eMERGE Network

electronic medical records & genomics

External Scientific Panel

packet

Steering Committee & ESP Meeting

December 4-5, 2014

Bethesda, MD

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Human Genome
Research Institute
31 Center Drive MSC 2152
Building 31, Room 4B09
Bethesda, MD 20982-2152

November 14, 2014

Dear eMERGE External Scientific Panel members,

We are happy to announce that eMERGE will be entering its third phase next summer. The goal of eMERGE Phase III is to continue genomic discovery and implementation research using large biorepositories linked to electronic medical records (EMRs).

We appreciate all of the time and effort that you have devoted to the eMERGE Network in the past, and we look forward to your continued input, especially at our in-person meeting on December 5, 2014 at Hyatt Regency, One Bethesda Metro Center, Bethesda, MD 20814.

To ensure a productive meeting, the eMERGE Coordinating Center (CC) has prepared two booklets in collaboration with the eMERGE investigators: a main packet and background materials. Within these booklets, you will find the following important items:

- Agenda for eMERGE Steering Committee (December 4, 2014) and External Scientific Panel meeting (December 5, 2014) – ***Note: You are welcome to attend the Steering Committee meeting as well.***
- Network documents:
  - eMERGE Network Overview
  - eMERGE Genomic Medicine Translation
  - Response to ESP Recommendations
  - eMERGE Network Achievements
  - eMERGE Workgroup Updates
  - Genomic Medicine Site Updates
- Background Information

If you have any questions or would like additional information or materials, please do not hesitate to contact us or the CC program staff (contact information is provided in this booklet).

We thank you again for your help in making this network as successful as possible, and we look forward to seeing you in December.

Sincerely,

Rongling Li, MD, PhD
Project Director, eMERGE
Division of Genomic Medicine
NHGRI, NIH
lir2@mail.nih.gov

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AGENDA

December 4-5, 2014
Bethesda, MD

Thursday, December 4th

Venue:	Hyatt Regency
Meeting:	Waterford/Lalique Suite
7:30-8:30 a.m.	***Networking Breakfast – Waterford Foyer***
	Full Session
8:30-8:40 a.m.	Welcome, Opening Remarks, General Updates – Rongling Li
8:40-8:50 a.m.	Announcements, Opening Remarks – Rex Chisholm
8:50-9:10 a.m.	Integrating Clinical Genomics Into the EHR: Using Interface Terminology (IMO) and Interoperable Standards (SNOMED, LOINC, FHIR) – Jennifer Pacheco (Northwestern)
9:10-9:30 a.m.	Appendicitis – John Harley (CCHMC)
9:30-9:50 a.m.	New Method to Link Gene Discovery to Genomic Medicine in EHR-linked Biobanks: Uncovering Surprisingly High Incidence of Steel Syndrome in Puerto Ricans – Eimar Kenny (Mt. Sinai)
9:00-10:05 a.m.	***Networking Break – Waterford Foyer***
	Full Session
10:05-11:25 a.m.	eMERGE PGx Plenary Session
11:25-11:45 a.m.	Implementation of Clinical Decision Support for Pharmacogenomics – Pedro Caraballo (Mayo)
11:45-12:15 p.m.	***Working Lunch – Waterford Foyer***
12:15-1:05 p.m.	ENCODE Presentation
	Workgroup Meetings
1:05 -2:35 p.m.	Workgroup Breakout Session (3 workgroups) • Return of Results (Waterford/Lalique Suite) • Phenotyping (Diplomat/Ambassador Room) • Pediatric (Cartier/Tiffany Salon)
2:35-2:50 p.m.	***Networking Break – Waterford Foyer***
	Full Session
2:50-3:10 p.m.	Simulation of the Clinical and Economic Impact of Preemptive, Multiplexed Pharmacogenomic Testing – Josh Peterson (Vanderbilt)

3:10-3:30 p.m.	Post Mortem Whole Genome Sequencing: A Genomic Autopsy – Murray Brilliant (Marshfield)

Workgroup Meetings

3:30-5:00 p.m.	Workgroup Breakout Sessions (3 workgroups) • CERC/CERC Survey (Waterford/Lalique Suite) • EHR Integration (Diplomat/Ambassador Room) • Genomics (Cartier/Tiffany Salon)
5:00 p.m.	Meeting Adjourned

Friday, December 5th

Meeting:	Waterford/Lalique Suite
7:00-8:00 a.m.	***Networking Breakfast – Waterford Foyer***
7:30-8:00 a.m.	Executive Session with ESP (Cartier Salon)

Full Session

8:00-8:15 a.m.	Opening Remarks – Teri Manolio & Rongling Li, NHGRI
8:15-8:25 a.m.	Comments from ESP Chair – Howard McLeod
8:25-8:45 a.m.	eMERGE Network Overview: Priorities and Goals; Review of Progress of Prior ESP Recommendations & Best Practices Topics – Rex Chisholm, Chair
8:45-9:05 a.m.	Optimal Management of Different Types of Genetic Information in the EHR: An eMERGE-CSER Collaboration – Brian Shirts (UW) & Casey Overby (UMD)
9:05-9:25 a.m.	Initial Analysis of Whole Exome Sequence Data from 10,000 Geisinger Patients: Implications & Opportunities – David Carey (Geisinger)

Workgroup Presentations– 20 minutes for report, 10 minutes for discussion

9:25-9:55 a.m.	CERC Survey Project Update & Discussion – Ingrid Holm & Maureen Smith
9:55-10:10 a.m.	***Networking Break – Waterford Foyer***
10:10-10:40 a.m.	Genomics – Gerard Tromp & David Crosslin
10:40-11:10 a.m.	Phenotyping – Josh Denny & Peggy Peissig
11:10-11:40 a.m.	Pediatrics – Hakon Hakonarson & John Harley
11:40-12:10 p.m.	eMERGE PGx – Josh Denny & Laura Rasmussen-Torvik
12:10-12:35 p.m.	***Working Lunch – Waterford Foyer***
12:35-1:05 p.m.	Return of Results – Gail Jarvik & Iftikhar Kullo
1:05-1:35 p.m.	EHR Integration – Justin Starren & Marc Williams
1:35-2:05 p.m.	Consent, Education, Regulation and Consultation – Ingrid Holm & Maureen Smith
2:05-2:20 p.m.	***Networking Break – Waterford Foyer***
2:20-2:50 p.m.	Input-Feedback from ESP, General Discussion
2:50-3:00 p.m.	Closing Remarks
3:00 p.m.	Meeting Adjourned

End Full Session

3:00-3:30 p.m.	Executive Session with ESP (Cartier Salon)

Electronic Medical Records and Genomics (eMERGE)

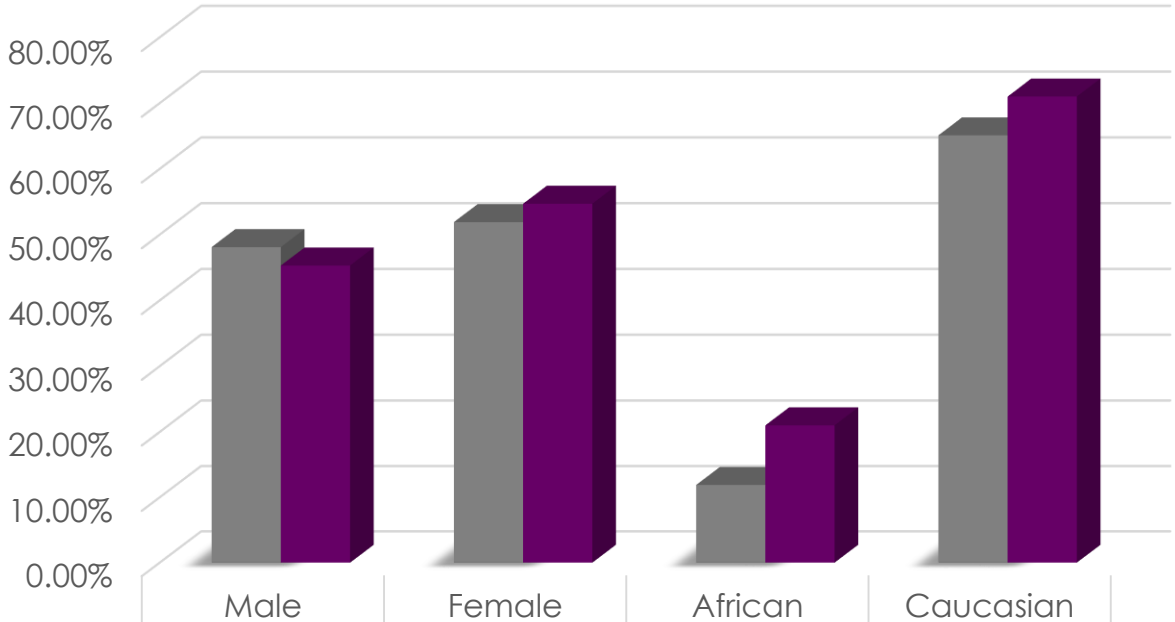
Network Overview

eMERGE is a national consortium organized by NHGRI to develop, disseminate, and apply novel approaches to research. It combines DNA biorepositories with electronic medical record (EMR) systems for large-scale, high-throughput genetic research with the ultimate goal of returning genomic testing results to patients in a clinical care setting.

