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**Summary of Steering Committee Meeting: Fall 2019**

October 3rd- 4th, 2019 Rockville, MD

**eMERGE Day 1: Thursday, October 3rd, 2019**

* [**NHGRI program official report** | Robb Rowley (NIH/NHGRI)](#jrhmfd6tht6t)
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* [**Choices, expectations, and attitudes about genomic screening in Latino and Ashkenazi Jewish individuals** | Julia Wynn (Columbia)](#bqq3iivg68s3)
* [**Results of comparative study of participant reported adherence with adherence reported in the EHR**| Alanna Kulchak Rahm (Geisinger)](#nk57q3h3x5i)
* [**Genomic medicine for Chronic Kidney Disease: lessons and opportunities from eMERGE**| Ali Gharavi (Columbia)](#xt3yh2vq8ip9)
* [**Making work visible for electronic phenotype implementation: Lessons learned from the eMERGE Network**| Ning Sunny Shang (Columbia)](#jyp8fikb6nts)
* [**Closing remarks** | Rex Chisholm (SC Chair, Northwestern)](#nlx2gxqlqgik)

**eMERGE Day 2: Friday, October 4th, 2019**

* [**eMERGE Network overview: Priorities, goals, progress and ESP recommendations** | Rex Chisholm (SC Chair, Northwestern)](#chp6xm7lx7ti)
* [**GWAS, Polygenic Risk Scores & PheWAS demonstrate a polygenic determination of vesicoureteral reflux** | Miguel Verbitsky (Columbia)](#mmpdbtwi5rgj)
* [**Phenotype Associations of LPA variants differ by race: A phenome wide association study** | Benjamin Satterfield (Mayo)](#pbze6hojvpyu)
* [**The clinical utility of predicted family histories for Mendelian and genetically complex forms of disease** | Scott Hebbring (Marshfield)](#2ocx4cf1k0tn)
* [**Informing and harmonizing variant interpretation**| Heidi Rehm (Partners/Broad), Iftikhar Kullo (Mayo), & Adam Gordon (Northwestern)](#r5pwqa8198um)
* [**Return of results pathways, barriers, and harmonizing across sites** Ingrid Holm (BCH) & Iftikhar Kullo (Mayo)](#8op62x8yb12b)
* [**Impact of ROR process on Outcomes assessment** | Josh Peterson (VUMC/CC) & Marc Williams (Geisinger)](#y8bim623z24x)
* [**Interim Data Analysis: Clinical Outcomes** | Wendy Chung (Columbia), Christin Hoell (NU), Iftikhar Kullo (Mayo)](#gcugund26v6o)
* [**Status of eMERGE FHIR Specification and Implementation Project** | Larry Babb (P/B)](#h28kc55cbi54)
* [**Input/Feedback from the ESP, general discussion**](#wci7ymvipsfk)
* [**Closing remarks** | Rex Chisholm (SC Chair, Northwestern)](#iapf5rpri4cz)

[**Meeting Action Items**](#rmyfjarp00i7)

[**ESP Executive Session notes & recommendations**](#4skkjthxtny3)

**eMERGE DAY 1: THURSDAY**

* **NHGRI program official report** | Robb Rowley (*NIH/NHGRI*)| [slides](https://drive.google.com/file/d/1cyyfOBCmV0l4z-1pNrAjccJ4o9KRKqhu/view?usp=sharing)
	+ The AnVIL was approved on July 5th, 2019 with the publication of [NOT-HG-19-024](https://grants.nih.gov/grants/guide/notice-files/NOT-HG-19-024.html) as an NIH-designated data repository for the storage, management, and sharing of genomic data. AnVIL has two separate uses:
		- AnVIL provides a resource to deposit consortium data. The control of access and analysis is restricted and managed by the consortium members.
		- AnVIL provides controlled access to datasets made available to the public, similar to dbGaP.
	+ The AnVIL team is currently working on documentation that explains data access that will be explained later in the Steering Committee meeting by Ken Wiley.
	+ eMERGE dataset is currently only accessible to the eMERGE Network members and has not been released more broadly.
	+ NIH funding opportunity, [PA-18-906](https://grants.nih.gov/grants/guide/pa-files/PA-18-906.html), is for supplements that support health research from underrepresented investigators. NHGRI’s specifics related to this announcement is explained in [NOT-HG-19-010](https://grants.nih.gov/grants/guide/notice-files/NOT-HG-19-010.html). A key point for those considering applying is that the supplement investigator cannot be listed on the parent grant. Because of a few other unique aspects of the application process, investigators interested in applying are encouraged to talk with a NHGRI program staff prior.
	+ Baergern Schultz is the new eMERGE analyst for the NHGRI, who is taking over for Sheethal Jose.
	+ NIH and the American College of Human Genetics (ACMG) have partnered to increase the pool of physicians that are trained in managing research and implementation programs in genomic medicine. Applications for a two-year fellowship are due annually on November 1st. The 2019 Fellows are Marie-Luise Brennan, M.D., Ph.D. and Hwaida Hannoush, M.D..
	+ NIH [clinical trial policy](https://clinicaltrials.gov/ct2/about-site/new) was amended and affects applications submitted on or after September 25th, 2019. There are two ways that that applications can be misclassified:
		- Submitted as not a clinical trial, but meets NIH criteria as a clinical trial will be withdrawn
		- Submitted as a clinical trial but not a clinical trial the IC can determine to review the application

* **Announcements, opening remarks** | Rex Chisholm (*SC Chair, Northwestern*) | [slides](https://drive.google.com/file/d/12uBsZq2g88So7u9C7nXZ-goiwJlorGJ-/view?usp=sharing)
	+ eMERGE has completed 95% ROR across sites. Non-responder categories have been further clarified to facilitate analyses.
	+ Outcomes data Freeze 1 (August 19, 2019; representing ~68% of overall data collected) was disseminated to investigators.
	+ CDS implementation survey showed CDS based on genetic test results was established or under development across all sites.
	+ There have been nine Network-wide lessons learned manuscripts published and 11 Network-wide lessons learned manuscripts are in development. There have been 854 published and in-development projects.

* **Integrating and harmonizing EHR data from multiple institutions across mother and child dyads** | Brett Harnett (*CCHMC*) | [slides](https://drive.google.com/file/d/1nzMbxB5FQkJrR1KdmpA3uyUaYZ0qTCEx/view?usp=sharing)
	+ Brett Harnett from the CCHMC Biomedical Informatics discussed integrating and harmonizing EHR data from multiple institutions
	+ Harmonization efforts are in progress between University of Cincinnati (UC) and Childrens Hospital despite both using the same EMR vendor. The goal is to combine data that has been gathered over the last 4.5 years.
	+ All neonates in the study were born at UC and if complications arose then baby was then transferred to Children's Hospital.
	+ The two sites have distinct versions of Epic and combining the datasets for mothers and infants has been difficult, even utilizing OMOP. There are 16,000 EHR records between maternal and infant data, with a success rate of 94% with regards to pairing mother/baby dyads. The data are updated quarterly.
	+ Protected health information and other Identifiers were removed from the data prior to transfer to UC.
	+ Currently the group is working to integrate the [TriNetX](https://www.trinetx.com/) tool with Children's Hospital. TriNetX is a highly capitalized and innovative company whose goal is to streamline the ingestion and harmonization of data.

