of covariates in some Phase I and II phenotype data dictionaries.
  - Volunteers are converting their data model to OMOP. The group will discuss the possibility of cross-platform work.
  - Determine possible phenotypes for HLA studies.

ACTION ITEM: The Phenotyping Workgroup will continue to (re)implement the remaining Phase I and II Phenotypes.
ACTION ITEM: CC will reach out to lead authors of Phase I and II manuscripts with a status summary.
ACTION ITEM: The Phenotyping Workgroup will work to complete development/implementation of Phase III phenotypes by February 2018.
ACTION ITEM: The Phenotyping Workgroup will clinically define and validate the Consistent Care definition and add it to PheKB.

eMERGE PGx Project Update & Discussion – *Laura Rasmussen-Torvik (Northwestern)*

- Laura provided the group an overview of the aims of the workgroup, described the role and function of the group in Phase III, and gave an update on the accomplishments and progress of group project.
  - Four manuscripts have been published to date, two more are currently in review.
  - The CC remapped and recalled the PGRNSeq dataset.
  - Five projects are ongoing, with an additional 7 PGx phenotype project in progress (several other e-III phenotypes have indicated they will use PGRNseq data in addition to GWAS and e3 sequencing data).
- Next steps
  - Haplotype level analysis

- Develop a schema to prioritize PGx Phenotypes among the rest of the e-III phenotypes
- How to/should the group work to capture PGx outcomes outside the EHR.

EHR Integration Workgroup Report – *Sandy Aronson (Partners/Harvard) & Casey Overby (Geisinger/JHU)*

- The co-chairs provided update on work-to-date: 1) facilitating establishment of the network infrastructure for clinical genomic report delivery; 2) an upcoming network-wide paper (description of first stage of establishing a multi-lab-multi-site network infrastructure for structured delivery of results); 3) establishing a process to capture factors influencing implementation; 4) current and planned projects.
- The workgroup focused on the transfer of clinical reports in a robust manner. Co-chairs approached their workgroup goal by gathering requirements, determining the network topology and setting file formats. Note: SFTP and XML are manageable by all sites, and real-time data access is not a requirement.
- The workgroup discussed milestones the to be captured throughout this project, both network and site-specific. The workgroup will also conduct a retrospective review of barriers as compared with collected anticipated barriers collected.
- Next Steps:
  - The eMERGE EHRI WG contributed to defining requirements for common eMERGE network infrastructure
    - EHRI community input on requirements for sites to receive lab report content
    - Implement next steps for approved network-wide paper concept sheet – NT184: Establishing Electronic Genetic Report Flow Within the eMERGE Network to Enable Genomic Clinical Decision Support
  - Facilitate next phase of network buildout
  - Establishing a process to capture factors influencing implementation
    - Site-contacts to prepare milestones and projected timelines
  - Research focus – upcoming concept sheets
    - Longitudinal study of barriers to implementation
    - IT capabilities and mechanisms for decision support delivery & reporting
  - Planned interactions and collaborations with liaison groups with the knowledge that there are multiple delivery mechanisms that should be considered.
    - ROR WG – categories of results & decision support delivery mechanisms
    - Outcomes WG – reporting process and intermediate outcome metrics
    - EHRI WG - IT capabilities and mechanisms for decision support delivery & reporting
    - Includes Infobuttons
    - Shared responsibility in some areas (e.g., user response to CDS

ACTION ITEM: EHRI Workgroup sites will prepare milestones and projected timelines to establish a process to capture factors influencing implementation.
ACTION ITEM: EHRI Workgroup will liaison with ROR/ELSI and Outcomes Workgroups.
ACTION ITEM: EHRI Workgroup will continue progress on barriers concept sheet and develop a concept sheet for IT capabilities and mechanisms for decision support delivery and reporting.

RoR/ELSI Workgroup Report – *Ingrid Holm (BCH) & Iftikhar Kullo (Mayo)*

- Collected data from all sites on return of results projects and plans at each site, as well as outcome measures – Completed
- Project to study the ELSI impact of ROR on health care providers (HCP) across the eMERGE sites
  - Applied for a supplement through eMERGE and received an award funded by the ELSI branch. Pilot study across the eMERGE sites, and subgroup of ROR/ELSI workgroup.
  - The goals of the pilot project are to develop and test a survey of HCP that can be implemented across the eMERGE Network with future funding.
  - In discussion for applying for additional NIH funding to facilitate goals of the overall study: To assess the impact of disclosure of unsolicited genetic results on provider perceptions of appropriate clinical

management, including both HCPs' perceptions of clinical benefit/utility, and their perception of their responsibilities in relationship to the role of other HCPs

- Project to study the ELSI impact of ROR on patients across the eMERGE sites: Develop data collection tools to implement across sites
    - How to harmonize baseline and post-disclosure participant surveys to understand the impact of return of genomic information to participants: subgroup of ROR/ELSI. Baselines were previously developed, making harmonization difficult. Domains in baseline: disclosure. Domains in post-disclosure: privacy, intent to share with family members, decisional regret, and impact of genetic results.
- Patient Motivations Project – patient motivations for seeking elective genetic counseling in the context of clinical genomic sequencing.
    - Richard Sharp (Mayo) is leading this project at Mayo. Discussing how to transform this into a network-wide project.
- Process of Disclosure Project – returning genomic results to eMERGE III participants, the process of disclosure
    - Georgia Wiesner (Vanderbilt) is leading this project. Goal is to develop a core set of processes that will be employed the eMERGE sites in returning results.
- IRB Perspectives Project – gather experiences at sites with IRB interactions around return of unsolicited genetic results
    - Robyn Fossey and Iftikhar Kullo at Mayo will lead this project. Goal: to learn about the alternative IRB perspectives, concerns and insights, which will be informative to investigators/IRBs outside of eMERGE.
    - As a reminder, discussions regarding how results are being returned at each site:
        - Positive results
            - Automated deposit in HER
            - Letter ("bland" vs "informative")
            - Face to face with a genetic counselor (ex: Mayo)
            - Primary care provider, specialist
            - Participant choice
        - Negative results
            - Letter (ex: Mao, but with disclaimers)
            - Placement in patient portal
- Familial Implications of ROR - family communication supplement designed to understand how to contact family members
    - Janet Williams at Geisinger leads this project, which is a collaboration with the Outcomes Workgroup.
    - Joint meetings with the Outcomes WG to coordinate efforts across the WG
- Joint publication with Clinical Annotations group – eMERGE process and criteria for actionability of variants for return – Formulating concept sheet

ACTION ITEM: ROR/ELSI Workgroup will finalize and deploy data harmonized post-disclosure survey across sites.
ACTION ITEM: ROR/ELSI Workgroup will develop a concept sheet for developing a core set of disclosure processes that will be employed across eMERGE sites in returning results.

Outcomes Workgroup Report– *Hakon Hakonarson (CHOP), Josh Peterson (Vanderbilt) & Marc Williams (Geisinger)*

- The workgroup has completed mapping the possible outcomes for returned genes and subsequently prioritized gene(s)-outcomes pairs the workgroup intends to study (added 22q with CHOP leading). It is now defining specific outcomes projects.
- Process, intermediate and clinical outcomes (not actively capturing clinical outcomes)
- Initially prioritizing the following gene-outcomes pairs:
    - Familial hypercholesterolemia (site lead: Mayo for adults & Geisinger for pediatrics)
    - Breast cancer (site lead: Columbia)
    - Polyps/Lynch Syndrome (site lead: UW)
    - HF/cardiomyopathy (site lead: Northwestern)

    - Arrhythmias (site lead: Vanderbilt)
- Outlined a process to reconcile and synchronize site outcomes assessments and provided a basic example for Familial hypercholesterolemia.
- Familial implications of ROR (Janet Williams at Geisinger)
    - Collect outcomes directly from proband around this cascade testing issue. The subgroup was formed with representation from both the Outcomes and ROR workgroups, and meets on a monthly basis.
- Economics subgroup
    - Waiting for more info about outcomes collected
    - General approach: analysis of standardized costs attached to differences in healthcare utilization between Variant Positive (+) and Variant Negative (-) cohorts
    - Projected (outside scope of workgroup): analyze projected savings over time for when health outcomes are expected to change as a result of ROR
- Pediatrics subgroup:
    - Pediatric-specific outcomes for workgroup phenotypes
    - Focus on two phenotypes: asthma and TPMT
- Next steps:
    - Focus on completing protocols; develop standardized data collection forms; develop a workgroup manuscript around measuring outcomes for large sequenced panels.