eMERGE studies and pilots **Genomic Medicine Translation** through **Discovery, Implementation, Tools, and Policy**. During Phase I and II, the Network has applied more than 30 electronic phenotype algorithms across more than 52,000 subjects with dense genomic data. Various models of returning clinical results have been implemented or planned for pilot at sites across the Network. A large-scale survey of patient attitudes regarding data sharing is in development. Themes of bioinformatics, genomic medicine, privacy and community engagement are of particular relevance to eMERGE.

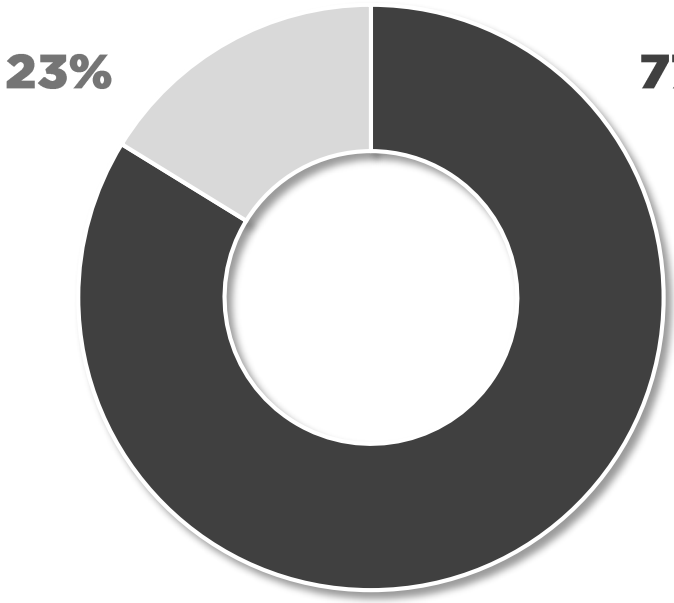
Site	Principal Investigator(s)
Children's Hospital of Pennsylvania (CHOP)	Hakon Hakonarson, MD, PhD
Cincinnati Children's Hospital Medical Center/Boston's Children's Hospital (CCHMC/BCH)	John Harley, MD, PhD (CCHMC) & Ingrid Holm, MD, MPH (BCH)
Geisinger Health System	David Carey PhD & Marc Williams, MD
Group Health Cooperative & University of Washington (GHC/UW)	Eric Larson, MD, MPH (GHC) & Gail Jarvik, MD, PhD (UW)
Essentia Institute of Rural Health & Marshfield Clinic (Marshfield/Essentia/PSU)	Catherine McCarty, PhD, MPH (Essentia) & Murray Brilliant, PhD (Marshfield Clinic)
Mayo Clinic	Christopher Chute, MD, DrPh, & Iftikhar Kullo, MD
Icahn School of Medicine at Mount Sinai	Erwin Bottinger, MD
Northwestern University	Rex Chisholm, PhD & Maureen Smith, MS
Vanderbilt University	Dan Roden, MD
Coordinating Center	Paul Harris, PhD

GWAS Cohort Demographics



	Male	Female	African American	Caucasian
System Wide	48.10%	51.90%	11.90%	65.10%
eMERGE Network	45.30%	54.70%	21.00%	71.00%

SOURCE System Wide: CERC Survey Site Characteristics Grid / eMERGE Network: eMERGE Record Counter



Adult Records

Pediatric Records*
*age less than 18

SOURCE eMERGE Record Counter

eMERGE: Genomic Medicine Translation

Discovery

Phase I

- 18,663 GWAS
- 13 Phenotype Algorithms

Phase I & II (Total)

- 55,288 GWAS
- 4,718 Sequences
- 33 Phenotype Algorithms (complete)
- 8 Phenotype Algorithms (in process)

Implementation

8 of 9 sites implemented CDS for CYP2C9/ Warfarin and VKORC1 / Warfarin

6 of 9 sites implemented CDS for CYP2C19 / Clopidogrel

5 of 9 sites implemented CDS for SLCO21B1 / Simvastatin

4 of 9 sites implemented CDS for TPMT/Thiopurines

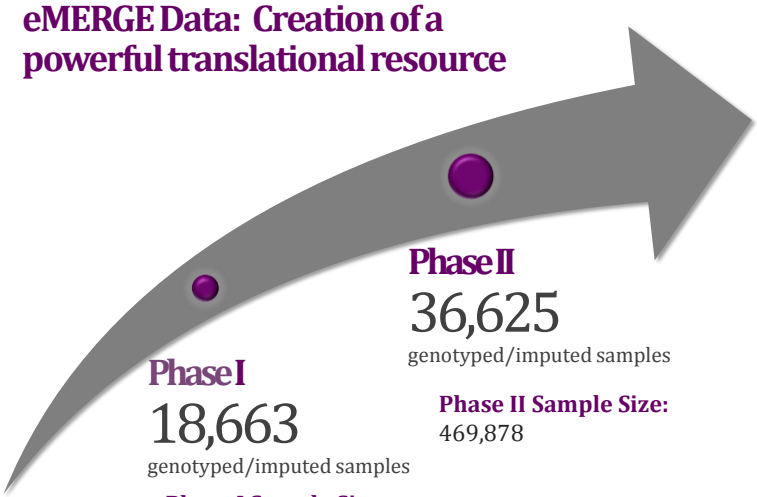
3 of 9 sites implemented CDS for CYP2D6 / Codeine

Single site implementation of CYP2D6 / tamoxifen; CYP2D6 / tramadol; HLAB1502 / carbamazepine; IL28B / interferon response; CYP2D6 / SSRIs; CYP2D6 / tricyclic antidepressants; HLAB1502 / carbamazepine

Tools & Policy

- **PheKB.org** – phenotype knowledge base
- **Myresults.org** – return of results; genomic medicine interpretation
- **SPHINX** – open access for sequencing data
- **InfoButton** – genomic medicine information for clinical care
- **Model Consent Language**
- **Data Sharing Survey** – patient attitudes regarding broad data sharing

eMERGE Data: Creation of a powerful translational resource



cumulative GWAS/imputed sample size: **55,288**

Phase II of **eMERGE** added **four** new sites, including **two** pediatric sites. These four sites contributed **21,597** new samples for Phase II.

Each site's contribution to Phase II is listed below:

Site	Sample Size (2014)	Phase I & II GWAS
Group Health/UW	5,859	3,520
Marshfield	20,000	4809
Mayo	42,701	6,872
Northwestern	11,000	4,858
Vanderbilt	187,402	13,632
Geisinger*	62,959	3,111
Mt. Sinai*	31,047	6,290
CHOP*	64,987	6,850
CCHMC/BCH*	43,923	5,346
Total	**469,878**	**55,288**

*denotes new site for Phase II

eMERGE
Expert Scientific Panel Recommendations

December 2014

ESP Recommendations – May 2014

1. **Impact**
   - The Network should continue to disseminate its products and best practices to the broader scientific community to increase visibility.
2. **Pediatric Integration**
   - Pediatric sites need to work together to take advantage of this network, such as data sharing, and network project development.
   - The Pediatric Workgroup should identify and document the challenges preventing collaboration between pediatric sites.
3. **Translation**
   - The Network should consider having more of a focus on implementation in the future.
4. **Future Directions**
   - Future directions stated by all workgroups should have wording that is consistent and reflects the priorities of the Network as a whole.