* **FHIR, SV analysis & Year 5 updates** | Eric Venner (*BCM/HGSC*) | [slides](https://drive.google.com/file/d/1JLEdZwnTT1Wh7QQI1s5atFKVE97nmoIz/view?usp=sharing)
	+ Baylor has identified 83 variants of undetermined significance(VUS) that trended toward pathogenic, half are related to cardiomyopathy or arrhythmia genes. Baylor contacted all the clinical sites and has received phenotypic information to determine if variants should upgrade to likely pathogenic (LP).
	+ The team is working to keep reports up to date with ClinVar and had initially identified 158 potential variants with the new L/LP classification. Manual review lowered this number to 8 variants.
	+ The extent to which these variants can be automatically determined is still under consideration.
	+ The sex discrepancy issues the CSGs encountered during analysis plans to submit a manuscript shortly ([NT337](https://emerge.mc.vanderbilt.edu/wp-content/uploads/2019/04/NT337-Hu-Gender-Genotype-Analysis-for-Clinical-Quality-Assessment.docx), Gender Genotype Analysis for Clinical Quality Assessment).
	+ Baylor is working with Larry Babb and Mullai Murugan to help establish the FHIR specifications while conducting pilot implementation.
		- Northwestern and Johns Hopkins University plan to test the integration of the FHIR standards. Validation is important for the system to be successfully locally.
		- FHIR enables interoperability by standardizing the end points, the work done here established draft specifications based on existing FHIR elements. Though this was imperfect, it is suitable for many genomics use cases and adjustments after validation across sites will improve the standards.
	+ FHIR draft specifications handle reporting of ACMG variants, but not CNVs or PGx.
	+ The work conducted on FHIR is helping establish standards. The eMERGE Network effort used an XML model to implement the results into Epic. The Network realized that the FHIR/HL7 standards need to be adjusted. After discussing with the HL7 working group, the FHIR standards were revised.
	+ Baylor is also working with Lisa Bastarache to evaluate PheRS, especially in testing ACMG PS4 category.
	+ Phenotype information alone is not always enough evidence to reclassify a given variant.

* **Re-analysis of variants identified in eMERGEseq** | Hana Zouk (*Partners Broad*) | [slides](https://drive.google.com/file/d/1H1bdy1sO2oT1UqhXrqOpB76W6LHUJM-X/view?usp=sharing)
	+ Partners/Broad is reassessing ongoing real-time variant reclassification alerts which have affected 2.2% of reported variants. There are two categories.
		- Category 1: Does not reach reportable thresholds for reclassification (61%). The category includes reasons like proband counts, rule changes, function guidelines that may have been revised.
		- Category 2: This has ‘higher impact’ and reach reportable thresholds that affect LP/P variants and have been downgraded to VUS (39%).
	+ A proportion of sites reports have been amended per site request, and with additional clinical information.
	+ GeneInsight Clinic Alerts regarding reclassifications can be set up for each site to alert the site representative that a variant has been changed. Investigators can also search for a specific variant to determine if reclassifications have occurred.
	+ The next analysis goals are to re-analyze variants using ClinVar to compare discrepancies between our (P/B) classification and ClinVar, examining “2-star status” and above.
	+ Out of the 1858 unique eMERGE III variants, 292 were 2 stars LP/P. Of the 292, 33 were found to be a VUS by PB and LP/P in ClinVar. Of the 33 discrepancies found, 11 were eliminated due to phenotype (10) or had known risk factor (1). Of the 11 remaining, 5 are expected to be upgraded to LP/P.
	+ Of the 1858 unique eMERGE variants, 454 were found to be 2-stars and above VUSs. None of the variants were potential downgrades.
	+ Sites requested re-assessment of two variants. RYR1 was initially classified as VUS-LP and an updated literature review identified additional segregations that led to reclassification to LP. PMS2 was initially classified as VUS, site supported their request with Immunohistochemistry (IHC) data supporting pathogenicity, and with additional proband and family data to support the IHC studies that resulted in the variant being reclassified to LP.
	+ The goal of combining Baylor and LMM VUS-LP lists was to identify additional common VUS-LP variants to send to sites. Six variants were found in common, however none collectively would require additional EHR mining. The next step is to harmonize the list of classification differences (VUS-LP versus VUS) which is difficult as no guidelines exist.
	+ A question was raised about how long GeneInsight would be accessible by sites after the end of eMERGE. P/B has contracted with GeneInsight until May of 2020 for eMERGE. Plans for future variant reassessments beyond eMERGE III are still being developed at each of the CSGs..
	+ The Network’s experience in Return of Results and classifying clinical variants may be an opportunity to set guidelines or provide a statement to reduce variability and assuaging liability concerns.
	+ There is much collaboration involved, including between ClinVar and the sites to resolve variant discrepancies. The biggest challenge in every lab is to streamline and automate processes. There are nuances in the phenotypes and in extracting data that require thorough examination. The focus has been on primary findings, determining how variants interact would add on an additional layer of complication and has not been addressed at this point.

* **Network datasets**  | David Crosslin (UW/CC) | [slides](https://drive.google.com/file/d/10og1TZ7HKDVNbGIs4FqBTszrpbYbySVB/view?usp=sharing)
	+ Imputation data for the imputed GWAS and structural variation sets are finished, QC’ed, and available to the Network. The data include ABO blood type calls that align with expected US distributions.
		- Ian Stanaway (CC) has been running PheWAS with structural variation data and is trying to classify the structural variations in a “structured” manner moving forward.
	+ The goals for the SPHINX enhancements have been completed.
	+ The CC has been working with the AnVIL team to migrate all eMERGE datasets into AnVIL. The AnVIL team is very collaborative. Investigators interested in being involved should email a member of the CC.
* **The** **AnVIL & eMERGE data access** | Ken Wiley (NHGRI) | [slides](https://drive.google.com/file/d/1hrx5WuHbnLsvuFBcAp7CJgNEusKh0aLn/view?usp=sharing)
	+ There have been some questions by the Network concerning the AnVIL, particularly around the security, access, and availability of datasets.
	+ The AnVIL is designed so that individuals who do not have extensive coding experience are able to upload data and utilize analysis tools in a cloud environment. The AnVIL is intended to work with other repositories, including dbGaP.
	+ The AnVIL will serve as the primary data repository for submitting and accessing controlled access datasets including associated metadata and phenotype data from NHGRI funded programs.
	+ The AnVIL follows the [NIH Genomic Data Sharing (GDS) policy](https://osp.od.nih.gov/scientific-sharing/genomic-data-sharing/) for submitting and accessing controlled-access datasets. The policy is consistent with other NIH repositories for data hosting and sharing. The AnVIL is a certified NIH designated repository.
	+ **Public access:** There are two types of public access: open and controlled.
		- ‘Open access’ is accessible to the public without prior approval. This designation is indicated during the dataset registration process with dbGaP, or the investigator can submit written intent of this to the AnVIL.
		- ‘Controlled access’ consists of data that is publically available but access is controlled through through a data access committee (DAC) which is determined during the registration process at dbGaP. Investigators need to request access and have it reviewed by an NIH or NHGRI DAC. Those who are approved for controlled access would be added to a ‘white list’ managed by dbGaP to have access to the data on AnVIL.
	+ **Consortium access:** Consortium members control access to the consortium data. The data would not need to be registered on dbGaP until the Network decides to register the data for Public Access either as open or controlled access.
	+ Key points regarding AnVIL include:
		- A point of contact, determined by the consortium, will generate and maintain a white list for access to Consortium data. The AnVIL team will use the white list to grant access to consortium datasets.
		- Investigators or sites can upload data not planned for Public access to their individual workspaces. Consortia data is encouraged to be shared via Public access, but is not required.
		- Storage costs for data not registered on dbGaP would be covered by the site or the CC depending on the situation.
		- Data that are uploaded on the AnVIL will not automatically be public as the AnVIL does not ‘own’ the data. Data access is determined by the consortium members or designated during the dbGaP registration process.
	+ **QC/Operational Access:** The AnVIL staff will have access to all datasets hosted on the AnVIL for operational use only for improving the functions of the AnVIL. In order to utilize datasets for research or other purposes, the AnVIL staff will need to undergo the same process and gain all the approvals required for other investigators to access data.
	+ The CC should continue to upload the eMERGESeq V2 and GWAS 105k sets to dbGaP due to the timing of the AnVIL public launch. Moving forward, datasets can be uploaded to the AnVIL with just the registration forms being sent to dbGaP; no need to also submit the datasets to dbGaP.
	+ Datasets can be present on the AnVIL even if they are not initially or immediately registered on dbGaP. Once the dataset is registered on dbGaP, and after an embargo period if requested, they would be made public.
	+ Storage costs for public open access data and controlled access (dbGaP registered data) will be covered by the AnVIL. Investigator uploaded data (non-public), analysis and egress costs will need to be covered by the site or consortium.
		- Consortiums (or investigators) will be charged for storage, compute, and egress costs associated with the use of non-public access data on the AnVIL.
		- Consortium (or investigators) will be charged for compute and egress costs associated with the use of public access (open or controlled access) data on the AnVIL.
		- The AnVIL is piloting a program to subsidize compute and egress costs through the NIH Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) initiative. .
	+ The science in the next round of eMERGE will be computationally intensive, which could factor into costs as well as concerns about how to do analyses on Polygenic Risk Scores (PRS). The AnVIL will learn and adapt to these challenges as they develop, the team is interested in determining what models work best for the AnVIL in different research environments.