ACTION ITEM: Outcomes Workgroup will complete protocols.
ACTION ITEM: Outcomes Workgroup will develop standardized data collection forms for prioritized gene-outcomes pairs.

External Scientific Panel: Executive Session

Attendance:

ESP: Stanley Huff (IMH); Kimberly Doheny (JHU); Eta Berner – Interim Chair (UAB); Gerardo Heiss (UNC); Lisa Parker (U Pittsburgh); Vandana Shashi (Duke)*; Howard McLeod (Mofitt)*; NHGRI: Jyoti Gupta; Sheethal Jose; Rongling Li; Teri Manolio; Ken Wiley;

- The External Scientific Panel (ESP) met with members of the NHGRI Program Staff in an Executive Session before and after the Steering Committee (SC) meeting on October 7, 2016. Since some ESP members attended the first day of the SC meeting held on October 6, 2016, Rongling provided a brief update on Day 1 of the meeting. The ESP gave a brief overview of their previous recommendations and what the Principal Investigators (PIs) have addressed in their reports to the ESP members.
- Overall, the ESP was extremely impressed with the Network activities and progress. The investigators' presentations clarified the ESP members' concerns on consistency of variant annotation, data pipeline and data sharing, and clinical data reporting. The ESP made some recommendations to improve the network research approaches according to the current progress.
- The ESP stressed that the Network should strive for consistency across sites wherever possible throughout its process of return of results (RoR). Particularly where consistency is not achieved, the Network should use the differences as a naturally occurring experiment and study the implications of the different practices. They suggested that the researchers should explore best practices among the different sites and work together to resolve any conflicts so as to ensure consistency in the RoR process.
- The ESP recommended that the Network sites create a timeline that details the period between receiving the clinical reports from the sequencing centers and returning results back to the patients. It was not clear in the presentations how long it would take before the reports are returned to the patients.
- The ESP stressed that it is critical to address the ELSI issues as well as the scientific issues that come up when PIs decide what results they will return to the patients. In addition, they should publish on challenges faced, issues unresolved, lessons learned, and best practices developed. They noted that decision-making on pathogenic and likely pathogenic variants to be reported back to patients seems to differ across sites but these differences and the

reasons for them are not clear. The ESP recommended that PIs record their decision-making process on which variants they choose to return to their patients, record the number of times PIs make changes in what was proposed to be returned, analyze these decisions systematically and then disseminate this analysis through publications. It may also be valuable to include ELSI investigators or those who have research experience/interest from a philosophy of science perspective as observers of these decision-making processes.

- The ESP had concerns on the reporting done by the sequencing centers (CSGs) and what is given back to their respective sites. They noted that inconsistency remains between the 2 CSGs on the types of reports (i.e. negative, positive, and inconclusive) being generated. NHGRI staff explained that there were budgetary constraints which prevented them from achieving full consistency between the CSGs. Baylor has an automated process for reporting while LMM has a largely manual process. However, LMM has agreed to provide specific variant categories such as variant of uncertain significance (VUS) and negative reports to some sites to achieve their scientific objectives. The ESP felt that it is necessary to assess the impact of the inconsistency between the 2 CSGs' reports on the Network goals and attempt to minimize differences across clinical sites based on the CSG to which they are assigned. This assessment can be of both ELSI and scientific significance.
- The ESP recommended that eMERGE PIs should work with the HL7 standards group through the HL7 Clinical Genetics Working Group (WG) teleconferences. They can have one person from the EHRI WG attend HL7 calls and provide input to the developers. The HL7 standard is getting a lot of support and is being adopted by several EHR vendors. This is a great opportunity for the researchers to simplify the phenotyping process for research. It will also benefit the standards group to understand the needs of the researchers.
- The ESP felt that the NHGRI Program Staff should make sure that the sites continue to collect outcomes data and study the impact on return of results for the PGx project. They asked whether, decades from now when more genetic variants are known for commonly used drugs, those new risks will be reported to relevant variant carriers among the PGx participants.
- The ESP suggested that the Network take the opportunity to describe and analyze the process of switching EMR systems and its impact on eMERGE research and implementation. Both Mayo and VUMC are switching from their homegrown EMR systems to Epic. It may benefit the network to hear about the sites' experience of switching EMR systems and what implications it may have. The ESP felt that the PIs should consider reporting that experience beyond the network, (e.g. publishing on how the challenges are addressed) for the benefit of others who will face similar decisions and implementation issues.
- The ESP recommended that the Network members work together to create more collaborative, network-wide products. For example, the phenotyping and EHRI WGs should work together and NHGRI staff should encourage them to do so.
- The ESP felt that investigators should consider the 'ancillary study' mechanism as a collaborative approach, which was successfully implemented by many NIH-supported studies, in order to broaden access by the scientific community to the national resource represented by the eMERGE Network.
- Lastly, the ESP encouraged the Network to actively disseminate lessons learned, best practices, experiences in conducting research, and results from the genomic discovery and clinical implementation research using EHR and biorepositories to the scientific community.

ESP Recommendations

To investigators:

- The Network should explore best practices among the different sites and work together to resolve any conflicts so as to ensure consistency in the process of return of results.
- The Network sites should create a timeline that details the period between receiving the clinical reports from the CSGs and returning results back to the patients.
- The Network should address the ELSI issues as well as the scientific issues that come up when PIs decide what results they will return to the patients and they should publish on challenges faced, issues unresolved, lessons learned, and best practices developed.

- The Network PIs need to document their decision-making process regarding which variants they choose to return to their patients, record the number of times PIs make changes in what was proposed to be returned, analyze these decisions systematically and then disseminate this analysis through publications.
- The sites should assess the impact of the inconsistency between the 2 CSGs' reports on the Network goals and attempt to minimize differences across clinical sites based on the CSG to which they're assigned.
- The Network PIs should work with the HL7 standards group through the HL7 Clinical Genetics Working Group (WG) teleconferences.
- The Network should take the opportunity to describe and analyze the process of switching EMR systems and its impact on eMERGE research and implementation.
- The Network members should work together to create more collaborative, network-wide products.
- The investigators are encouraged to consider the 'ancillary study' mechanism as a collaborative approach in order to broaden access to the national resource represented by the eMERGE Network.
- The Network should actively disseminate lessons learned, best practices, experiences in conducting research, and results from the genomic discovery and clinical implementation research using EHR and biorepositories to the scientific community

To NHGRI:

- NHGRI Program Staff should make sure that the sites continue to collect outcomes and study the impact on return of results for the PGx project. NHGRI should ensure that any newly discovered risks are reported to variant carriers in the PGx participants.
- NHGRI Program Staff should encourage more collaborative projects among the eMERGE Network members.

Summary of Action Items

1. Members are encouraged to investigate other funding mechanisms for supplements that were not funded.
2. The Phenotyping Workgroup will develop an overall timeline for completion of all 42 eMERGE phenotypes.
3. Review the DocUBuild Platform, and provide feedback to Luke Rasmussen regarding what is practical and pragmatic at your respective institutions and within your workflow. Login email: demo@emerge.com; Login password: emerge
4. CSGs will work to develop near real-time synchronization of variant curation.
5. CSGs will complete the addition of CNV calls to reports.
6. Baylor will complete the DNANexus dashboard and tool development.
7. The Clinical Annotation Workgroup will develop a list of experts to support variant interpretation.
8. The Clinical Annotation Workgroup will work with CSER to plan the joint meeting scheduled for February 2017.
9. CC will make all documentation around imputed/merged dataset available to the Network.
10. CC will make a coordinated phenotyping dataset available to the Network.
11. CC will complete Q/C and make all documentation around the PGRNSeq data available to the Network.
12. The Phenotyping Workgroup will continue to (re)implement the remaining Phase I and II Phenotypes.
13. CC will reach out to lead authors of Phase I and II manuscripts with a status summary.
14. The Phenotyping Workgroup will work to complete development/implementation of Phase III phenotypes by February 2018.
15. The Phenotyping Workgroup will clinically define and validate the Consistent Care definition and add it to PheKB.
16. EHRI Workgroup sites will prepare milestones and projected timelines to establish a process to capture factors influencing implementation.
17. EHRI Workgroup will liaison with ROR/ELSI and Outcomes Workgroups.
18. EHRI Workgroup will continue progress on barriers concept sheet and develop a concept sheet for IT capabilities and mechanisms for decision support delivery and reporting.
19. ROR/ELSI Workgroup will finalize and deploy data harmonized post-disclosure survey across sites.