Impact

eMERGE Publication Awards

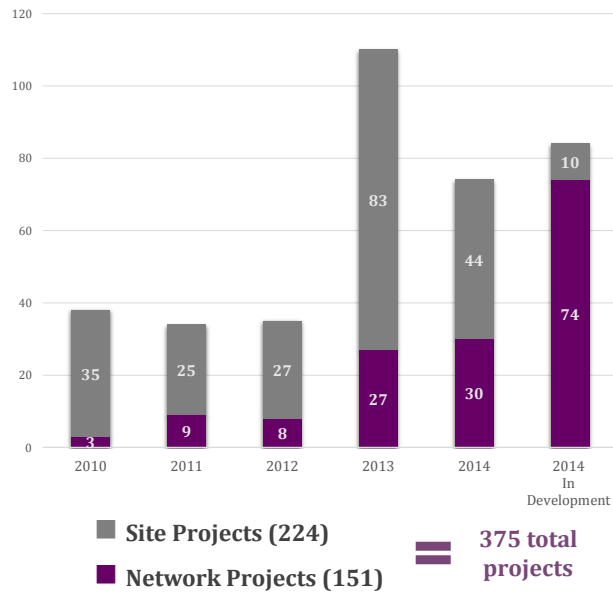
eMERGE Papers Nominated as Distinguished at AMIA 2014
(27% of nominated papers were co-authored by eMERGE members)

- "**What is Asked in Clinical Data Request Forms? A Multi-site Thematic Analysis of Forms towards Better Data Access Support**" DA Hanauer, GW Hruby, DG Fort, LV Rasmussen, EA Mendonca, C Weng
- "**A Template for Authoring and Adapting Genomic Medicine Content in the eMERGE Infobutton Project**" CL Overby, LV Rasmussen, AL Hartzler, JJ Connolly, JF Peterson, R Hedberg, RR Freimuth, BH Shirts, JC Denny, EB Larson, CG Chute, G Jarvik, J Ralston, AR Shuldiner, IJ Kullo, P Tarczy-Hornoch, M Williams
- "**Development and Validation of an Electronic Phenotyping Algorithm for Chronic Kidney Disease**" GN Nadkarni, O Gottesman, JG Linneman, H Chase, RL Berg, S Farouk, R Nadukuru, V Lotay, S Ellis, G Hripcsak, P Peissig, C Weng, EP Bottinger
- "**SOEMPI: A Secure Open Enterprise Master Patient Index Software Toolkit for Private Record Linkage**" C Toth, EA Durham, M Kantarcioglu, Y Xue, B Malin

eMERGE Paper included as "Best of AJHG 2012 & 2013"

- "**Return of Genomic Results to Research Participants: The floor, the ceiling, and choices in-between**" Jarvik GP, Amendola LM, Berg JS, Brothers K, Clayton EW, Chung W, Evans BJ, Evans JP, Fullerton SM, Gallego CJ, Garrison NA, Gray SW, Holm IA, Kullo IJ, Lehmann LS, McCarty C, Prows CA, Rehm HL, Sharp RR, Salama J, Sanderson S, Van Driest SL, Williams MS, Wolf SM, Wolf WA; eMERGE Act-ROR Committee and CERC Committee; CSER Act-ROR Working Group, Burke W

Number of published projects through October 2014



Impact

Citation Analysis through Oct. 31, 2014

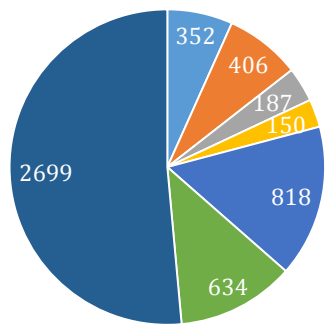
Cumulative Citation Count

- 2007-October 2014: **5,971**
- Phase II Publications Only: **1,585**

eMERGE Foundation Papers

- Phase I : *The eMERGE Network: A consortium of biorepositories linked to electronic medical records data for conducting genomic studies. (205 Citations)*
- Phase II: *The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. (48 Citations)*

Citations of eMERGE Publications by Category



All Network / Foundation: 352(84)
Privacy: 406(34)
EHRI: 187(187)
PGx/Implementation: 150(150)
CERC/RoR: 818(128)
Phenotyping: 634(214)
Genomics: 2699(758)

Total # Citations (# Citations of Phase II publications alone)

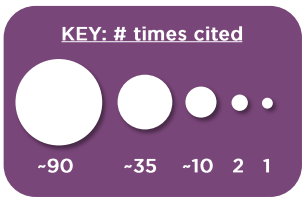
SOURCE: Google Scholar

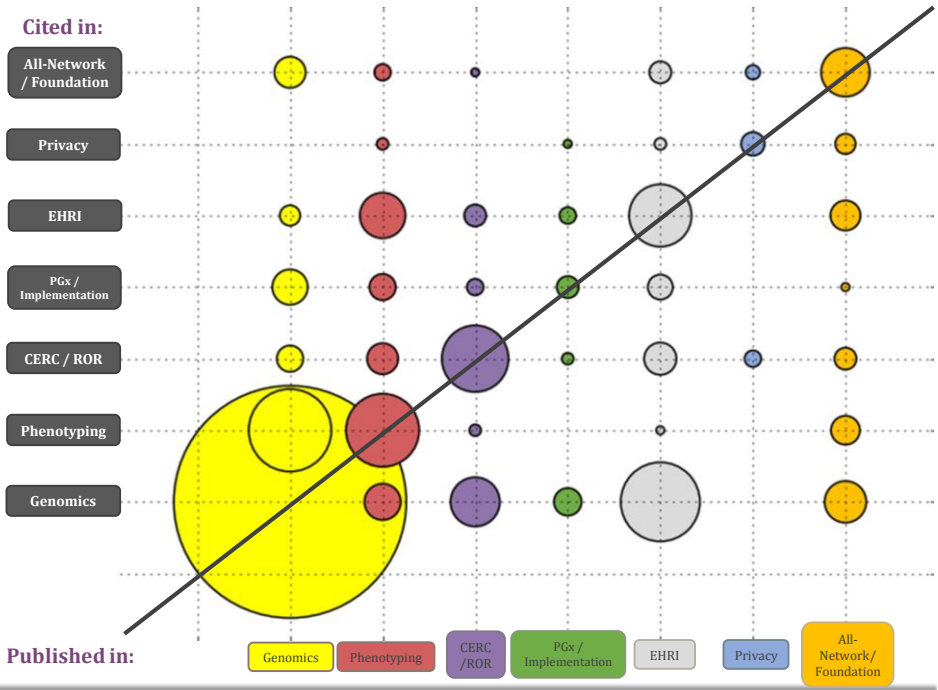
Impact

Citation Analysis

Diversity of Citing Journals Indicates Breadth of eMERGE Publication Impact
(*publications from 2013-14*)

- *Each circle represents a publication.*
- *Circle size is proportional to the number of times any article published in a journal topic category (x-axis) was cited in the particular journal topic category given by the y-axis.*
- *Cross-Discipline citations represented by off-diagonal dots.*



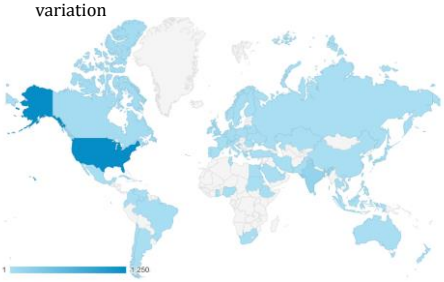


Impact

Share eMERGE science and products

GWAS.org - The eMERGE website provides a one-stop shop for updates and additional information on eMERGE science as well as tools for sharing. GWAS.org receives over **1,780 unique visits** per month.