* **Choices, expectations, and attitudes about genomic screening in Latino and Ashkenazi Jewish individuals** | Julia Wynn (*Columbia*) | [slides](https://drive.google.com/file/d/1LSSUJ9l6kxjl2BOBQdlY9FSE6vLmvLC9/view?usp=sharing)
	+ A pilot study that included over 400 Columbia University Medical Center (Columbia) participants was conducted. The study targeted the enrollment of Ashkenazi Jewish (AJ) and Latino individuals; These groups were chosen due to their distinct genetic experiences and needs.
	+ AJ individuals are genetically homogenous, and Latinos are genetically heterogeneous and are underrepresented in population/genetic screening.
	+ Columbia has begun exploring founder mutations for genetically homogenous communities. Columbia looked at the results between the two groups to understand more about how culture and religion can influence results regarding genetic screening.
	+ Participants were given options regarding how results were received. These options include how patient received their results: with treatment, with partial treatment, or with no treatment.
	+ Participants were asked whether or not they preferred their healthcare provider to make decisions for them regarding treatment. The Latino population more frequently indicated (25% vs 11%) that they would like for their providers to make their decisions regarding treatment options.
	+ Results showed that there were more genetic risks in AJ than there were in the Latino population, with the bulk of the findings being from founder mutations.
	+ After the results were returned, 40% of people expected to have more results than what was received. These results were uniform across both groups.
	+ The understanding of results was uniform across both groups. In the AJ community, there was a lack of knowledge regarding what they would need to do to stay healthy.
	+ The AJ participants were less likely to share their genetic information than Latino individuals. There was also more concern in the AJ community regarding their results remaining confidential, and what safeguards were in place regarding their EHR and sensitive materials.

* **Results of comparative study of participant reported adherence with adherence reported in the EHR** | Alanna Kulchak Rahm (*Geisinger*) | [slides](https://drive.google.com/file/d/1CNfolfly0UViZ1P7LPFhkpD8HYvow5Oy/view?usp=sharing)
	+ This study examined the results of 22 individuals for patient-reported adherence to the six-month outcome surveys and compared these results to the follow-up adherence from the patient's chart.
	+ Adherence guidelines were based on national guidelines related to clinical adherence, including the Hereditary Breast and Ovarian Cancer, Familial Hypercholesterolemia, and Hypertrophic Cardiomyopathy.
	+ About half of the participants reported that they were not surprised by their results. The remaining half of the participants felt that their results informed them of what they should do to take better care of their health.
	+ Differences between self-reported adherence were found in the medical records in relation to cardiomyopathy, FH, and HBOC. HBOC had the most substantial non-adherent rate.
	+ This difference could have been due to differences in how six-month guidelines applied, and whether or not there was sufficient time to complete guideline recommendations
	+ Researchers found instances where a participant visited a PCP, and there were no further follow-ups recommended.
	+ Limitations to the study include a small sample size, lack of tests in the EHR, and the short follow up of six-month may not have been enough time to get satisfactory results.
	+ Clear communication is needed regarding whether or not the provider communicated the patient's results/ follow-up needs or if the patient brought up their results to the provider.
	+ It is crucial to communicate effectively to ensure participants understand their results.

* **Genomic medicine for Chronic Kidney Disease: lessons and opportunities from eMERGE** | Ali Gharavi (*Columbia*) | [slides](https://drive.google.com/file/d/1zVMLXCmYCsQku2-kT2ubXsyF3D4XZRVr/view?usp=sharing)
	+ Renal disease affects ~10% of the population in the US, and kidney failure affects 4% of the population. These statistics are doubled in underrepresented minorities.
	+ WES offers a diagnostic yield of 9.3% in patients with Chronic Kidney Disease (CKD) and was highest in cases of those who had comorbid congenital or cystic renal disease.
	+ CKD of unknown cause had a diagnostic rate of about 17%. There were 66 genetic disorders identified in this study. Alport syndrome is due to mutations/structural defects in COL4A3/4/5.
	+ Sixty-six genetic disorders were discovered in 307 participants that had undergone whole exome sequencing at Columbia.
	+ The lab developed a program with web interfaces called diAGnosTiCator, which integrates ACMG classifications for diagnostics, known disease associations, variant frequencies, variant characteristics, and patient genotype characteristics.
	+ Columbia is interested in understanding how to manage current treatment plans for clinical conditions not causally related to the P/LP variant, and examine any potential changes in therapy or medication.
	+ Tailoring ROR to non-English speaking populations and the cognitively impaired individuals is essential. The development of a genetic literacy test may be useful in understanding health education needs. Even in English about half of the participants do not understand some of the standard terms used in genetics. There is a lot of fear among clinicians in terms of ACMG 59, and clinicians feel that they may not have the answers that their patients may need.
	+ Columbia is interested in seeing how PheWAS for GWAS is related to CKD and other similar traits in eMERGE. The algorithm may be a good model for identifying cases of CKD and understand the impact of clinical contexts on populations.
	+ Given the complexity of the etiologies that may be associated with CKD, a negative result may have clinical implications.
	+ Columbia utilized ACMG criteria to review classifications to confirm clinical actionability and accurately identify ‘cases’ for CKD phenotyping identification.