20. ROR/ELSI Workgroup will develop a concept sheet for developing a core set of disclosure processes that will be employed across eMERGE sites in returning results.
21. Outcomes Workgroup will complete protocols.
22. Outcomes Workgroup will develop standardized data collection forms for prioritized gene-outcomes pairs.

Next Meeting: February 1st and 2nd, 2017 in Bethesda, MD

emerge network
ELECTRONIC MEDICAL RECORDS & GENOMICS

eMERGE Network: Summary of the Steering Committee Meeting

February 1, 2017 in Bethesda, MD

The winter Year Two, Phase III eMERGE Steering Committee was held on February 1st, 2017 in Bethesda, MD. In order to ensure that the Network continues on a productive note midway through our second year, please find highlights from the Meeting below. Day 2 of the meeting (February 2nd) was joint with the CSER consortium.

Presentation slides are available here (login required).

Full Session

Welcome, Opening Remarks, General Updates | *Rongling Li (NIH/NHGRI)*

- Rongling Li, on behalf of the NHGRI eMERGE Team, provided the Program Official Report for the 29th eMERGE Steering Committee Meeting. It is noted that Carolyn Hutter, Ph.D. is now the Acting Director of the Division of Genomic Science at the NHGRI.
- The Network reviewed the eMERGE Phase III Timeline, specifically noting the inclusion of an Interim dbGaP Data Submission after July 2017 at which time at least a portion of the sequencing data will be available from all sites. The Interim dbGaP Data Submission will serve as a work product of the first half of eMERGE Phase III and position the Network favorably for a potential eMERGE Phase IV continuation.
- A high level overview of eMERGE's data contribution to the scientific community at large as of 1/27/2017 was provided, specifically noting 1617 approved data access requests. In addition, eMERGE data availability was reviewed, including data type, size (n), DNAnexus date, and dbGaP submission.
- The Program's goals for the meeting were outlined, which are included below:
    - Update on genomic sequencing status and dataflow
    - Report on eMERGE data imputation
    - Refine timelines for sequencing, phenotyping, network data management, and dbGaP data submission
    - Set up site-specific timeline for RoR
    - Update on ongoing scientific projects
    - Propose new network-wide projects/studies
    - Identify gaps in genomic medicine that can be filled continuously by combining biorepositories and EMRs
    - Suggest possible directions for potential eMERGE IV initiatives
- Questions for workgroups to address in their breakout sessions are listed below. Any questions unable to be addressed in the allotted time today can be discussed within the workgroups monthly meetings or at the next Steering Committee meeting in June.
    - What are the deliverables in eMERGE III?
    - What is the timeline for completing these deliverables?
    - What are the barriers that are hindering the ability to complete the goals of the workgroup?
    - How will the workgroup products build the foundation for a possible eMERGE IV?

Announcements, Opening Remarks | *Rex Chisholm (Northwestern/SC Chair)*

- In response to feedback from the Network, the agenda has been structured in a format that allows for more time to be spent in workgroup breakout discussions.

- The following day is the second joint CSER/eMERGE meeting conducted since CSER's inception. Participation was encouraged as there are many synergies between the two Networks.
- Upcoming Steering Committee & ESP meetings and the publication status were reviewed, as well as developments since the prior Steering Committee/ESP meeting (October 2016), which are included below.
    - eMERGE received a favorable ESP report. The ESP suggested the Network collect outcomes and study impact of ROR for PGx, which the Network addressed by elevating PGx to full workgroup status and acquiring an additional co-chair (Cindy Prows of CCHMC). The ESP also suggested initiation of more collaborative projects amongst the Network members. Rex pointed towards the 1800 available whole genomes (CHOP and NU) and the exomes from Columbia as potential areas for collaboration.
    - Imputation of eI/eII/eIII array data on the Michigan Imputation Server (MIS) is in process with intended completion by March 2017.
    - The CSGs have begun return of sequencing results and clinical reports to sites. To date, 6800 samples received, 3800 sequenced, and 293 clinical reports issued.
    - PGx dataset is finalized, and the dbGaP upload is in process.

Addressing Ethical Challenges in Networked Biorepositories | *Kyle Brothers (CC/U. of Louisville) & Aaron Goldenberg (Case Western)*

- This project's goals are: 1) to characterize the ethical and regulatory challenges created by current networked biorepositories, and 2) to identify policy and practice solutions to address these challenges. It is funded through the ELSI program of the NHGRI, *NHGRI 1R01HG008988-01A1.* The project's website: www.BiobankNetworks.org
- Specific aims of the project include:
    - Examine the ethical and regulatory challenges in existing networked biorepositories and the solutions they use to address them ("Bio-network" Survey and Interviews)
    - Longitudinal observations of the governance, oversight, and problem-solving processes utilized by networked biorepositories (Participant Observations): Mayo Clinic Biobanks, Kentucky Cancer Registry, eMERGE Network, Sage Bionetworks, NBSTRN Virtual Dried Bloodspot Repository, Others?
    - Create best practices or other recommendations to address consent, privacy and data security, data access, governance, and oversight in networked biorepositories (Translational Aim): National Symposium/Workgroup on /Networked Biorepositories

Undiagnosed Genetic Disorders in Adults with Chronic Kidney Disease (CKD) | *Ali Gharavi (Columbia)*

- This work focused on the relationship between Chronic Kidney Disease and genetic disorders. Specifically, 1.5% of adults with CKD have a diagnosable genomic disorder that may have implications for medical management. Exome sequencing offers the opportunities to define late onset complications of known disorders, identify new mechanisms of injury, and establish their genetic basis.
- Ali presented a study that showed enrichment for 5 genomic syndromes with specific associations. In addition, his study indicated a global association between CKD and neurocognitive phenotypes.
- eMERGE is developing CKD and autoimmunity phenotypes in eIII, as well as developing network wide concept sheets to identify CNV associations with CKD and kidney developmental phenotypes and GWAS/CNV analysis of autoimmunity traits. Further there are three genes on the eMERGE-Seq panel that will serve to confirm the penetrance of known phenotypes and discover new associations.

Sequencing and Genomic Data Update | *Heidi Rehm (Partners/Broad), Eric Venner (Baylor) & David Crosslin (CC/UW)*

- Sequencing Center Update

- Sequencing Centers oriented the group to the Network's current status in the sequencing ecosystem and provided metrics/summary statistics for samples that have already been sequenced. In addition, sequencing centers addressed sample requirements, and their plan to complete CAP mandated proficiency testing.
    - Partners/Broad has sequenced 1221 samples from the KPW/UW and 91 samples from Geisinger. An example of the variant curation form and CNV output files was presented and will be circulated to sites. The variant curation form will include ALL variants assessed with annotations and interpretation notes. The CNV output file will include all CNVs (note that likely pathogenic/pathogenic CNVs ≥ 3 exons will be reported clinically). Partners/Broad reviewed plans for PGx reporting. Case studies of secondary/incidental findings were presented. eMERGE's VariantWire application was approved, allowing eMERGE sites to view interpreted variants in that network.
    - 406 samples are completely through the Baylor pipeline. The group discussed site specific reporting requirements, which will be accommodated as allowed by assay design, with additional tables added to clinical reports.