- Phenotyping Tools
  - ✓ PheKB.org – phenotype knowledge base
  - ✓ eleMAP– data sharing standardization
- Personalized Medicine Tools
  - ✓ Myresults.org – patient education
  - ✓ SPHINX – explore drug response implications of genetic variation



zotero LinkedIn twitter

Analytic Overview:

~1500 views/month

- Mean session duration: 3:05 minutes
- Mean # of page views: 5.21
- 78% of visitors are new to the site
- 1,135 patients registered as of end of Aug, 2014

MyResults.org

Recent Updates:

- Development of a "For health professionals" section.
- Collaborating with the EHRI workgroup's Infobutton project for EHR integration.

Analytic Overview:

~3,086 views/month

- Mean session duration: 5:52 minutes
- 46.2% of visitors are new to the site
- 95 phenotypes with 147 impl. posted
- 283 users representing 30 insts.

PheKB a knowledgebase for discovering phenotypes from electronic medical records

Recent Updates:

- Integration of data dictionary and data validation tool

Analytic Overview:

~166 views/month

- 62.6% of visitors are new to the site
- 4,998 samples available in Variant Repository

SPHINX A resource of the eMERGE Network

Recent Updates:

- Incorporating additional subjects to resource
- Develop new use cases

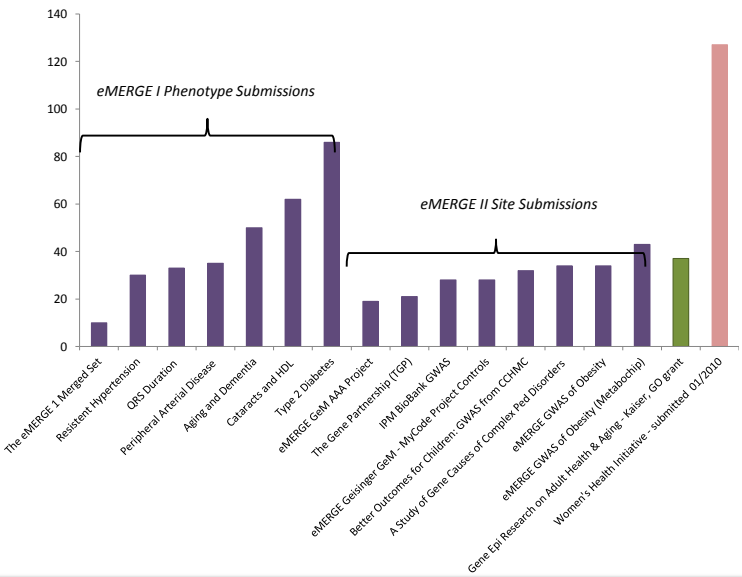
Impact

-Share eMERGE science and products
-Measure and assess impact

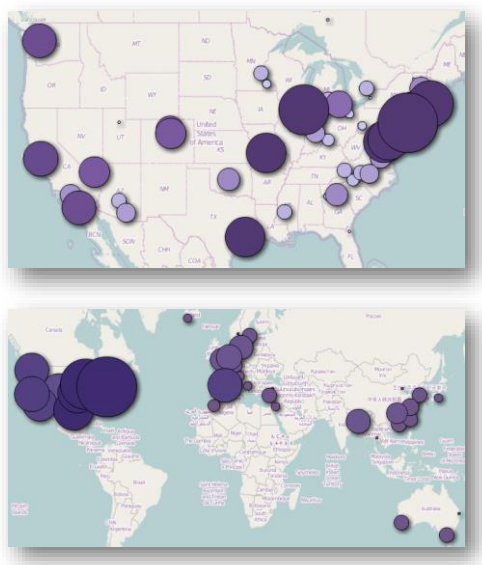
	Other Tools Available to Public
Phenotyping	**eleMAP (Mayo/CC)** *113 users representing 70 institutions* **PheWASCatalog (Vanderbilt)** *1,205 unique visitors to the website since release*
Genotyping	**PennCNV/ParseCNV (CHOP)** *Widely-used: 738 Citations to date* **NGS data Analysis Pipeline (CHOP)** *Over 1,700 subjects whole exome sequencing with over 100 different rare medical disorders, resolved over 30 rare disorders; sequencing an average of 50 exomes per week at 70x coverage* **Biofilter, BioBin (Penn State/Marshfield)** *Provides methods for prioritizing and analyzing variants singly or in groups, over 279 downloads since June 2013* **PLATO, ATHENA (Penn State/Marshfield)** *Provides platforms for QC and integrating multiple methods of analysis, over 285 downloads since June 2013* **Synthesis-View, PheWas-View, Phenogram (Penn State/Marshfield)** *Provides visualization tools for genome and phenome-wide data, over 116 downloads since June 2013.* **ANNOVAR (CHOP)** *Widely used: 737 citations to date*
Consent	**eMERGE Model Consent Language (eMERGE Network)** *Freely available on NIH website, over 730 downloads since October 2013*

Impact

Data Reuse: # Downloads of eMERGE dbGaP Submissions



eMERGE dbGaP downloads by location



Impact

Collaborations to Share Expertise, Extend Best Practices, and Increase eMERGE Visibility

Existing Collaborations

- PGRN
  - eMERGE PGx Project
  - Clinical Pharmacogenetics Implementation Consortium (CPIC)
  - Joint Publication: *Design & Anticipated Outcomes of the eMERGE-PGx Project: A Multicenter Pilot for Preemptive Pharmacogenomics in Electronic Health Record Systems*
- CSER
  - Joint Publication: *Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices in Between*
- University of Utah
  - OpenInfobutton Project – Dr. Guilherme del Fiol

Potential Collaborations

- PCORI
- IGNITE – RoR/CERC/EHRI
- HL7 – CDS/EHRI
- **N**ewborn **S**equencing **I**n **G**enomic medicine and public **H**eal**T**h (NSIGHT) Consortium - CERC
- Undiagnosed Diseases Network - CERC
- CDSC – CDS/EHRI
- REDCap Consortium
- IRBShare
- ENCODE

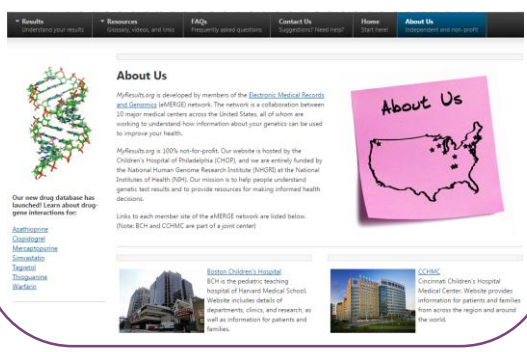
Pediatric Integration

MyResults.org

C C A G T G C C T C T C C T G G C C C T G

Integration – across sites and across drug:gene pairs

- Design and Development Led by John Connolly, CHOP
- Includes videos and information for all sites
- Patient-oriented content
- Information about the impact of genomics on the family



"Practical Guidance on Informed Consent for Pediatric Participants in a Biorepository"

Kyle B. Brothers, MD; John A. Lynch, PhD; Sharon A. Aufox, MS; John J. Connolly, PhD; Bruce D. Gelb, MD; Ingrid A. Holm, MD, PhD; Saskia C. Sanderson, PhD; Jennifer B. McCormick, PhD; Janet L. Williams, LGC, MS; Wendy A. Wolf, PhD; Armand H.M. Antommaria, MD, PhD; and Ellen W. Clayton, MD, JD

In Press from MAYO CLINIC PROCEEDINGS

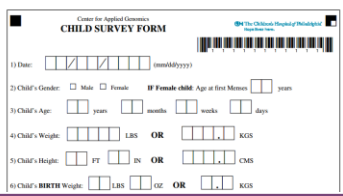
"When Research Participants Grow Up: Recontact and Reconsent at the Age of Majority."

Kyle B. Brothers, MD, et al. (author list not yet finalized)

- Publications will build off the Phase I Model Consent Language
- Will provide practical guidance on how to address the pediatric-specific issues in biobank consent.

Center for Applied Genomics (CAG) Shared Pediatric Participant Entry Form

Data collected for all entering their biobank



Pediatric Integration

Working together to take advantage of this network & identify and document challenges

Phenotypes being executed by both Pediatric and Adult sites	Primary Site	Number of Sites Participating	Status
ADHD	CHOP	4	In Development
Appendicitis	CCHMC/BCH	5	Algorithm Distributed
Asthma	CHOP	9	Analysis in Progress
Atopic Dermatitis	CHOP	8	Analysis in Progress
C. Diff	GH/UW	9	Analysis in Progress
GERD	CHOP	9	Analysis in Progress
VTE	Mayo	8	Analysis in Progress

Translation

*Focusing more on **implementation***

Current Actions

The Network continues to plan for the remainder of eMERGE Phase II and the future of eMERGE beyond Phase II. These plans include genomic medicine implementation plans along with continued discovery.