* **Making work visible for electronic phenotype implementation: Lessons learned from the eMERGE Network** | Ning Sunny Shang (*Columbia*) | [slides](https://drive.google.com/file/d/1k50xerIF5BXrhrn94nf_YNN3V3-WCRAJ/view?usp=sharing)
	+ Electronic phenotyping identifies a cohort of patients with specific clinical profiles, including utilizing knowledge engineering and machine learning methods. Investigators have worked with experts to develop different rule-based strategies in the EHR.
	+ Implementation of algorithm requires phenotype engineers to develop the algorithms and translate the description into computable phenotypes that can be easy to implement and are portable.
	+ It can take between 6-8 months to develop and share phenotypes. Each site implements the phenotype, which takes between 2-3 months, depending on the algorithm complexity and workload.
	+ A portable phenotype algorithm is one that could be implemented easily and maintains performance. The way to measure that portability includes ability to identify the phenotype consistently across the Network. The time and effort required as well as identifying challenges for algorithm portability have yet to be analyzed systematically.
	+ Current strategies to improve portability of phenotypes include NQF Quality Data Model, the phenotype execution and modeling architecture, and algorithm design patterns.
	+ Investigators analyzed implementation methods by identifying algorithms in PheKB and looking at phenotype criteria, looking specifically at ophthalmology cases.
	+ An estimation of implementation time consumption was generated, about 95% of the algorithms took more than one hour to finish. The most time-consuming tasks are for NLP-related algorithms or tasks requiring external domain expertise. Variance across different researchers and sites was large. OMOP standardization can reduce time consumption.
	+ Findings showed that it was feasible to implement OMOP across sites, however, standardizing the local LOINC code may still be difficult. All sites use different LOINC codes. However, OMOP implementation takes less than a day on average.
	+ Implementation efforts can be made visible and need a novel metric to measure the portability of phenotype algorithms.

* **Closing remarks** | Rex Chisholm (*SC Chair, Northwestern*)
	+ 162 network-wide MCS are in-progress. The Network could consider joining MCS’s to create one Network-wide lessons learned publication. MCSs that are still planned to be published individually should proceed. However, publications that have stalled or are not very impactful on their own, could be considered for combination into a larger, Network-wide MCS.

**eMERGE DAY 2: FRIDAY**

* **eMERGE Network overview: Priorities, goals, progress and ESP recommendations** | Rex Chisholm (*SC Chair, Northwestern*) | [slides](https://drive.google.com/file/d/1C6rxPmJvG6ud9knj2VCz1e6rCG9XhWmG/view?usp=sharing)
	+ The work in eMERGE happens both locally at the sites, as well as the within the workgroups.
	+ The main aim of Phase III, consisting of sequencing 25,000 participants (eMERGEseq) has been completed. The returnable results that have been captured are consistent with what was expected (2-5%). The Network has an ongoing duty to continually update and assess interpretations of variants as knowledge improves over the course of time.
	+ Twenty-two phenotypes have been implemented across the network this phase. Between all the phases, the Network generated 68 total phenotypes. In addition, common clinical variables have been collected across the Network in order to increase the quality of the datasets.
	+ eMERGE is the interdisciplinary network capable of transmitting results using formats such as XML. eMERGE has been able to impact and help guide national standards, such as HL7 Genomics and FHIR and shape how to transmit data from a laboratory into EMRs and into clinical care.
	+ There are six eMERGE data sets that represent about 158,000 samples, including the GWAS imputed set, eMERGEseq, Exome chip, PGRNseq, Whole Exome, and Whole Genome Sequencing.
	+ The ESP has reminded us that we need to be sure to maximize activities through collaborations. There have been many consortium collaborators in Phase III, such as AoU, ACMG Secondary Findings groups, CPIC, CSER, IGNITE, and the MeTree family history tool.
	+ There are also several informatics tools that harness data for public and researcher use, such as SPHINX providing annotated data, and PheKB collects and stores e-phenotypes.
	+ ESP Recommendations from the April 2019 eMERGE-ESP call have been [addressed](https://drive.google.com/file/d/1ePAlBEnpJL6EVqr1V_JD-CM138V07XZi/view?usp=sharing) by the Network.

* **GWAS, Polygenic Risk Scores & PheWAS demonstrate a polygenic determination of vesicoureteral reflux** | Miguel Verbitsky (*Columbia*) | [slides](https://drive.google.com/file/d/1daOU2PGxa4xLHH5n7qPyi-Ssn88vvm3Q/view?usp=sharing)
	+ Vesicoureteral Reflux (VUR) is the most common type of congenital anomaly of the kidney and urinary tract that results from the incorrect insertion of the ureter into the bladder wall during development. VUR can lead to hydronephrosis and recurrent urinary tract infections.
	+ VUR affects 30-40% of children who present with a UTI and is more prevalent in females. VUR is mainly a familial disease, reported prevalence among is 27-51% among siblings of and 66% among children with a parent affected by VUR.
	+ GWAS results were from 1,500 unrelated VUR cases, and 5,500 matched population controls across seven cohorts of European ancestry.
	+ GWAS was run under additive, recessive, and dominant models adjusted for specific principal components.
	+ Three SNPs were significant genome-wide, and four other SNPs were considered suggestive of significance. The top SNPs were in genes that were important in embryonic development and/or kidney disease.
	+ Summary statistics from GWAS estimate SNP-based heritability around 15%. The investigators believe that multiple common variants of small effect that are less than the genome-wide statistical threshold might account for other variants might explain the risk of developing VUR. In order to understand this, the investigators created a polygenic risk score for VUR.
	+ A separate PheWAS was run in pediatric participant using the VUR PRS, and moderate to large effects for VUR-associated loci were identified.
	+ The power of PheWAS was leveraged in order to understand the total polygenic “architecture” of VUR. Findings show that Polygenic Risk Scores (PRS) could be a useful predictor of VUR and relevant comorbidities.
	+ Chip based PRS was not compared to low pass genome PRS.
	+ This study could be expanded to more phenotypes, and could compare European to non-European ancestry.

* **Phenotype Associations of LPA variants differ by race: A phenome-wide association study** | Benjamin Satterfield (*Mayo*) | [slides](https://drive.google.com/file/d/1OSodGx1DWCnODOyKqXNX0uBM2gAL40x_/view?usp=sharing)
	+ Lipoprotein (LPA) physiology role is unclear and causes many health problems. Health issues are associated with LPA isoform size. Isoform size is inversely related to blood levels. The study investigated if LPA variants were associated with disease in addition to atherosclerotic cardiovascular disease (ASCVD).
	+ In African Americans, on average LPA levels are twice what is non in European ancestry individuals. The study aimed to clarify what LPA variant phenotypes were related to race/ethnicity.
	+ Interaction analyses were conducted for the entire study population. PheWAS was performed, and results showed 36 variants in the European American group and 53 in the African American group.
	+ In the African American population, allele frequency is very different than the European American group.
	+ There were no overlapping associations between the European and African cohorts
	+ Associations have been found between various LPA levels and depressive disorders, however investigators found no differences in LPA levels between individuals with major depressive disorder and controls, nor did investigators find that LPA levels were affected by treatment of major depressive disorders.
	+ Interaction analyses were conducted but had lower power due to the low allele frequency of variants.