- Genomic Data Update
    - eMERGE Imputed dataset: All eMERGE array date including legacy data is being re-imputed against the HRC reference using the Michigan Imputation Server. The total merged set (pre-QC) has a sample size of 85,150. CC will provide the following deliverables to the network:
        - A merged PLINK file with posterior probabilities at .7, .9 or both.
        - A merged VCF file
        - A merged posterior probability file
    - PGRNSeq re-alignment: All ID issues have been resolved and BAMs have been re-aligned to the same reference. The new annotated, QC'd dataset with individual BAMs and VCFs will be uploaded to dbGAP and made available to the network (SPHINX) imminently. The Genomics Workgroup will address privacy concerns and finalize SPHINX private/public side updates by April 2017.

Meharry Medical College (Site Update) | *Samuel Adunyah (Meharry) & Phil Lammers (Meharry)*

- Drs. Adunyah and Lammers presented an overview of the Meharry Translational Research Center (MeTRC), including MeTRC's goal for its current cycle (2014-2019), leadership/governance structure, and background information about Meharry Medical College, specifically noting that it is a historically black medical college and focuses on providing care to underrepresented minorities. In addition, they detailed MeTRC's marketing and recruitment strategies, timeline for recruitment/enrollment/ROR/data analysis and reporting, and current progress to date for achieving their eMERGE goal.
- MeTRC's role within eMERGE is to recruit and obtain blood samples for DNA extraction for germ-line sequencing from up to 500 African American participants with cancer or at high-risk for cancer. Results will be returned to physicians and patients via EMR, and sequencing data will also be shared across the eMERGE sites. As part of their protocol, MeTRC will obtain both RNA and protein from blood samples for additional studies in various projects by Meharry and external investigators.
- Recruitment population: Breast cancer, prostate cancer, colorectal cancer, lung cancer. The goal is to have equal cohorts in each risk sub-category (affected cohort and high-risk cohort).
- Demographics: Age 22-44 represents 42% of their total ~226k population, and age 45-64 represents 30%. Of the total population, 74% identify as Not Hispanic of Latino.

Closing Remarks | *Rex Chisholm (Northwestern/SC Chair)*

- Steering Committee is reminded of the goal to generate eMERGE/CSER joint projects.

- Interim dbGaP submission: The group raised no concerns, therefore it is agreed that the interim dbGaP submission in late summer or early fall is acceptable. The 109 genotype panel will be submitted.
- Marylyn Ritchie (Geisinger) will circulate a concept sheet to run an eMERGE-wide GWAS submission for the Global Lipids Genetics Consortium's next round of global GWAS meta-analyses.

Workgroup Report-Outs

Genomics Workgroup & Geocoding Supplement | *Megan Roy-Puckelwartz (Northwestern), Patrick Sleiman (CHOP) & David Crosslin (CC/UW)*

- Genomics:
  - Deliverables/Timeline for completion:
    - Imputed genotype data: Imputation/merging will be complete March 2017. The group may want to re-visit calling indels in the future, as they will not be included in this dataset.
    - PGRNSeq realignment: The re-aligned dataset will be available to the Network in February 2017.
    - eMERGE-Seq Data: Sequencing will be complete in 2018
    - HLA region investigations: This is a collaboration/group effort and is expected to yield eMERGE deliverables.
    - DNAnexus Tools: Geisinger has already made some tools available and will make project data (input/tools used/output) available for testing. The group will develop more tools for use in the eMERGE analysis pipeline.
    - WGS: 1800 diverse samples are available for analysis, and will be made available to HRC for enhancement of that dataset. The dataset is currently in dbGaP, with the goal of moving it to DNAnexus.
    - SPHINX: The SPHINX resource will be expanded to include realigned PGRNSeq and eMERGE-Seq data. Expanded annotation and the addition of phenotype data are being discussed.
  - Challenges with data generation and analysis have been overcome
  - Foundation for eMERGE IV: eMERGE III will focus on discovery/lessons learned. A tremendous amount of data has been/will be deposited into dbGaP, and eMERGE IV could continue to explore the richness of this data. Developing a core dataset of common demographics and covariates, and generating best practices on implementing a common data model could also be addressed in eMERGE IV.
- Geocoding:
  - Patrick outlined the methods, variables, and address format the Geocoding group will use to produce its deliverables.
    - Centralized vs distributed method. The group is investigating using DNAnexus as a web-based, centralized method of generating and analyzing geocoded data.
    - Environmental variables have been prioritized, and as many as possible will be incorporated.
  - Next steps include defining and testing the analysis pipeline, disseminating the SOP to the group, and depositing demographics/exposure data in a central repository (DNAnexus).

EHR Integration Workgroup | *Sandy Aronson (Harvard/Partners)*

- The EHRI workgroup remains focused on fulfilling the goals of their charter. They have established a core network. Data is flowing into the core repositories, and data is almost at the point of flowing to the

individual sites. This flow of data is mediated by a common file format working across the network for moving results.

- The workgroup's next step is to move data into the sites, and ensure that it is properly digested and used at the site-level. Because the data flow will vary across sites, the workgroup is now focused on determining internal workflows and how to best accomplish fulfillment of establishing end-to-end data flow across the network. It is noted that each site will have to utilize a parser and has different clinical/research workflows into the EHR system.
- Science: The workgroup is writing a manuscript on inter-institutional network capabilities thus far; tracking milestones with anticipation of writing a manuscript on the sites' experiences with establishing infrastructure based on structured files; developed a subgroup focused on infobuttons.
- Community: The workgroup is involved with the HL7 Clinical Genomics Working Group, the CSER EHR Working Group (DIGITizE Lynch Syndrome Collaboration, Evaluating Cost of CDS), and Infobutton Work (multiple synergies including with ClinGen)
- Next steps for the workgroup include evaluating site digestion processes and estimating timelines. Members will also discuss eMERGE Phase IV on their next workgroup call.

PGx Workgroup | *Laura Rasmussen-Torvik (Northwestern) & Cindy Prows (CCHMC)*

- The PGx workgroup participated in Clinical Annotation, Genomics, and Phenotyping workgroup breakout sessions. For the report out, Laura gave a brief summary of what was discussed in the other workgroup sessions (described in their respective sections), and gave an update on phenotype and non-phenotype projects being developed by group members.
- Ongoing PGx workgroup activities include tracking CDS activities, collecting additional outcomes data, and developing a PGx analysis pipeline.
- Barriers: Group participation will help overcome barriers.
- PGx reporting in eIII: Sequencing centers will provide signed CLIA reports. The group discussed what individual sites will do with the information on the reports as this could be an opportunity to expand PGx work with varied responses. This depends, in part, on format standards used and if they are compatible with site EMRs. Sequencing centers will provide mock reports to the group when available. The group discussed whether the report is clinical or research oriented and what responsibility/obligation the network has to returning results to patients. This discussion will be continued.
- Information on the overlap of participants in PGx/eI-III will be updated and circulated.

Outcomes Workgroup | *Josh Peterson (CC/Vanderbilt), Hakon Hakonarson (CHOP) & Marc Williams (Geisinger)*

- As a reminder, the Outcomes Workgroup will develop cross-site outcomes to track implementation and impact of eMERGE III sequencing. The workgroup will focus on answering the overarching question of whether returned eMERGE III-generated genomic results impact health care utilization and outcomes of importance to patients and families.
- The workgroup is in Stage 3/3 in its progress towards preparing for outcomes studies, which is to define specific outcomes projects. To facilitate this stage, the workgroup is in the process of developing data collection instruments. The workgroup is focused on prioritizing higher frequency phenotypes across sites to collect outcomes, and will talk further with Columbia about prioritizing Chronic Kidney Disease (CKD).
- The outcome assessment workflow is split between Variant Positive Results (Case, N=~1000) and Variant Negative Results (Control, N=~24000). Variant Positive Results will go through a detailed manual and EMR-based abstraction, whereas Variant Negative Results will run through automated extraction from EHR. Most of this will occur around 6 months after ROR that way there will be patient and EHR data available at

the same time point to cross-analyze. Many of these outcomes assessment forms, which are phenotype-specific, will be formatted in REDCap.