- Document best practices and barriers in EHR Integration
  - Extending to local genomic medicine implementation
- Explore OpenInfoButton framework as part of clinical decision support across several sites
  - Nominated for 2014 AMIA Annual Symposium Distinguished Paper Award:
    - *A Template for Authoring and Adapting Genomic Medicine Content in the eMERGE Infobutton Project*
- Address Issues around returning incidental genomic findings to patients
- Inform determination of "pathogenic' in variants of unknown significance

Translation

*Focusing more on **implementation***

Open infobutton

- ✓ Collected scenarios from involved sites
- ✓ Designed eMERGE template
- ✓ Content development completed template
- ✓ Completed site surveys
- ✓ Configured EHRs for InfoButtons

American Journal Human Genetics: *Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between*

Gail P. Jarvik[1, 2], Laura M. Amendola[1], Jonathan S. Berg[3], Kyle Brothers[4, 5], Ellen W. Clayton[6], Wendy Chung[7], Barbara J. Evans[8], James P. Evans[3], Stephanie M. Fullerton[9], Carlos J. Gallego[1], Nanibaa' A. Garrison[6], Stacy W. Gray[10, 11], Ingrid A. Holm[12, 13, 14], Iftikhar J. Kullo[15], Lisa Soleymani Lehmann[10], Cathy McCarty[16], Cynthia A. Prows[17], Heidi L. Rehm[10], Richard R. Sharp[18], Joseph Salama[1], Saskia Sanderson[19], Sara L. Van Driest[6], Marc S. Williams[20], Susan M. Wolf[21], Wendy A. Wolf[12, 14],

eMERGE Act-ROR Committee and CERC Committee ,

CSER Act-ROR Working Group ,

Wylie Burke[9]

Mentioned by

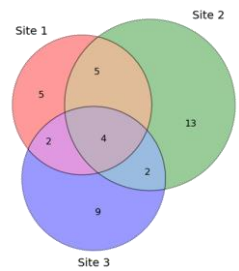
2 news outlets

1 blog

53 tweeters

2 Facebook users

← Multi-group collaboration



Rare SCN5A and KCNH2 Variants of Unknown Significance Determined "Pathogenic"

- 127 Variants sent to 3 sites for expert review
- 40/127 (31%) "pathogenic"
- Only 4 called "pathogenic" by all 3 sites

Translation

Comparative Implementation of PGx: across sites, across systems

Site	Simvastatin	Clopidogrel	Warfarin	Local Genomics
Northwestern	**Live**	**Live**	**Live**	Recruitment Underway. CDS Under development. For Hemochromatosis and Factor V Leiden. Working on implementation details with local lab.
Marsh/Essentia/PSU	**Live**	**Live**	**Live**	CDS for AMD genetic risk live.
Geisinger	**Live**	Go live by Nov. 30 (Epic version upgrade)	Delayed pending further discussion with clinicians	Implemented: I28B chronic hepatitis C
Vanderbilt	Operational and on hold	**Live**	**Live**	Implemented: TMPT / thiopurines and CYP3A5 / tacrolimus
Mt. Sinai	**Live**	**Live**	CDS revision for AA patients	APOL1 qualitative study complete; CDS development/implementation in coordination with IGNITE Program; target July for APOL1 CDS
Mayo	**Live**	**Live**	**Live**	MIGENES study of disclosing genomic risk for coronary heart disease to complete in Q4, 2014; risk communication occurs using the EHR. Pharmacogenomic CDS is in place for SLCO1BI, CYP2C19, VKORC-1, CYP2C9, TPMT, HLA-B 5701, CYP2D6 variants.
GHC/UW	Returned as research results. Not being incorporated into EMR	Returned as research results. Not being incorporated into EMR	Returned as research results. Not being incorporated into EMR	Ongoing patient and provider qualitative studies and prototyping to inform CDS and return of results.
CHOP				Building a new framework with EpicCare team. Awaiting final approval to go live with TPMT gene and azathioprine/mercaptopurine/thioguanine drug pairing
BCH		Under development	Active with decision support.	EHRI components focuses on testing of hypothetical scenarios. Other Genomic Decision Support active: TPMT. Under development HLA-B*15:02 and HLA-A*31:01 - carbamazepine
CCHMC		CYP2C19 WGS and WES		"Integration of Genomic Results into the EHR Complete" CYP2D6 live.

Future Directions

Consistent wording that reflects Network-wide priorities

Actions

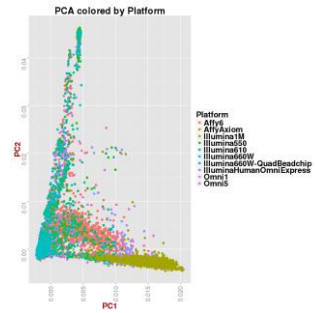
- The CC will work to unify wording of future directions materials by all workgroups should these be presented again in the future.
- A specific template will be created and distributed to workgroups for all future slide decks that will create a comprehensive and cohesive feel throughout the workgroup presentations.
- The template emphasizes a retrospective look across the grant period through the workgroup charter, accomplishments, and important opportunities made possible through these accomplishments.
- Specific updates will connect to:
  - Genomic Medicine Discovery
  - Genomic Medicine Implementation

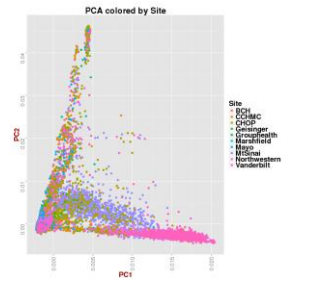
eMERGE Network Achievements

Imputation by Site & Platform

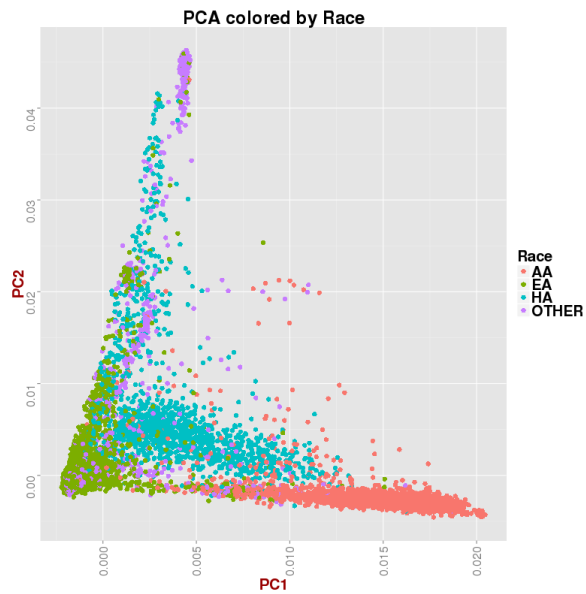
Site Sample Datasets	Genotyping Platform	Total Samples used Merged Imputed Data
eMERGE-I 1M	Illumina 1M	2,634
eMERGE-I 660	Illumina 660	16,029
Geisinger OMNI	Illumina HumanOmni Express	3,111
Geisinger Metabochip	Illumina Cardio Metabochip*	-
Mayo	Illumina Human 550, 610, and 660W Quad-v1	3,117
MtSinai AA	Affymetrix 6.0	863
MtSinai EA	Affymetrix 6.0	700
MtSinai HA	Affymetrix 6.0	1,212
MtSinai OMNI AA	Illumina HumanOmni Express	3,515
NU	Illumina HumanOmni Express 12v1_C	2,951
Vanderbilt	Illumina HumanOmni Express 12v1_C	3,461
Grouphealth/ACT	Illumina HumanOmni Express	398
Grouphealth/NWIGM	Illumina 660W-Quad Beadchip	333
CCHMC	610/660W/AffyA6/Omni1/omni5	4,322
BCH	Affymetrix Axiom	1,024
CHOP	550/610/Beadchi/AffyA6/AffyAxiom/OmniExpress	6,850
Marshfield	Affymetrix/Illumina 660	500
Marshfield ACE	Illumina660	116
Vanderbilt Omni1	Omni1	2,171
Vanderbilt Omni5	Omni5	1,981
Vanderbilt Immunochip	Illumina Immunochip*	-
Vanderbilt Metabochip	Illumina Cardio Metabochip*	-
Totals		55,288