* **The clinical utility of predicted family histories for Mendelian and genetically complex forms of disease** | Scott Hebbring (*Marshfield*) | [slides](https://drive.google.com/file/d/1etJXIdJIc9UA16Cn0lhdEfL0W4fYGRLu/view?usp=sharing)
	+ Family histories are being used to predict risk because it captures shared genetic factors, as well as environmental exposures that contribute to disease.
	+ Family histories can also be useful in predicting more complex non-Mendelian diseases, such as type II diabetes, heart disease, obesity, breast cancer.
	+ The goal of the study was to sequence 3,000 patients. Currently approximately 1500 reports have been received.
	+ There are challenges in obtaining and using comprehensive family histories in clinical practice due to the significant time requirements to capture and continually evolving information. To improve the process, family history could be generated using the information in the EMR.
	+ If the information contained in the EMR could be gathered and shared in a HIPPA-compliant way, a family history could be generated to understand patients’ unique risk and help personalize screening and treatment.
	+ Family history was gathered and cross-referenced with tumor registry data.
	+ Family history of cancer categories were established as low (one history), medium/high (two or more cancer cases in the family). pFamHx was able to categories was able to stratify a patients probability of having a cancer VUS or LP/P variant.
	+ A similar approach was used for identifying individuals with Familial hyperlipidemia (FH) and compared to the Dutch Criteria. The approach was also used in~300 patients demonstrating maturity-onset diabetes of the young (MODY).
	+ The method was then used to compare 239 polygenic risk could be improved by combining the p-FamHx. The f-FamHx positive individuals PRS risk was significantly higher than those with a negative f-FamHx.
	+ A nuance to this approach is that it may be more difficult to track family patterns in individuals with large families in an EHR and small families may risk divulging personal medical information about other family members.
	+ KPW has a supplement looking at patients with P/LP, and that identifies blood relatives in the KPW system. The next steps involve determining how to remove barriers between Kaiser systems to identify family structures better.

* **Informing and harmonizing variant interpretation** | Heidi Rehm (*Partners/Broad*), Iftikhar Kullo (*Mayo*), & Adam Gordon (*Northwestern*) | [Rehm slides](https://drive.google.com/file/d/1v_4uyhXaQ8tDnas8zXp5nv0MDXlpnBNn/view?usp=sharing) | [Kullo slides](https://drive.google.com/file/d/10I-ogidlcMOT4BYlF_OLTPrdUNCLmo2l/view?usp=sharing) | [Gordon slides](https://drive.google.com/file/d/1JePe0bzhgo12uOuUUG0KO3rCwf-GyBQW/view?usp=sharing)
	+ Heidi Rehm presented current efforts by the ClinGen Low Penetrance/Risk Allele working group led by Matt Lebo and Ryan Scmidt. The working group was established to understand how to address low penetrance and risk genetic variants for monogenic disorders.
		- Low penetrance variants have high-discordance rates in ClinVar due to inconsistent classifications. Current terms in ClinVar are benign, likely benign, uncertain significance, likely pathogenic, and pathogenic.
		- A survey of low penetrance variants from 2017 on low penetrance variant results found that 32/67 labs describe such variants using the standard terms (e.g. pathogenic, likely pathogenic, etc.) but add standard qualifier to denote low penetrance or mild effect such as “pathogenic, low penetrance”, 9/67 labs describe such variants as “risk alleles”, 17/37 labs have no specific terminology used, and 9/67 labs have another term such as uncertain significance or modifier.
		- The working group created a survey assessing adoption of the ACMG-AMP guidelines for interpreting sequence variants and identification of areas for continued improvement ([publication](https://www.ncbi.nlm.nih.gov/pubmed/?term=a+survey+assessing+adoption+of+the+acmghttps://www.ncbi.nlm.nih.gov/pubmed/?term=a+survey+assessing+adoption+of+the+acmg)). The Delphi Survey on terms and thresholds received 124 responses from participants representing 18 countries, diverse roles and affiliations. Responses were in likert scale from strongly agree to strongly disagree. Findings include:
			* The term risk ‘variant’ was relevant when a single variant defines risk versus risk ‘allele’ when multiple variants may define risk. Risk ‘variant’ was more impactful when variant has been functionally shown to have effect, and risk ‘allele’ was preferred when it is uncertain if it is a tag SNP.
			* Three classification tiers for risk ‘alleles’ were prefered: established risk allele, likely risk allele, and uncertain risk allele; with extra guidance for when to use “uncertain risk allele”.
			* Use of “low” in low penetrance would require a quantitative definition and for many genes/diseases that would be difficult and the term “reduced” has multiple meanings.
		- The working group plans to present the findings to additional groups and subspecialties, continue surveys and discussion to finalize terms and thresholds, move into defining evidence needed to categorize risk alleles, and classify some of the more common risk allele variants observed in Mendelian genes.
		- Some variants may be risk alleles for a subset of phenotypes. If the data only points to one element of the phenotypes, then the association would be just for that particular phenotype feature.
	+ Iftikhar Kullo presented Mayo’s work on informing and harmonizing variant interpretation using phenotype data.
		- At Mayo, a genetic counselor reviews and returns all results (P/LP). The VUS are mostly recorded in this setting by the clinician. If there are any questions about a VUS being reclassified the study site will discuss the possibility with the sequencing lab and present phenotypic or other evidence for why a VUS lean P/LP in that participant.
		- Most of the patients that have an indication feature a genetic condition that has a diagnostic oddity. Depending on if a given participant is being screened or actually has a disease phenotype diagnosis the available phenotypic information may differ. The more phenotypic information available about the participant can influence the sequencing lab’s decision regarding moving a VUS to a P/LP.
		- Mayo conducted an exhaustive review of all the phenotypes, and is interested in understanding how all the different phenotype information relates to interpreting the variant.
		- In Mayo’s RAVE study on hypercholesterolemia, Baylor initially did not report VUS. Mayo reviewed the results using clinical context and lit review followed by discussion with CSGs. Of the six LDLR VUS 2/6 were upgraded to LP and 4/6 were not re-classified, however they would have been reclassified as LP/P using ClinVar classification. The approach helped inform how EHR data and clinical context may improve variant interpretation.
		- Next steps include understanding more about the EHR data and clinical context and how they inform variant interpretation, specifically in large scale sequencing projects as the feasibility of labs to sift through phenotypic data is a concern.
	+ Adam Gordon presented return of results and reinterpretation lessons learned.
		- The initial 2017 classification of the PMS2 p.Gly72Glu variant was VUS. However, there was a re-review due to a publication that revealed the possible need to reclassify the variant. Data was requested and collected from ClinVar and sequencing center to be able to re-classify the variant as LP.
		- In a second scenario, a 53 year old woman MYL3 variant was not P/LP but after son’s collapse the team decided to return the variant as pathogenic and since then this variant has been seen in two other eMERGE participants.
			* The variant resulted in a pathogenic report from Northwestern and Mayo, and Baylor classified as pathogenic. Outcomes and penetrance data that is being generated will provide additional evidence that could potentially alter the interpretation.
		- There is current reinterpretation work on MYBPC3 and LMNA. In the MYL3 report, there have been reports that have been generated with the upgraded variant. The variant is currently discrepant between LMM and Baylor.
		- Penetrance data that is collected from individuals can be useful in classifications, especially if the prevalence and frequency is similar.
	+ It is important to not let ‘perfection’ not be the enemy of good. ClinVar is an evolving tool that will hopefully have a space for people with different interpretations to view different variant classifications.
	+ Although there is not always a consensus on the interpretation, these discussions are useful for the physician and ultimately better inform the clinicians taking care of these patients.
	+ Sites can report their own perspectives, especially on phenotype data, to ClinVar. Geisinger has been doing this from the autism clinic and have been doing this from the patient phenotype library.