- Familial Implications of ROR Subgroup: The subgroup aims to evaluate outcomes related to cascade genetic testing, and working on clear challenges related to consent and accessibility of data on family of a proband. In addition, the subgroup is collaborating with the ROR/ELSI workgroup on and ancillary R01 studies to survey patients.
- Economics: The economics subgroup aims to focus on analysis of standardized costs attached to differences in health care utilization between Variant Positive and Variant Negative cohorts. The challenge is assessing which process measures are attributable to ROR. The economics subgroup also aims to analyze projected savings over time for when health outcomes are expected to change as a result of ROR.
- Pediatrics: The pediatrics subgroup aims to expand its pediatric asthma exacerbation frequency study to a larger cohort, match findings with other eMERGE cohorts and write a manuscript on its current findings within ~470 asthma cases.

Clinical Annotation | *Gail Jarvik (UW) & Heidi Rehm (Partners/Broad)*

- Heid and Gail presented the group's work interpreting and developing return of results protocol for secondary/incidental findings, which have been found in about 3% of each sequencing center's samples.
- The group has developed a feedback loop to interpret variants and finalize return plans for borderline or unanticipated results. Two case studies were presented to illustrate the process and its outcome.
- Most of the group's deliverables have been completed. The group is interfacing with the RoR/ELSI group to formalize eMERGE's role in informing ClinGen priorities and the ACMG list. The group is also providing input into PGx reporting plans.
- Processes and best practices for panel-based actionability determination, variant interpretation, and return of results are expanded products that could inform eIV work.

ROR/ELSI Workgroup & HCP Supplement | *Ingrid Holm (BCH) & Iftikhar Kullo (Mayo)*

- Disclosure of ROR project: Georgia Wiesner (Vanderbilt) and Kathy Leppig (Kaiser/UW) are leading an effort to survey site return of results processes. This will help inform the HCP survey and will also enable compare/contrast of ROR processes across sites.
- Participant Survey Subgroup: This subgroup is trying to harmonize participant surveys across sites in the hopes that sites will be able to collect similar data in order to enable compare/contrast studies.
- IRB Perspectives Project: This project, led by Robyn Fossey (Mayo) aimed to collate interactions with IRBs across sites and formulate lessons learned. A manuscript is in circulation for review amongst the group, and will be submitted shortly thereafter.
- Potential Workgroup Projects for 2017: Fragmented nature of family communication is a topic of interest for the group. Further additional projects include: qualitative analyses of Provider-Participant ROR encounter; Audio vs Videotaping; MyResults.Org expansion; re-contact by phenotype; collaboration with the Networked Biorepositories Project by Kyle Brothers and Aaron Goldenberg.
- Collaborations: The workgroup is aiming to collaborate with the Clinical Annotation Workgroup to address the meaning that participants attribute to results and if this will inform future ROR. Also with the Clinical Annotation Workgroup, the workgroup aims to address how patients and providers react to variant reclassification. The workgroup also aims to collaborate with the Outcomes Workgroup on the time of ROR, costs and healthcare utilization, and personal costs that the patients might incur as a result of ROR. With CSER, the workgroup aims to harmonize surveys with the CSER network as well as clinical education, and also provide input on the ACMG59.

- Health Care Provider (HCP) Supplement: This is a one-year supplement funded by the NHGRI ELSI Branch. The aims are 1) to develop a survey that will elicit the preferences of HCPs who are receiving genomic information as part of eMERGE Phase III, and 2) to pilot test the survey in a subset of HCPs at two of the eMERGE III sites, analyze that data, and finalize the survey for administration in the eMERGE III Network. Methods include literature reviews, interview of HCP to inform survey, survey development, cognitive interviews and piloting the study. The group has developed domains to structure survey and a timeline. Since the group was only funded to develop, and not implement, the survey, the group is working on submitting an R01 for implementation funding.

Phenotyping Workgroup | *George Hripcsak (Columbia) & Peggy Peissig (Marshfield)*

- The group reviewed the current status of Phenotype development and reimplementation. While progress was made, the group is concerned about the number and complexity of the phenotypes left to develop and implement.
    - Recommendation: each site develops 3 eIII phenotypes and implements 5-7 PGx Phenotypes.
        - The group will re-prioritize remaining phenotypes and generate a new timeline. Genomics workgroup representation at Phenotyping meetings is encouraged to assist in identifying common project interests.
        - The group will consider a new non-sequential and iterative workflow.
        - The group will simplify phenotypes and data dictionaries.
        - The group will develop a core set of covariates
        - Commitment to timelines is essential. The group expects to complete phenotype development by August of 2018 and will complete implementation in early 2019.
- Deliverables/timelines:
    - Phenotypes (Ongoing)
    - dbGaP Submissions (July 2017 and May 2019)
    - CardioCore resource (2018)
    - SPHINX and eRC data updates (ongoing)
    - Manuscripts
- Barriers:
    - Expanding scope of phenotypes (quantity and complexity)
    - Prioritization
    - Commitment to timelines
- Foundation for eIV:
    - Common Data Model validation and best practices. This could be accomplished with other funding.
    - New phenotype development workflow.
- How to make one consistent view of clinical conditions (phenotype) across case/control, covariate, and/or outcome status.

Summary of Action Items

23. Sequencing centers will complete CAP proficiency testing in March 2017.
24. Sequencing centers will complete pharmacogenomic pipeline validation/report format and begin issuing reports by April 2017.
25. Baylor will finalize their pipeline for submitting variants to ClinVar.

26. The Genomics workgroup will complete the imputed genotype dataset by March/April 2017 and make it available to the Network.
27. The Genomics Workgroup will complete QC on the re-called PGRNSeq dataset and make it available to the Network by March 2017.
28. The Genomics workgroup will finalize the data management pipeline for the eMERGE-Seq dataset by June 2017.
29. The Genomics workgroup will continue to develop the data analysis pipeline and tools available in DNAnexus (no timeline, continuous as needed development).
30. The Genomics workgroup will finalize SPHINX enhancement plans by the end of first quarter.
31. The Geocoding subgroup will define and test and gene x environment analysis pipeline.
32. The Geocoding subgroup will disseminate standard operating procedures for gene x environment analyses.
33. The Geocoding subgroup will deposit a dataset of demographic/environmental exposure in a central repository accessible by the Network.
34. The EHRI workgroup will complete its paper (NT184) on inter-institutional network capabilities that have been established thus far by May 2017.
35. The EHRI workgroup will track milestones in anticipation of formulating a manuscript by February 2018 depicting the experience of establishing infrastructure based on structure file based result transfer to sites.
36. The EHRI workgroup will continue collaboration with CSER's EHR working group on DIGITizE Lynch Syndrome, with an anticipated completion date of December 2017.
37. The EHRI workgroup will continue collaboration with CSER's EHR working group on evaluating cost of CDS, with an anticipated completion date of December 2017.
38. The PGx workgroup will work with the Phenotyping workgroup to integrate and prioritize PGx related phenotypes in the overall phenotype prioritization list and timeline. (Done)
39. The PGx workgroup will work with the Clinical Annotations workgroup and sequencing centers to develop a pipeline for return of PGx results in eIII (including providing input on what is on reports, coordinating return plans across the network).
    a. Laboratory representatives will provide updates and receive input on pipeline and reporting mechanisms. This began with 2/21/17 workgroup call.
        i. Both sequencing centers expect to begin delivering PGx data to sites in April 2017.
    b. Sites' ROR plans initially discussed during 2/21/17 workgroup call.
    c. Will present draft tracking sheet for sites' ROR plans at March 2017 meeting
    d. Will implement tracking sheet during Spring 2017 that sites can update as their PGx projects evolve
40. The PGx workgroup will create an analysis pipeline for common/rare PGx variant analysis on DNAnexus.
    a. Discussed during 2/21/17 workgroup call. Geisinger has an analysis structure for common and rare variants already developed in DNAnexus and can open it up to rest of the network.
        i. To provide demonstration at future call – targeting workgroup session before next SC
    b. Will discuss testing once PGRNseq realignment of BAMs and recalling of VCFs completed (anticipate testing to begin in Summer 2017)
41. The Outcomes workgroup will evaluate outcomes related to cascade genetic testing, specifically working on clear challenges related to consent and accessibility of data on family of a proband. This will be facilitated through their Familial Implications of ROR Subgroup.
42. The Outcomes workgroup will collaborate with the ROR/ELSI workgroup and ancillary R01 studies to survey patients.