* Do not impute well genome-wide; not included in merged dataset





Results: High quality data on 55,288 samples & 5,206,443 SNPs



SPHINX: open access resource of the eMERGE Network PGx Project

http://emergesphinx.rcc.psu.edu

HapMap control comparisons across sequencing facilities

Filtered, where both called:

	CIDR	UW	MSSM	GHS	Mayo
CIDR		99.91%	99.91%	99.86%	99.96%
UW	99.85%		99.86%	99.86%	99.90%
MSSM	99.87%	99.84%		99.81%	99.90%
GHS	96.04%	96.15%	96.04%		99.85%
Mayo	99.91%	99.87%	99.86%	96.15%	

SNP Only

SNP + INDEL

Site	Sample Size
Group Health/UW	894
Marshfield	748
Mayo	1,013
Northwestern	349
Vanderbilt	427
Geisinger*	0
Mt. Sinai	598
CHOP	396
CCHMC/BCH	295
Total	**4,720**

*Ion Torrent data not released in SPHINX yet

Phenotyping Progress (eMERGE II – completed phenotypes)

Phenotype	Primary Site	Case Count	Control Count	No. of Participating Sites	Implementation Date
AAA	Geisinger	1,110	17,071	7	September 2012
Ace-I Cough	Vanderbilt	1,792	8,476	7	March 2013
AMD	Marshfield/Essentia	2,363	11,749	6	December 2013
Asthma	CHOP	6,779	20,137	9	June 2013
Atopic Dermatitis	CHOP	2,056	15,121	8	February 2014
Autism	CCHMC/BCH	23	717	3	June 2014
C. Diff	Group Health/UW	1,923	10,552	9	September 2012
Cardio Respiratory Fitness	Mayo	5,684	N/A	6	April 2013
Childhood Obesity	CCHMC/BCH	163	379	3	September 2013
Diabetic Hypertensive CKD/Rapid Renal Decline in Diabetic HTN Nephropathy	Mt. Sinai	12,562	2,131	7	March 2014
Diverticulosis	Northwestern	5,814	4,295	7	November 2012
Extreme Obesity	Geisinger	1,293	7,239	7	May 2013
Glaucoma	Marshfield/Essentia	1,124	4,568	6	January 2013
Heart Failure	Mayo	3,654	10,638	6	January 2014
Ocular HTN	Marshfield/Essentia	771	7,477	6	November 2012
Statins for MACE	Vanderbilt	2,187	7,010	7	December 2013
VTE	Mayo	4,460	23,153	8	September 2012
Zoster	Group Health/UW	2,446	24,396	7	February 2013

InfoButton

OBJECTIVE 1: Develop a new information resource based on eMERGE II & PGx scenarios

completed

- ✓ Collected scenarios from involved sites
- ✓ Designed eMERGE template
- ✓ Content development completed template

in progress

- ❑ Engaging physicians & patients
- ❑ Developing content to customize local implementation
- ❑ Evaluating InfoButton resource via survey

OBJECTIVE 2: Implement InfoButtons within EHRs at eMERGE sites

completed

- ✓ Completed site surveys
- ✓ Configured EHRs for InfoButtons

in progress

- ❑ Engaging institutional stakeholders
- ❑ Providing training and support for installation
- ❑ Configuring information resources

in preparation

- ❑ Migrate content from Objective 1 to local content management system
- ❑ Evaluate usage over time

PROJECT TIMELINE

Return of Results

HFE

- The HFE project includes C282Y homozygotes and C282Y/H63D compound heterozygotes to address the question of penetrance of hemochromatosis in this population and have systematically abstracted charts in each eMERGE chart.
- Further data on the clinical presentation in patients with the diagnosis of hemochromatosis is pending until all abstractions are obtained.

Publication Collaboration with CSER

Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between

Gail P. Jarvik[1, 2], Laura M. Amendola[1], Jonathan S. Berg[3], Kyle Brothers[4, 5], Ellen W. Clayton[6], Wendy Chung[7], Barbara J. Evans[8], James P. Evans[3], Stephanie M. Fullerton[9], Carlos J. Gallego[1], Nanibaa' A. Garrison[8], Stacy W. Gray[10, 11], Ingrid A. Holm[12, 13, 14], Iftikhar J. Kullo[15], Lisa Soleymani Lehmann[10], Cathy McCarty[16], Cynthia A. Prows[17], Heidi L. Rehm[10], Richard R. Sharp[18], Joseph Salama[1], Saskia Sanderson[19], Sara L. Van Driest[8], Marc S. Williams[20], Susan M. Wolf[21], Wendy A. Wolf[12, 14],
eMERGE Act-ROR Committee and CERC Committee ,
CSER Act-ROR Working Group ,
Wylie Burke[9]

AJHG
Volume 94, Issue 6, 5 June 2014, Pages 818–826

HFE: Partial Results on the Differential by Gender, Genotype and Site

	C282Y Homozygotes (N=106)		C282Y/H63D Hets (N=395)	
Site	**Males**	**Female**	**Males**	**Females**
Geisinger	0% (0/9)	0 % (0/3)	4.3% (1/23)	2.6% (1/38)
UW/Group Health	33.3% (1/3)	11.1% (1/9)	0% (0/22)	0% (0/26)
Marshfield	42.9% (3/7)	25.0% (2/8)	3.4% (1/29)	0% (0/23)
Mayo	33.3% (5/15)	20.0% (3/15)	3.1% (2/64)	1.9% (1/53)
Mount Sinai	0% (0/0)	0% (0/1)	0% (0/9)	0% (0/4)
Northwestern	60% (3/5)	9.1% (1/11)	0% (0/6)	5.6% (1/18)
Vanderbilt	11.1% (1/9)	0% (0/11)	2.8% (1/36)	4.5% (2/44)
Total	**27.1% (13/48)**	**12.1% (7/58)**	**2.6% (5/189)**	**2.4% (5/206)**

Special Journal Issues

Genetics in Medicine
Official Journal of the American College of Medical Genetics and Genomics

Leads: Marc S. Williams & Joseph Kannry

- Published October 2013: Features nine articles specific to EHR implementation and integration experiences of the eMERGE Network.
- Articles have been cited a combined 101 times and have been viewed a combined 19,235 times*
- Joseph Kannry, Marc S. Williams, Christopher G. Chute, Joshua C Denny, Abel N. Kho, & Peter Tarczy-Hornoch, presented "PP6: Integrating Genomic Data into the EHR: The eMERGE Experience," a 2013 AMIA President's Pick Session.

JAMIA
A SCHOLARLY JOURNAL OF INFORMATICS IN HEALTH AND BIOMEDICINE

Leads: Jyoti Pathak, Abel Kho, & Josh Denny

- Published December 2013.
- Features articles specific to challenges, advances, and perspectives of EHR-driven phenotyping.
- Three eMERGE investigators served as editors for this edition.
- The issue includes 24 published articles, 12 which feature eMERGE authors.
- eMERGE co-authored articles & abstracts gathered 32,313 total online views.

frontiers in GENETICS

Leads: Marylyn D. Ritchie, Mariza de Andrade, & Helena Kuivaniemi

- Issue titled "Genetic Research in Electronic Health Records Linked to DNA Biobanks."
- The issue features nineteen published articles.
- There have been 25,030 total views online, with individual article views at upwards of 4,000 views.
- Combined individual article views are over 24,245.

Affiliate Membership & External Network Collaborations

Affiliate Membership criteria were established early in Phase II to open the eMERGE Network to all academic, government, and private sector scientists interested in participating in an open process to facilitate genomic research in biorepositories with electronic medical records and application of genomic results to clinical care, and who agree to the criteria for participation.