* **Return of results pathways, barriers, and harmonizing across sites** | Ingrid Holm (*BCH*) & Iftikhar Kullo (*Mayo*) | [slides](https://drive.google.com/file/d/16ZgjwSw4ZqUqnrIAXfPNwzCfIjEyTwwh/view?usp=sharing)
	+ There are different return of result pathways differs across the sites. These methods differ regarding when the participant receives results and who returns the results, for example a genetic counselor or primary care physician. These differences create the opportunity to analyze different methods across multiple populations.
	+ Out of the 25,000 individuals sequenced there were 24,526 reports issued to sites. 1,643 results issued to sites were potentially returnable (pathogenic/likely pathogenic) which led to 1521/1643 P/LP results potentially returned and 122 results belonging to participants that were not contacted due to site specific reasons (e.g. age, already in EHR).
		- For pediatric sites, consent is initially obtained from parents for their child participants, but after the child turns 18 they must re-consent to receive results.
	+ There are 299 unreturnable results belonging to participants that have declined to receive results, were unreachable after multiple phone or mail attempts, or passively withdrew.
		- A few eMERGE participants have been placed in foster care or incarcerated since enrollment.
		- When a participant was deceased a few sites tried to return the result to a family member, however most results were not returned.
	+ None of the participants actively withdrew or asked to be removed from the study.
	+ Return of result challenges were split into three categories: logistical challenges, sequencing-related challenges, and participant-related challenges.
		- Logistical challenges included IRB approval, EHR integration, the need for reconfirmation of results, and the need for bilingual study coordinators for Spanish speaking participants.
			* *Ethical considerations related to return of results from genomic medicine projects: the eMERGE Network (Phase III) experience* ([publication link](https://www.ncbi.nlm.nih.gov/pubmed/29301385)) describes the analysis of IRB processes at nine eMERGE sites to identify common questions and concerns with consenting and returning results in a federated environment.
		- Sequencing related challenges were gender mismatch, mosaicism, genotype-phenotype discrepancy, and reclassification. There was variant reclassification from LMM of seven variants (VUS to LP).
		- Participant related challenges were changes in participant contact information, non-responding, declining, deceased, incarcerated, results already in the EHR, and pediatric participants need to re-consent at age 18.
		- The return of result process is dependent on institutional cultures and priorities which make it challenging to create standard guidelines. The differences in return of results processes across sites makes it challenging to study the impact of return of results across sites. The Healthcare Provider survey and Participant survey will help analyze the impact of return of results on healthcare providers and participants.
	+ In the pediatric data set, there were variants that do not manifest until later in life. CHOP cannot return adult onset diseases to pediatrics participants but will attempt when they turn 18. Written consent is gained from participants over the age of seven. Patients between 7-17 may not have fully understood the implications.
		- CCHMC biobank adolescents were not sequenced for adult onset conditions, however CCHMC eMERGE adolescents were sequenced for adult onset conditions and given the option to learn their results.
		- CCHMC has received IRB approval for consent for text message contact, which may help interact with participants who have turned 18 and need to be re-consented as they are unlikely to answer the phone from an unknown number. This has led to the consideration of modernizing the contact for groups that respond differently.
	+ Site outreach processes depend on the site IRB and standards in place. It was difficult to predict the issues regarding re-consenting and returning results to newly adult participants.
		- Best practices should be captured from the site heterogeneity.

* **Impact of ROR process on Outcomes assessment** | Josh Peterson (*VUMC/CC*) & Marc Williams (*Geisinger*) | [slides](https://drive.google.com/file/d/1Y-4InauAA380-g5zMomU2QBa7WboS9mn/view?usp=sharing)
	+ The eMERGE Outcomes workgroup has created 15 forms for specific phenotypes and a generic form for rare phenotypes. Eleven phenotype-specific implementation guides have been created to assist with the forms.
	+ As of September 2019, six-month outcomes has been collected for 856 participants representing 70% of the total returned cohort (total possible outcomes assessment).
	+ Over the last three years, the outcomes forms have grown to collect data for the entire Network: the Return of Result Information form was added to the beginning of the phenotype specific form, Familial Implications form added to the end, and family history questions to each form.
	+ The structure of outcomes forms includes questions regarding previously recognized variant(s), pre-ROR and post-ROR testing and procedures, pre-ROR and post-ROR diagnosis and findings, consultations, therapies, and family history.
	+ A key challenge has been determining if ROR was causally linked to testing and clinical outcomes during follow up. To answer this, abstractors indicate on outcomes form if the clinical test completed was prior to eMERGE result return, after eMERGE result return, or after eMERGE sequencing but not linked to return. This was difficult to determine and EHR data may not be able to capture this either.
		- An alternative would be to examine the rates of common clinical tests and procedures preceding and post return of eMERGE results.
	+ Individual phenotype analysis is planned for Tier 1 condition. An idea is being proposed to the Network to combine analysis across the phenotypes with lower counts, though age range and other factors would need to be considered.
	+ The group plans to summarize metrics across phenotypes by total follow-up test rate, total referral, total follow-up drug therapy, total follow-up procedures or surgeries, and total clinical outcomes.
	+ Lessons learned include understanding more about the heterogeneity of the population and return of results, understanding the increased complexity from non-standardized IRB and ID restrictions, developing a clear definition of return of results, and establishing a date for penetrance involving the ambiguity of EHR date references.
	+ Currently, there are eight manuscripts in progress on the outcomes analysis work. A publication on limitations and consideration would be useful. The Outcomes Harmonization paper has been [published](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6164315/). The paper details the comparison of ClinGen defined outcomes with eMERGE defined outcomes and lessons learned related to this analysis.

