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.
  - 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”.
  - 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), FKR (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:
  o 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
    o They will attempt to identify relatives based on first name/last name/DOB provided by eMERGE participant
    o 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 assess family sharing/communication activities.
  o Some sites conducting baseline pre-results disclosure survey
  o All sites will include small number of consistent items in a post-results survey
  o Some sites will survey immediately after return of results
  o 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.
  o Collect site-specific activities currently planned to promote family communication
  o Assess factors that lead to variation in methods of communications including materials, approaches and measures of success
  o Test various methods of contact
• Geisinger patient experience interviews:
  o 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
  o 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:
  o eMERGE can work with NQF to develop quality measures for familial hypercholesterolemia as this is a specific phenotype of interest to both.
  o eMERGE can work with NQF to develop quality measures for Lynch syndrome.
  o eMERGE experts can become members of NQF.

**NIH GenomeTV Livestream Summary Statistics**


• 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 see below for a detailed breakdown of the unique views per country and a heat map of the views around the world.

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*Bethesda – 24 views
*Outside of Bethesda – 191 views