Current Affiliate Member:

U.S. AIR FORCE

The Air Force has actively participated in Network activities since 2012, with regular attendance on workgroup calls and project update presentations to the Steering Committee. Most recently:

- ***AFMS Personalized Medicine Program*** – Lt. Col. Catherine Witkop (Winter 2014 Steering Committee Meeting)

External Network Collaborations

- **Clinical Sequencing Exploratory Research Consortium (CSER):**
  - EHRI Workgroup – Joint Publication: "Optimal management of different types of genetic information in the Electronic Medical Record"
  - CERC Workgroup - CERC co-chairs regularly join CSER relevant workgroup calls. Currently, a joint eMERGE/CSER project is underway: Age of Majority, focused on ethical issues within the Pediatric realm

Featured Network Collaboration:

Fluomics Project

- Ellie Sang Sukerman and Steven Wolinsky (NU) and Adolfo Garcia-Sastre (Mt. Sinai): requested eMERGE site participation in the "Multiscale Analysis of Influenza Host-Pathogen Interactions (Fluomics) program" funded by NIAID.
  - Purpose: search for possible causal variants for disease severity by association analysis and systems biology (bioinformatics, in-vitro and in-vivo) approaches.
  - Cohort of cases diagnosed with Influenza Type A by PCA assay or culture.
  - Genomic DNA samples will be used for exome sequencing, with 40-100x coverage depth
  - Association analysis between identified rare variants in candidate host factors and proxy markers for disease severity, especially indicators of care settings and types.

Workgroup Updates

CERC | **EHR**integration | **Genomics**

Phenotyping | **PG**x | **Pediatrics**

Return of **Results**

Consent, Education, Regulation, and Consultation (CERC) Workgroup

Co-Chairs: Maureen Smith & Ingrid Holm

Project	Status
MyResults.org: A Centralized Repository of Patient Education Materials	Launched 2013, contains videos and written information, site-specific study information, J Connolly lead
Seeking Informed Consent for the Inclusion of Samples from Children & Adolescents in Biorepositories: Practical Approaches and Model Language	Accepted for publication in Mayo Proceedings, K. Brothers lead
Re-consent of Minors at the age of Majority	Joint project with the Pediatrics WG, K. Brothers lead, ongoing
Developing Consents for Returning Pharmacogenomics Results: The eMERGE Experience	Project on hold
Infobutton (In collaboration w/ EHRI)	Contributed physician and patient content, evaluated survey
PGx Outcomes (In collaboration w/ RoR & PGx)-Patient and physician education	Reviewed documents, document near final 9/2014

CERC Workgroup

Project	Status
Survey: Patient Perspectives on Broad Consent in Biobank Research in the eMERGE Network	See next slide for details
Return of results	Joint calls with ROR WG; contributed to paper: Return of genomic results to research participants: the floor, the ceiling, and the choices in between. AJHG, 2014 Jun 5;94(6):818-26. New paper in process: Numbers and Processes for Returning Incidental Findings in PGRNSeq (PGx Site Comparison)
Physician Consultation	Collaboration with the EHRI WG: Stakeholder Engagement: A Key Component of Integrating Genomic Information into Electronic Health Records, A. Hartzler lead
Collaborations	Across eMERGE – EHRI and ROR Work Groups Beyond network – CSER

CERC Workgroup

Survey: Patient Perspectives on Broad Consent in Biobank Research in the eMERGE Network

- Administrative supplement (2 y) to the parent eMERGE grant – awarded September 2013
- Includes all 10 institutions across the 9 eMERGE sites.
- Goal: To understand factors that influence patients' willingness to give broad consent for samples and information to be stored in biobanks and used for multiple types of research.
- Tasks completed
  - ✓ Literature review
  - ✓ A common IRB protocol – approved at all sites
  - ✓ Survey developed (randomize participants to 1 of 3 hypothetical biobanks with different data sharing plans)
  - ✓ Cognitive Interviews coordinated across sites to test the survey (complete 9/18/14)
  - ✓ Sampling strategy developed – through geocoding populations at each site
  - ✓ REDCap survey (online) and website developed
  - ✓ Scantron contracts
- Additional Tasks and Timeline
  - Pilot survey: send out November 2014
  - Final survey: send out February 2015
  - Data collection: begin March 2015
  - Project funding period ends: July 31, 2015 for most sites

EHRI Workgroup

Co-Chairs: Justin Starren & Marc Williams

Progress to Date

- CDS Status: 8 of 10 sites have live CDS
- Publications: 29 total
  - Genetics in Medicine Special Issue
  - CSER/eMERGE Location Genomic Information in EHR (in prep.)
  - Implementation Barriers Paper (in prep.)
  - JAMIA (Casey Overby)
  - JAMA Omic Chasm paper (Starren, Williams, Bottinger)
- AMIA Sessions
  - AMIA 2013
  - AMIA Translational Bioinformatics 2014
- Development of outcomes for CDS as part of eMERGE PGx
- EHRI Membership in EPIC Genomics Special Interest Group
- Participation and leadership in National Collaborations in Genomics and Informatics
  - AMIA Genomics Working Group
  - Clinical Decision Support Consortium
  - Clinical Pharmacogenomic Implementation Consortium Informatics Workgroup
  - ONC S&I Health eDecisions
  - HL7 Clinical Genomics Workgroup
  - IOM Roundtable on Translating Genomic-Based Research for Health

EHRI Workgroup

Innovation & Future Opportunities

Innovation:

- Myresults.org (materials for patients and professionals)
  - Exploration of presenting genomic results tied to point-of-care education materials in EHR
  - Freely available on the web
- Patient facing Infobuttons to present educational material
- Dynamic XML Event-driven Ophthalmologic Data Capture Framework

Unique Opportunities Delivered:

- Diversity of Implementation Strategies Across Sites
  - Differences have been catalogued, analyzed and disseminated through presentations and publications
- Infobutton Project (see page 30)
  - Nominated for Distinguished Paper Award at 2014 AMIA Annual Symposium

Genomics Workgroup

Co-Chairs: David Crosslin & Gerard Tromp

Progress to Date

- Held monthly conference calls (last Mondays of the month) to discuss the charter topics
- Led Network PGx analysis activities
  - Variant calling
  - Variant annotation
  - Variant interpretation
  - Merging of clinical data
- Led many Frontiers of Genetics manuscripts
- Null variant identification and association in eMERGE Phase I
- Led efforts to provide CNV analyses derived from array data to the Network
- Shared scripts and sample code with the eMERGE Genomics CC for service to the Network

Genomics Workgroup

Innovation & Future Opportunities

- Innovation:
  - Assessment and characterization of multiple annotation packages for the PGx data
  - PCA assessment of the eMERGE cohorts; developed alternative method of deriving PCs through sample/SNP loadings
  - Led Network PGx analysis activities
- Unique opportunities delivered:
  - Led special issue in Frontiers in Genetics: *Genetic Research in Electronic Health Records Linked to DNA Biobanks* – 18 manuscripts
  - Null variant identification and association
  - Variant annotation features
  - CNV association analyses

Pediatrics Workgroup

Co-chairs: Hakon Hakonarson & John Harley

Pediatric-led Algorithms

Phenotype	Primary	Secondary	Status
Asthma	CHOP	Marshfield CCHMC/BCH	Completed by all Centers GWAS ongoing
Asthma Severity	CHOP	Northwestern	Validation due 10/14
Atopic Dermatitis	CHOP	Marshfield	Completed by all Centers, GWAS ongoing
Obesity	CCHMC/BCH	CHOP	Validated, awaiting data submission by all centers
Autism	CCHMC/BCH	CHOP	GWAS ongoing
ADHD	CHOP	CCHMC/BCH	Validated, awaiting data submission by all centers
GERD	CHOP	Northwestern	Undergoing validation
Appendicitis	CCHMC/Boston	--	In development
N - ALL Algorithms	**Cases**	**Controls**	
TOTAL	**9,964**	**55,222**	

Return of Results

Result to Return	Goal	Progress	Complete before end of eMERGE II
CCHMC: Opioid CYP2D6 to parents via telephone	200	150 enrolled, 130 genotyped, 85 returned	Enrollment, genotyping, ROR, analysis of initial survey data
BCH: hypothetical Opioid CYP2D6 to parents via telephone	200		
CCHMC: pre-emptive opioid CYP2D6 to EMR	300	112 to EMR, 96 to NWGC	Enrollment, CYP2D6 genotyping, Process Measures, PGRN-Seq submitted to NWGC
PGRNseq only, potential ROR incidentals	500	300 to CIDR	
BCH: pre-emptive	250		
CHOP	NA	491 results sent to EMR (Go Live: Sept, 2014).	491 – Enrolled, genotyped, validated, returned to EMR
CHOP	NA	160 individuals had CNV results returned	160 – Enrolled, genotyped, validated, returned
CHOP (PGx)	>1200	>1100 individuals recruited, analysis ongoing	RoR for TPMT, omeprazole, tegretol, validated and returned. Range of discovery projects underway.