* **Interim Data Analysis: Clinical Outcomes** | Wendy Chung (*Columbia*), Christin Hoell (*NU*), Iftikhar Kullo (*Mayo*) [Chung slides](https://drive.google.com/file/d/1wABVhV3lqywcbyNQZw0NijaGBKqgqyJG/view?usp=sharing) | [Hoell slides](https://drive.google.com/file/d/1YFkE0BsWILOAv4DsH0HxR0JM7hUfD3BS/view?usp=sharing) | [Kullo slides](https://drive.google.com/file/d/1u2AzKPJ_WonpKvXo5LQ3EJUl2IzC95DJ/view?usp=sharing)
	+ Wendy Chung presented interim analysis of Breast Cancer genes clinical outcomes.
		- The outcomes workgroup pulled an interim dataset to analyze as well as check for data quality issues. Columbia has noticed some issues with the data: gender discrepancies in outcomes forms, gender discrepancies between outcomes forms and ICD data, missing data, duplicate eMERGE IDs, EHR results not concordant with outcomes forms, and these are being addressed.
		- Two breast cancer genes (JAK2 and P53) were not included in the analysis since they are somatic mutations and the numbers were low.
		- Most of the results were returned to participants that did not have previous knowledge of their risk, (BRCA1 (65%) and BRCA2 (51.7%)).
		- Genes that have high clinical impact (BRCA1, BRCA2, CHEK2) were more likely to be returned by genetic counselors than study coordinators.
		- Follow-up actions linked to ROR were tracked for mammograms, breast MRI, ultrasound, prophylactic mastectomy, and prophylactic oophorectomy. One female participant underwent a prophylactic mastectomy linked to eMERGE ROR, and five female participants had prophylactic oophorectomy. Fifteen women received a hormone therapy, 41 women consulted with an oncologist, and 39 women consulted with a breast surgeon; four men consulted with oncologist. There were no new cancer diagnosis for either men or women.
		- When considering penetrance for the different genes, BRCA1 has the highest penetrance, as expected. BRCA2 had the second highest penetrance, with CHEK2, PALB2, and ATM penetrance being much lower than the BRCA genes.
			* The penetrance curve looked different than the typical BRCA2 penetrance curve because the numbers are small. The deviation between BRCA1 and BRCA2 on the graph is around 70 years of age and typically occurs at an earlier age around 30 years.
		- Due to participants possibly taking preventative actions, penetrance was censored for only mastectomy and oophorectomy.
	+ Christin Hoell presented on Cardiomyopathy outcomes data analyzed by Northwestern.
		- From the full cardiomyopathy records (140), analyses were conducted on 78. Of the 78 participants, six were diagnosed with hypertrophic cardiomyopathy pre-ROR and two were diagnosed with dilated cardiomyopathy pre-ROR; none received changes in management due to ROR. Three of the 70 participants with no prior clinical diagnosis were diagnosed with cardiomyopathy post-ROR.
		- At six months, 30% of the participants had clinical activities that were linked to the return of results. Participants were more likely to have clinical activities conducted if they had met with a cardiologist.
		- In some cases new clinical activities were not observed, however depending on the timing of clinical testing prior to the return of eMERGE results some physicians may not have reordered a given clinical test. For example, if someone had an echocardiogram conducted a year ago, a physician may not have ordered a new echocardiogram even in light of the return of the eMERGE results. When the study team relaxed the time frame and examined clinical activities association shortly before and after the time of ROR, approximately 66% of participants recently had an echocardiogram.
		- Most of the participants had clinical cardiac activities within the past five years. Of those, approximately 50% were related to the return of results.
		- Some limitations to the outcomes forms is that the form only surveys for data five years prior to ROR. Another challenge for six month outcome is that cardiology appointment wait times for new visits and procedures could be greater than 6 months and impact the post-ROR outcomes data collection.
		- Some individuals had defibrillators placed prior to the ROR. Columbia also removed individuals who had a known variant. It is not clear whether or not they had genetic testing prior to eMERGE, or whether they may have had genetic testing and that test did not identify the variant.
	+ Iftikhar presented interim Familial Hypercholesterolemia (FH) outcomes data analysis.
		- Across the data 96 participants were found to have a FH related gene or variant: 78 with LDLR, 15 with APOB, and three with PCSK9. Results were returned to all but one participant and 86/95 results were returned by healthcare provider. Of the 95 participants analyzed pre-return of results, 87 participants had a hypercholesterolemia diagnosis and 32 had a coronary heart disease diagnosis. There were 13 clinical diagnosis of Familial Hypercholesterolemia found and seven prior genetic tests for Familial Hypercholesterolemia.
		- For FH related tests, 51 lipid profiles were conducted post-ROR, eight Lipoprotein(a) analyses, thirty-seven electrocardiograms, ten stress electrocardiograms, six echocardiograms, five CT scans, and four coronary angiography. Twenty five post-ROR treatments were found.
		- Main findings from the interim analysis were that the prevalence observed was double of what is expected (1:125 vs 1:250), there is poor awareness with only 8% genetic testing and 15% clinical diagnoses, only 50% of treatments were statins, a majority had new tests performed and a significant number had initiated new drugs.
		- Some limitations include confirming whether an outcome is related to ROR or standard of care. Additional analyses related to change in LDL-C and cascade testing needs to be done. In conclusion, FH is underdiagnosed and awareness is poor and sequencing for FH in the eMERGEseq cohort resulted in new diagnosis, testing, and therapies.
	+ As FH is is a highly penetrant condition, family members are likely to also have high cholesterol. The pathogenic level may not indicate they have a condition, because the LDL level may have still been too low.
	+ Clinicians may now recognize the need for screening. There are no treatment differences between FH and high cholesterol, so providers may not bill FH but put FH in the records, however it is important to make an accurate diagnosis since the risk is three times higher in FH pathogenic variant carriers with the same level of cholesterol. Identifying the genetic contribution can also help prevent early death in siblings and children if FH is accurately documented and recorded in the EHR.

* **Status of eMERGE FHIR Specification and Implementation Project** | Larry Babb (*P/B*) | [slides](https://drive.google.com/file/d/1ZrFGMuq3gQKE6oAq4CBdmSI2qAL1pKnJ/view?usp=sharing)
	+ Larry Babb has worked with Mullai Murugan at BCM to generate architecture design for how to build FHIR specification for eMERGE results
	+ There is currently work being done with the clinical genomics workgroup to reconcile and move to publish the draft specification, and a pilot study has begun.
	+ HL7 has an FHIR spec and is heavily centered on resources that provide the ability and infrastructure to develop guidance and structure of doing things like returning genetic resources.
	+ The group is currently working with a Clinical Genomics Implementation Guide to build and assemble the specification for the General Genomics reporting. The Clinical Genomics Workgroups have been very receptive to reporting the informative changes.
	+ The LMM and Baylor reports were dissected in order to begin the specification architecture and design of the FHIR standards. This was done in order to review which results were incorporated in stories, and some of the trickier parts of integration. The Clinical Genomics Workgroup represents the profile of what is included in the diagnostic reports. There was a need to determine how is a standard created and who should be informed of this standard initially. The EHRI WG discussed these questions.
	+ BCM is currently implementing the FHIR specifications. Johns Hopkins University (JHU) is still working on how to implement the FHIR standards and Luke Rasmussen from NU is working on how to incorporate PGx clinical decision alerts and best practices.
	+ Baylor has developers on staff for the project, which involves creating a server which will aid in data validation.
	+ More extensive engagement will begin next quarter with development and testing implementation in clinical sites.
	+ The team uses “Example Data” which allows them to parse data from actual reports and map to FHIR specifications. This helps in understanding what the implementers are going to face and considers how to resolve gaps during the development process.
	+ Several resources have been created, and GA4GH is working on variant representation to solve the problem of how to represent variation in models.
	+ *All of Us* is discussing how to share their own genomic results, whether to do this in FHIR or set up a pipeline directly from Color Genomics.
	+ The challenge with HL7 is that the goal is to apply it to healthcare all over the world. The easiest way to accomplish this is to divide the process into smaller components.
	+ It is essential to understand how to add conditions to the problem list for the ACMG conditions because of the differences in the code

* **Input/Feedback from the ESP, general discussion**
	+ Lisa: No comments
	+ Eta: The Network should try to highlight the strength of having a geographically and health care system diverse Network by helping identify the challenges health care organizations will face when implementing genomic medicine.
	+ Vandana: The Network should explore how different testing results are communicated to patients, and how patient interprets the results. This is especially important to consider for results that may have “changed” by reassessment. Educating providers is essential, but the key to getting genomic medicine into practice is to educate trainees.
		- HCP surveys include interviews of how clinicians handle results/how patients handle different types of results. The effort is a separate R01, and not part of eMERGE. Although the results are discussed and shared with the eMERGE Network.
	+ Stan: One challenge of clinical decision support (CDS) is to move it into clinical practice as many components that are created may still not be used clinically. This may be because there is no common infrastructure which limits CDS portability, and why adopting a FHIR standard may be so important in the future. If the EHR systems can support the CDS, then the programs could be shared more broadly.
	+ Howard: It is important to keep tackling the important items and questions discussed in eMERGE since they have broad applicability. The impact of eMERGE efforts can continue to make a significant impact on patient care. For example, There has been a new drug approved for male breast cancer based on retrospective data ([link](https://www.biospace.com/article/fda-approves-pfizer-s-ibrance-in-men-with-breast-cancer/)). The Network should explore what opportunities currently exist, which issues occur more at one site versus another. Surveying these issues across the Network can help discover and implement significant change to the health care system and patients lives.
	+ Rex also mentioned eMERGE should be very proud of the training of the new investigators and juniors who have become leaders in the field.