43. The Outcomes workgroup will address analysis of standardized costs attached to differences in healthcare utilization between variant positive and variant negative cohorts. This will be facilitated through their Economics Subgroup.
44. The Outcomes workgroup will address analysis of projected savings over time for when health outcomes are expected to change as a result of ROR. This will be facilitated through their Economics Subgroup.
45. The Outcomes workgroup will replicate a pediatric asthma exacerbation frequency project on a larger cohort and match findings with other eMERGE cohorts. This will be facilitated through their Pediatrics Subgroup.
46. The Outcomes workgroup will finalize outcome assessment tools within next 3 months.
47. The Outcomes workgroup will conduct phenotype specific analysis in the next 12-24 months.
48. The Outcomes workgroup will conduct global outcome analyses in 24 months.
49. The Clinical Annotation and PGx Workgroups will work with sequencing centers to ensure pharmacogenomics reporting approaches are consistent with site needs.
50. The Clinical Annotation and PGx workgroups will seek consensus for returning structured pharmacogenomic data to sites so that it is consumable and conforms to informatics standards.
51. The Clinical Annotation workgroup will interface with the RoR/ELSI group (develop feedback loop from RoR studies to inform criteria/genes lists, formalize role of eMERGE and CSER in informing ClinGen priorities and ACMG list).
52. The ROR/ELSI workgroup will survey healthcare providers across sites to assess the impact of ROR on HCPs post-disclosure. This will be facilitated through their HCP Supplement Subgroup.
53. The ROR/ELSI workgroup will complete surveys of participants at baseline, post-disclosure and 6 months after disclosure. This will be facilitated through their Participant Survey Subgroup.
54. The ROR/ELSI workgroup will coordinate with the Outcomes Workgroup via the Familial Implications of ROR subgroup to address familial implications from the participant perspective.
55. The ROR/ELSI workgroup will complete a manuscript on IRB Perspectives across eMERGE.
56. The ROR/ELSI workgroup will complete a manuscript on the various process of ROR across eMERGE sites.
57. The ROR/ELSI workgroup will collaborate with the Clinical Annotation workgroup to address the meaning that participants attribute to results.
58. The ROR/ELSI workgroup will collaborate with the Clinical Annotation workgroup to address how patients and providers react to variant reclassification.
59. The ROR/ELSI workgroup will collaborate with the Outcomes workgroup to address the timing of ROR, costs and healthcare utilization, and personal costs.
60. The ROR/ELSI workgroup will assess the feasibility of potential additional projects discussed at the in-person meeting.
61. The Phenotyping workgroup will develop an overall phenotype prioritization list (including eIII, PGx, and eI/II phenotypes) and timeline for completion by the end of April 2017.
62. The Phenotyping Workgroup will develop a coordinated set of phenotypic variables that will form the base set of analysis variables used for all electronic algorithms. Data dictionaries will be kept succinct with few if any additional variables. This is anticipated to be defined/implemented by the June 2017 Steering Committee Meeting.
63. The Phenotyping Workgroup will define the phenotypic variables, led by David Crosslin, for inclusion in an interim dbGaP submission in July 2017.

64. The Phenotyping Workgroup will support SPHINX and eRC quarterly data refresh efforts.
Next Meeting: June 8th and 9th, 2017 in Boston, MA

eMERGE & CSER: The Convergence *of* Genomics *and* Medicine

Meeting Minutes *for* February 2, 2017

Opening Remarks

Lucia Hindorff *(National Human Genome Research Institute)*
Rongling Li (*National Human Genome Research Institute)*

- Provided a welcome to all and extended a big thank you to the program planning committee. Motivation for combining the Clinical Sequencing Exploratory (CSER) consortium and the Electronic Medical Records & Genomics (eMERGE) Network into a joint meeting evolved from acknowledgment that both CSER and eMERGE have similar areas of interests amenable to synergizing efforts. Goals of ongoing and future collaborations intended to advance genomics and medicine.

Top 5 Consortium-Wide Achievements from CSER & eMERGE

CSER Consortium | Gail Jarvik *(University of Washington)*

- Explores the application of genomic sequence data into the care of patients, with over 288 manuscripts published. Previous joint collaborations with CSER-eMERGE2 include CSER and eMERGE investigating the current and potential state of displaying and optimizing use of genetic information in the electronic health record (Shirts et al., *J Am Med Inform Assoc,* 2015) and undertaking efforts to identify consensus on returning genomic results to research participants (Jarvik et al. , *Am J Hum Genet,* 2014).
- Gail Jarvik summarized 5 key CSER-wide achievements thus far, including the following:
    - CSER calculated expected rate of actionable additional (secondary) findings (Dorschner et al., *AJHG,* 2013; Amendola et al., *Genome Res,* 2015).
        - Rates of known pathogenic variants, likely pathogenic variants, and novel variants expected to be disruptive amongst European and African ancestry were studied.
    - CSER has contributed more than 626 variant classifications to ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/)
    - CSER tested and clarified ACMG/AMP guidelines for variant pathogenicity classification in a CSER Act-ROR Working Group (WG) "Variant Bake-off" project (Amendola et al., *AJHG,* 2016)
        - Discussion and rule clarification increased classification concordance from 34% to 71%
        - Follow-up work included development of a pathogenicity calculator (Patel et al., *Genome Med,* 2017), proposed cosegregation criteria (Jarvik & Browning, *AJHG,* 2016), and a survey of practices for genomic sequencing test interpretation and reporting process amongst US laboratories (O'Daniel et al., *GIM*, 2016).
    - CSER investigated experiences with obtaining informed consent for genomic sequencing across all 9 CSER sites by evaluating consent forms and ascertaining participant questions and misperceptions (Bernhardt et al., *Am J Med Genet A,* 2015).
    - CSER's Pediatrics WG developed an ethical framework for responsibly and professionally disclosing genomic sequencing results in a pediatric setting (McCullough et al., 2015).
    - CSER's Practitioner Education WG has developed a just-in-time resource for to assist non-geneticist clinicians in navigating a genome test report. This is now available online at www.ashg.org/education/Health_Professionals.shtml.
- A more detailed summary of CSER to date can be found in in the CSER Marker Paper (Green et al. 2016)

eMERGE Network | Rex Chisholm *(Northwestern University)*

- eMERGE has entered into its 10th year of the network, with nearly 16,000 citations from published eMERGE work.
- Specific aims of the eMERGE III Network include the following:
    - Sequence and assess clinically relevant genes putatively affecting gene function in nearly 25,000 individuals.
    - Assess the phenotypic implications of the genetic variants from Aim 1 .
    - Integrate genetic variants into electronic medical records (EMRs) for use in clinical care 4) Create community resources.
- Rex Chisholm summarized 5 key eMERGE-wide achievements thus far, including the following:
    - High Throughput Phenotyping and PheKB (Kirby et al., *J Am Med Inform Assoc,* 2016)
        - Demonstrated that electronic health records (EHRs) can be used to define phenotypes useful for both discovery and implementation for Genomic Medicine.
        - PheKB (Phenotype KnowledgeBase): https://phekb.org/
    - 100K Participant Genomic Dataset
        - Over 100K participants and informatics tools that enable harnessing robust data.
        - eMERGE Record Counter (https://biovu.vanderbilt.edu/EmergeRC)
        - SPHINK (Sequence and PHenotype INtegration EXchange; Rasmussen-Torvik et al., *Clin Pharmacol & Ther,* 2014): https://www.emergesphinx.org
    - eMERGE Pharmacogenomics (PGx)
        - Cross-site analysis of concept that genetic sequence data can be coupled with EMRs for use in healthcare (Bush et al., *Clin Pharmacol Ther,* 2016).
        - 82 pharmacogenetic genes investigated, with many more opportunities for research on these data (i.e., PGx SNVs on the eMERGE-Seq panel).
        - Sites continue to collect utilization and outcomes data (https://emerge.mc.vanderbilt.edu/projects/emerge-pgx/)
    - eMERGE PheWAS
        - Phenome-wide association studies (PheWAS) analyze many phenotypes compared to a single gene-disease association (Denny et al., *Nat Biotechnol,* 2013).
        - https://phewascatalog.org/
        - Developed methods for large scale genotype/phenotype analyses and implemented across the collaborative network.
    - Integration of Genomic Data into EHRs to inform clinical care
        - Developed infrastructure and tools, most notably clinical decision support tools that enable genomic medicine.
        - InfoButton explored the use of infobuttons as a decision support tool to provide context specific links with the EHR to relevant genomic medicine content (Overby et al., *AMIA Annu Symp Proc,* 2014).
        - CDS_KB (Clinical Decision Support Knowledge Base): https://cdskb.org