* **Closing remarks** | Rex Chisholm (*SC Chair, Northwestern*) | slides
	+ This is the last ESP meeting for eMERGE III. The Network is grateful for the ESP regarding the input, directions, motivations, and the applicability of the Network to research.

**Meeting Action Items**

**CSGs**

* The CSGs will provide sites with an updated list of VUS-leaning path variants, based on number of observations across eMERGE.
* The CSGs will continue to work with sites and document changes regarding variant reclassifications.

**Network**

* The Network and site PIs should review all in development MCSs on the [publication tracker](https://docs.google.com/spreadsheets/d/1AKRY-RDWngzyAZn0UhCNXHAo1Ozq9I69S9FZnhoxpok/edit#gid=1606396516) and contact the CC if the MCS needs to be withdrawn, there are changes to lead authors, or if MCSs should be combined in order to create stronger publications.

**ROR**

* Sites should continue to monitor and track non-responders and update the [tracker](https://docs.google.com/spreadsheets/d/1e3oKFUbwCxwYa2KNnxqgNR0hvV5AIno3J21_p1GXSjg/edit#gid=1125188624) accordingly.

**Outcomes**

* Sites should prioritize documenting inconsistencies with the Outcomes Data Freeze 1 in order to ensure any issues are addressed prior to the final six-month data freeze in January 2020.
* Marshfield should determine if they will be able to contribute any six months outcomes data prior to the final January 2020 data freeze.

**Clinical Annotation**

* The CC will coordinate with Gail Jarvik and Geisinger to create a REDCap penetrance form for the HFE (hemochromatosis) data.
* The CC will add a ‘Case Report’ notes field to the penetrance only forms similar to those on the outcomes forms for additional related information found in the EHR.

**Genomics**

* The Genomics workgroup should review the [publication tracker](https://docs.google.com/spreadsheets/d/1AKRY-RDWngzyAZn0UhCNXHAo1Ozq9I69S9FZnhoxpok/edit#gid=1606396516) and determine if any in development MCS can be incorporated into their lessons learned paper.
* The CC will facilitate the transfer of legacy data to the AnVIL, including confirming that site-specific dbGaP submission can be linked for Network use on the AnVIL.
* The CC will work with the Genomics group to transfer the geocoding data to the CC prior to the end of Phase III.

**Phenotyping**

* The BMI data for Network use & dbGaP submission should be cleaned based on individual study specific requirements, median BMI may be preferred if longitudinal data is not needed.
* The CC will develop a standardized process with the Phenotyping group regarding moving phenotypes in development on PheKB to the ‘public’ side, including a plan for publicizing the 25 Phase III phenotypes prior to the end of eMERGE.

**ESP Executive Session Notes & Recommendations** | [notes](https://drive.google.com/file/d/1ZPDTqolqAe3Z11UWZPBVy0rf4GryQxTL/view?usp=sharing)

* The External Scientific Panel (ESP) met with NHGRI program staff members in an executive session before and after the October 4, 2019 External Scientific Panel and Steering Committee In-Person Meeting.
* Overall, the ESP was impressed with the eMERGE Network’s progress and encouraged them to continue sharing their knowledge and tools that have immense value beyond research. The ESP appreciated the Network’s effectual and timely responses to previous ESP recommendations and highlighted continued collaboration among such a large and transdisciplinary group. The ESP was particularly impressed with how ongoing efforts extend beyond the Network and are influencing broader adoption of genomic medicine. The Network appears to be making a natural progression to address many of the challenges that will arise in the next phase of eMERGE.
* eMERGE has more than 150 manuscripts in process: a testament to the Network’s significant ongoing work. However, with 6 months remaining in its current phase, and as the Network typically publishes ~50 papers a year, a strategy to finalize these manuscripts is needed. The ESP suggested reviewing and combining manuscript concept sheets into several impactful articles.
* The Return of Results (RoR) and Outcomes workgroups are making great progress consolidating heterogeneous forms for capturing outcomes and penetrance information. The ESP noted in particular that this improved process will be highly applicable across diverse health care settings, as well as for organizations considering implementing genomic medicine. The ESP recommended that the workgroups continue to share and publish their lessons learned.
* The ESP is also impressed by the Network’s recent collaboration that led to publication of “The Responsibility to Recontact Research Participants after Reinterpretation of Genetic and Genomic Research Results” (*American Journal of Human Genetics*). However, there is some concern about site-specific variability of methods for reclassifying and returning results to eMERGE participants. The ESP suggested that resolving heterogeneity across the Network will help elucidate the nuances of their proposed approach. For example, how did the Network consent participants, and how did this process differ across sites? The ESP acknowledged that the Network is limited by the small sample size of reclassified variants but recommended qualitative assessment to better understand how labs, providers, and patients interpret and respond to variant reclassifications. The ESP also recommended that the Network look for opportunities to collaborate with other groups to study the dynamic aspect of genetic reclassifications and reporting.
* The ESP continues to be pleased with the Network’s efforts to help establish standards for incorporating XML-based genetic-testing results into electronic medical record (EMR) clinical decision-support systems (CDSS). They were especially enthusiastic about eMERGE being a critical driver behind establishing Fast Healthcare Interoperability Resources (FHIR) standards, as it is a significant first step to enabling the use of genomics in clinical decision making. The Network’s adoption of these standards has provided insight into various challenges including who creates and maintains knowledge in CDSS. The ESP looks forward to seeing the Network lead a broader discussion about what is needed to successfully implement genomics into EMRs.

**There are four recommendations from the ESP given to investigators:**

1. Consider consolidating and prioritizing Network-wide and lessons-learned manuscripts in the last 6 months of this phase of eMERGE.
2. Continue to collaborate (RoR and Outcomes workgroups) to understand how different RoR processes used by various sites affect measured outcomes.
3. Regarding reclassification of genetic variants:
	1. Resolve site-specific heterogeneity across the Network in methods for reclassifying variants.
	2. The Network’s experience with consenting and returning reclassified variants provides essential information to help further discussion about optimal methods.
	3. Qualitatively assess how labs, providers, and patients respond to genetic variant reclassifications.
4. Continue to work with other consortia and commercial entities to help develop and implement FHIR standards and genomic CDSS. The Network should continue its leadership and educational roles within the broader scientific and clinical communities.