Session 1: Revision of ACMG Gene List

ACMG Incidental Findings list 2.0 | Wendy Chung *(Columbia University)*

- The term "Secondary Findings" (SFs) was adopted in 2014 and patients could opt-out of receiving SFs. The original list consisted of 56 genes, that has since been updated to 59 genes in 2016.
- The process for adjusting the original 56 genes was highlighted:

    - Nominations for genes/conditions to add or remove from the list were accepted from ACMG members via nomination forms.
    - Data collected via these forms included phenotypes, prevalence rates, and reported gene variants from ClinVar and the Human Genome Mutation Database.
    - The SFs WG also utilized efforts from the ClinGen Actionability WG.
    - In 2016, the "minimum list" updated to 59 genes
- In total, four genes were added (*BMPR1A, SMAD4, ATP7B, OTC*) and one gene removed (*MYLK*) from the list.
    - Added:
        - Juvenile Polyposis (*BMPR1A*, *SMAD4*)
        - Wilson Disease (*ATP7B*)
        - Ornithine Transcarbamylase Deficiency (*OTC*)
    - Removed:
        - Familial Thoracic Aortic Aneurysms (*MYLK*) was removed due to the rarity of known pathogenic variants and lack of effective confirmatory testing. It was deemed that insufficient evidence was available to determine appropriate age to begin medications and to evaluate the efficacy of intervention.
    - More information can be found in the Kalia et al., GIM, 2016 paper.

VUS or GUS? Variants or genes with weak or uncertain evidence | Sharon Plon (*Baylor College of Medicine)*

- There are numerous challenges in effectively classifying variants in the ACMG59 list for reporting SFs.
    - Some variants have clear loss of function alleles and phenotypes but missense alleles are difficult to classify.
    - Reclassification from pathogenic to benign is troubling in a clinical setting where “do no harm” is a critical ethical concern.
- A paper was referenced (Alfares et al., GIM, 2015) highlighting genetic misdiagnoses and the potential for health disparities.
- A case example provided was a reclassification of a pathogenic variant associated with VHL (done in 2009) that was reclassified 12 years later in ClinVar as benign.
- Some cursory analysis of the ACMG59 list, focusing on cancer (n=24) and cardiovascular (n=28) genes revealed trends that needed attention:
    - Almost all the genes were identified before the year 2000.
    - The newer genes on the list are not new, with the most recent one from the year 2013.
    - There are significant complications for interpreting and implementing a gene as a SF. Most conditions are autosomal dominant, but there are some with Mendelian conditions. Several conditions only have a few known disease alleles.
    - Unsurprisingly, the extraordinarily wide range of alleles and information quality is a concern.
- In summary, reporting variants in many ACMG59 genes remains difficult despite the wealth of information available.
- Recommendations offered include substantially simplifying the current SFs recommendations if reporting SFs is to continue, and a need to develop specific guidance for each gene on the ACMG59 list.

ACMG Gene Lists, Secondary Findings and Children | Ian Krantz (*Children’s Hospital of Philadelphia*)

- Highlighted comments from the 2013 ACMG Policy Statement on reporting incidental/secondary findings from exome and genome sequencing: "minimum" list-"must" report; "have a fiduciary duty to prevent harm"; "incidental variants should be reported regardless of the age of the patient".
    a. Noted, that conditions that are part of newborn screening were excluded.

- 2016: Opt-out option added; removed 1 gene (*MYLK*-thoracic aortic aneurysm) and added 4 genes (*ATP7B*-Wilson disease, autosomal recessive; *BMPR1A* & *SMAD4*-juvenile polyposis, autosomal dominant; *OTC*-OTC deficiency, X-linked).
- Notably, children are not little adults.
    a. Clinical manifestations vary by age; worth noting that severe disorders may not manifest in neonate or early years.
    b. Issues of consent and autonomy need to be more carefully considered when returning secondary findings.
- Relative frequencies of reported secondary findings (SF) from the chromosomal microarrays at CHOP generate an overall frequency of 1.7% CHOP Secondary Findings Inclusion List.
    a. Expanded list from ACMG59 gene list to include pathogenic or likely pathogenic variants that fit their criteria:
        i. Medically actionable condition (successful interventions and/or screening are available for the disease (and thus would be implement if condition is known).
        ii. Focus on pediatric onset disease.
        iii. The expected phenotype(s) for each gene is clearly defined.
        iv. Adequate literature available that supports the interpretation of the variant.
        v. Significant disease is anticipated based on the variant.
        vi. Pharmacogenomic variants could be considered within these criteria.
        vii. For autosomal and X-linked recessive conditions, carrier status would be reported if medical screening or interventions would change based on known carrier status in an individual.
    b. Includes: *SCRAP* (associated with arginosuccinic aciduria), *FKRP* (associated with long chain Acyl-CoA dehydrogenase deficiency); inclusion of metabolism SF genes that would not be picked up on newborn screening.
- CHOP Clinical Experience:
    a. 14/347 (4%) of exomes with an incidental finding.
        i. 12/14 were from ACMG gene list and 2 were not (*NR3C2* and *CF*).
    b. 43/390 (11%) declined to receive.
- Suggestion made included (a) A call for the need for more frequent updating of the gene list and (b) A need for pediatric specific list/recommendations.
- PEDISEQ Experience:
    a. Expanded SF approach does not result in significant increase in reporting of medically actionable SFs.

Session 2: Family Cascade Testing

Building a Family Network | Kathleen Leppig (*Kaiser Permanente Washington/University of Washington)*

- An overview of "Family Network" was provided
    - Providing information to family members at risk for their own health care
    - Sharing information because people are looking for support
        - How is it correlated with the severity of disease?
    - Barriers of sharing genetic information: family dynamics, HIPAA vs Duty to Warn
- A prior study, "Building a family network from genetic testing" (Leppig, KA, et al., 2016), wherein three families from eMERGE Phase II with PGRNSeq actionable variants were studied is relevant
- An eMERGE Phase III supplement: family network approach to assess the trickle-down effect of genetic testing was highlighted.

- eIII Supplement Specific Aim 1: To explore the feasibility of health systems-led identification and communication with family members of eMERGE participants.
    - Patients to be included are members of Group Health Cooperative (GHC)/Kaiser Permanente Washington (KPW) and enrolled in eMERGE. GHC/KPW will be returning pathogenic, likely pathogenic, VUS for CRC, and negative results to eMERGE patients. GHC/KPW is an integrated health system.
- In order to explore social, ethical and legal feasibility, the group will conduct semi-structured interviews with approximately 20 eMERGE participants before results have returned with:
    - Topics:
        - Family definition
        - Preferred role (if any) in GHC/KPW for sharing actionable results with likely affected family members who are also GHC/KPW members
            - GHC/KPW duty to contact relatives directly with the proband's consent
            - Use of EMR for sharing information, particularly between providers
            - Special considerations for minors
        - Hypothetical scenarios: clinical vignettes (CRC and Marfan syndrome) followed by questionnaire
- The group will also collect contact information for relatives identified by each participant
    - They will attempt to identify relatives based on first name/last name/DOB provided by eMERGE participant
    - They will not access relative's EMR or contact relatives directly
- *Currently questionnaire and vignettes are under IRB review.*

eMERGE Familial Implications of Returning Genome Results | Janet Williams *(Geisinger Health System)*

- Specific Aim 1: Explore attitudes of participants by convening focus groups and/or qualitative interviews. This is in pursuit of gathering participant perceptions of: importance of sharing information; importance targeted education for family members; barriers to effective communication with family; preferences/suggestions for methods or strategies to contact relatives
- Specific Aim 2: Conduct surveys, standardized for many components, across sites to asses family sharing/communication activities.
    - Some sites conducting baseline pre-results disclosure survey
    - All sites will include small number of consistent items in a post-results survey
    - Some sites will survey immediately after return of results
    - Some sites will utilize a more in-depth survey to supplement the items asked in the general survey
- Specific Aim 3: Collect and collate points to inform system-level guidance for policy-making or best practice development pertaining to family communication of positive variants in actionable genes.
    - Collect site-specific activities currently planned to promote family communication
    - Assess factors that lead to variation in methods of communications including materials, approaches and measures of success
    - Test various methods of contact
- Geisinger patient experience interviews:
    - Domains:
        - Initial experience with result
        - Medical follow-up
        - Communication with family and friends
        - Understanding of the results and resource seeking

        - ROR procedures
        - Psychosocial reactions to result
        - Financial implications of result
        - Satisfaction with participation in MyCode
    - Common Themes (Preliminary):
        - All participants share with some family members
        - There were some family members that participants chose NOT to share with for the following reasons: too old, too young, discord, would not be interested
        - Most used letter provided by ROR team, but some called to tell by phone or in-person
        - Thought result applied only to women (BRCA)
- Site-specific survey domains:
    - Intent to share with family members
    - Family communication: conflict, satisfaction
    - Empowerment
    - Information sharing
    - Language/literacy
    - Utilization
    - Life/health insurance issues
- HIPAA, privacy and ROR familial communication: Group Health initiated conversation with legal counsel regarding issues and methods for return of results to family members who receive care within the healthcare system. The hope is to convene a group of legal experts to more broadly address these issues.

Challenges Related to Family Involvement in Clinical Whole-Genome Sequencing: Views of Non-Genetics Providers | Leila Jamal *(Baylor College of Medicine)*

- Communicating genetic information to patient's families (family involvement) is a novel challenge for non-genetic providers. Current guidelines discourage providers from contacting relatives directly. While they do encourage providers to help patients to transmit risk information to relatives, they provide little clarity about how to do this, and guidelines differ for research and clinical spheres. See: Health-care professionals' responsibility to patients' relatives in genetic medicine: a systematic review and synthesis of empirical research (Dheensa, S. et al., 2016), and Returning a Research Participant's Genomic Results to Relatives: Analysis and Recommendations (Wolf, S., et al., 2015)
- Communication of genetic information is Important throughout the process, but MDs focused most on sharing results.
- Should there be different approaches for different result types?
- MedSeq Project: An overview of the MedSeq project was provided, and further details can be found online, http://www.genomes2people.org/the-medseq-project/
- Feedback received:
    - Patient's attitudes regarding family involvement specifically highlighted parents' desire to participate because of the impact it could have on their children's future
    - Familial risk assessment was an unexpected issue
    - MDs viewed family communication as patient responsibility
    - Special circumstances might make it ok to contact family members, such as in the event of death where there was no prior knowledge of the person's wishes
    - MDs expressed a need for tools, such as print materials

- Approaches to sharing genetic info with relatives include: group information sessions with voluntary follow-up, telephone counseling/telemedicine, and prospective consent to contact relatives obtained from index patient

Session 2: Discussion

- The group discussed challenges associated with family cascade health projects, including family dynamics, family dispersal, and coordination of genetic testing.
    - Genetic counselors can act as "family negotiators", making connections with consented, non-conflicting family members that can pass the information on; or obtaining consent to share genetic results with family before the result is given (though in these cases the third family member hasn't consented to be told).
- The group generally agreed that primary and secondary findings should be communicated to patients, with the communication focused on how the finding affects the patient.
    - Proband patients should be encouraged to communicate both primary and secondary findings to family members with a focus on how the finding could affect the family member. This can be facilitated by encouraging the patient to invite a family member to attend the return of results appointment.
- Opportunities for collaboration
    - Creating tools that bring the patient's family to the attention of the physician.
    - Creating a road map/process for coordinating family genetic testing.
    - Developing tools/best practices for implementing successful family cascade projects.

Session 3: Opportunities for Healthcare Quality Measurements in Genomics

Opportunities for Healthcare Quality Measurement in Genomics | John Bernot *(National Quality Forum)*

- The National Quality Forum (NQF) is an independent, nonprofit, membership organization that brings together all stakeholders working to improve health and healthcare through quality measurement.
- Types of measures, along with basic descriptions and examples were reviewed. These include: structural, process, intermediate outcome, outcome, patient reported outcome performance measure (PRO-PM), cost/resource, efficiency, and composite.
    - Other measurements to consider: Attribution (Who is responsible?), and Intended Use (How is this used? Quality improvement? Payment?)
- The National Quality Strategy aims to achieve the best healthcare value - the best outcome at the lowest value by focusing on:
    - 1) Better care
    - 2) Healthier People/Communities
    - 3) Smarter spending.
- Emerging priorities in quality measurement were highlighted, including: actionable & improvable, patient centered, outcome focused, and integrated care.
- Good genomics measures and opportunities were discussed, specifically noting NHGRI's Genomic Medicine workgroup's alignment of concepts with the NQF.
    - Potential genomics opportunities include: diagnostic quality & safety, cancer, patient safety, cardiovascular conditions, and person and family centered care.
    - Two topics have been identified as most ready for advancement in measurement development: familial hypercholesterolemia (FH) and lynch syndrome.

Session 3: Discussion

- The impetus for this movement is to identify best practices in healthcare quality measurement and implement them in general practice. Best practices are those that improve care and align reimbursement to high quality healthcare.
- The group discussed how measures are used, which measures matter most, and how/why types of measures matter. The best measures capture the right information with the lowest burden. This might be achieved with automation and information already in the EMR, though this would necessitate that the right information is available and the automation is technically interoperable.
- The National Quality Forum (NQF) has a list of reviewed and endorsed quality measures on their website for public consumption. The NQF uses federal payment programs, sponsor groups, and (informally) their connections with certification groups to implement healthcare quality measures. The bystander effect can also help make subsequent measures easier to implement than initial measures.
- The group discussed the need to deliver healthcare quality measures in a way that is equitable and does not penalize new, less established programs. The need to account for social determinants of health in quality metrics is also being addressed.
- The group discussed the importance of genetics in diagnosis, focusing on the question: Are patients who have indications of genetic disease being appropriately screened?
- Opportunities for collaboration:
    - eMERGE can work with NQF to develop quality measures for familial hypercholesterolemia as this is a specific phenotype of interest to both.
    - eMERGE can work with NQF to develop quality measures for Lynch syndrome.
    - eMERGE experts can become members of NQF.

NIH GenomeTV Livestream Summary Statistics

- Video and Slide Archive: https://www.genome.gov/27567557/emerge--cser-the-convergence-of-genomics-and-medicine/
- The Livestream had 251 total unique views from 22 different countries. Out of these 251 views, 215 unique views are from the United States. In the US, there were 191 unique views from 98 different cities outside of Bethesda. Please continue to the next page for a detailed breakdown of the unique views per country and a heat map of the views around the world.

Country	# of Unique Views
United States*	215
United Kingdom	9
Germany	2
Canada	2
Brazil	2
Colombia	2
Thailand	2
Mexico	2
Vietnam	2
Saudi Arabia	1
Hong Kong	1
Liberia	1
Sri Lanka	1
Czech Republic	1
Russia	1
Denmark	1
Australia	1
Kenya	1
Libyan Arab Jamahiriya	1
United Arab Emirates	1
India	1
Netherlands	1
*Bethesda – 24 views *Outside of Bethesda – 191 views