Pediatrics Workgroup

Innovation & Future Opportunities

Innovation:

- Studies of heritability as a function of development
- Pharmacogenomic studies: Methylphenidate/mGluR in ADHD, Malignant Hyperthermia, Post-surgical Narcotic Therapies, Neonatal Abstinence Syndrome

Publications:

1) Loss of Function (LoF) Variants: eMERGE catalogue: Published (Sleiman et al., 2014)

2) TPMT: Imputation of TPMT defective alleles in >87,000 samples: Published (Almoguera et al., 2014).

3) Autism/ADHD - mGluR paper: Published (Hadley et al., 2014)

4) CNVs: EMERGE-review published (Connolly et al., 2014).

5) QTL-BMI GWAS analyses –Complete (Namjou et al., 2013)

6) PheWAS (2 studies): 1Complete – (Namjou et al., 2014, submitted); 1 Undergoing validation

7) Pediatric Biobank Consent (Brothers et al., 2014 pending)

Opportunities :

Continue Algorithm development:

- Pediatric specific phenotypes (pyloric stenosis)
- Pediatric & adult phenotypes (fibromyalgia, appendicitis, asthma, obesity, lipids, atopic dermatitis)

Advance Analytic Methodologies:

- Proposed custom-based LoF variants chip
- Several CNV projects proposed
- Expand GCTA analyses
- PGx: ADHD, MoSO4, asthma opportunities

Phenotyping Workgroup

Co-Chairs: Josh Denny, MD, MS & Peggy Peissig, PhD, MBA

Progress to Date

1. **Coordinate and complete network phenotypes and support covariates for analysis**
   - **eMERGE I phenotypes:** (14)
   - **eMERGE II phenotypes**: completed (18); gathering data (2); development (7)
   - **Phenotypes in PheKB** (95); public (20), total implementations (147)
   - **SPHINX** – subjects with phenotype and PGRNSeq sequence data (4998 subjects)
   - **eMERGE Record Counter** – GWAS subjects with Boolean searchable ICD9, site, demographics (53,194 subjects)

3. **Coordination with all eMERGE workgroups**
   - **Functional Variant**: Tromp, Peissig, Denny
   - **EHRI WG:** Rasmussen, Pacheco, Peissig, Peterson, Denny, Tromp
   - **Genomic:** Tromp,
   - **PGx:** Denny, Rasmussen, Peissig, Pathak, Tromp

2. **Efficient, effective, transportable phenotyping methods, structure and standards**
   - PheKB.org: implemented validation script to check data files against rules and data dictionary
   - Data standardization committee active to create structured data dictionaries tools for validation
   - Modular phenotyping network project – identify building blocks for phenotype algorithm creation
   - ICD-10 discussion – planning analysis in progress to evaluate the impact of ICD-10
   - KNIME workflows as sharable logic. Work with DROOLS, JBOSS

4. **Coordinate with other networks**
   - **PCORI** – Trial underway with using PheKB to share/develop algorithms with PCORI
   - **AMIA**: recent AMIA Policy Forum on Personalized Medicine (9/4-5, Williams, Denny), Denny on writing committee for AMIA's Policy Statement
   - **PGRN, IGNITE, PheMA and CSER**

5. **Publications**
   - 20 Publications in progress; Phenotyping issue in JAMIA; and AMIC TBI/CRI presentations

Phenotyping Workgroup

Innovation & Future Opportunities

Innovation:

- SPHINX: (Public and Private side, Genomic+ICD9+Medications)
- eMERGE Record Counter (Diagnoses, procedures, demographics, future medications) – making study feasibility assessment fast and easy
- Structured data dictionaries and creation of data validation tools across the Network to increase poolability of data - PheKB
- PheWAS – phewascatalog.org launched
- PhEMA – Phenotyping Execution and Module Architecture grant to develop executable computable phenotype language. Several papers underway to cross with eMERGE.
- Creating "modular" phenotypes to facilitate transportability and restructuring into new phenotypes, specific workflows

Unique Opportunities Delivered:

- Developing new methods/tools to make phenotyping fast, accurate and reproducible and to account for cofounders for genomic discovery and implementation
- Leveraging the richness of EMR data by applying phenomic approaches and assessing longitudinal, rare, pharmacogenomics, and disease subtype phenotypes
- Identifying undiagnosed phenotypes in carriers of rare genotypes
- Addressing EMR transportability and standards for sharing data between institutions

Return of Results Workgroup

Co-Chairs: Gail Jarvik & Iftikhar Kullo

Progress to Date

- Manuscripts related to ROR working group
  - Kullo IJ et al. Return of results in the genomic medicine projects of the eMERGE network. *Front Genet.* Mar 26;5:50. 2014. (PMID: 24723935; PMCID: PMC3972474)
  - Jarvik GP et al. Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices In Between. *Am J Hum Genet*. (14)00181-5, 2014. (PMID: 24814192; Joint with CSER program)
- Ongoing network-wide ROR projects
  - Site-specific data abstraction for the network-wide project related to HFE penetrance is complete and analysis is underway
  - Analysis of phenotypic correlates of genomic copy number variation is underway
- Significant progress in support of site-specific projects
  - EHR-based genomic implementation projects
  - eMERGE PGX projects
- ROR working group is closely involved with the NHGRI's actionability forum

Return of Results Workgroup

Innovation & Future Opportunities

Innovation:

- Developing and sharing methods to return genomic results
- Implementing genetic risk scores for complex disease risk
- Association of copy number variation with EMR phenotypes across sites
- Assessing phenotypic correlates of VUSs from targeted sequencing
- Use of the EHR to annotate pathogenicity, penetrance, and actionability of pathogenic variants identified by sequencing

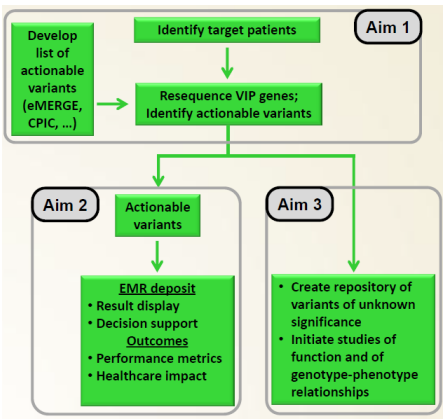
Unique Opportunities Delivered:

- Multi-site evaluation of the process of return of results from both genotyping as well as sequencing data
- Leveraging the EHR for estimating penetrance
- EHR-based ROR with linkage to Clinical Decision Support
- Collaborations across NHGRI and other genomic programs

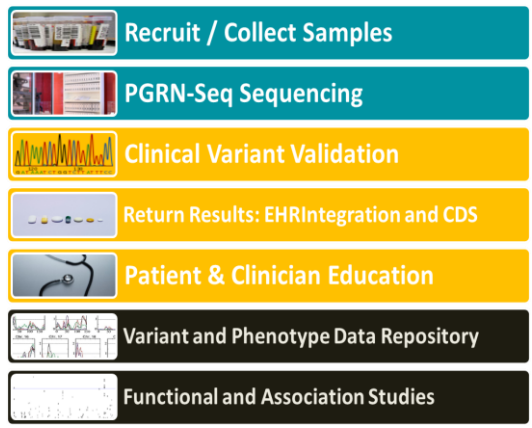
eMERGE PGx Workgroup

Co-Chairs: Josh Denny, MD MS, Laura Rasmussen-Torvik, PhD MPH & Dan Roden, MD

Original Prospective Genotyping Supplement Charter (June 2012)



eMERGE PGx Interpreted Aims



Project Design Paper: Rasmussen-Torvik, et al. *Clinical Pharmacology & Therapeutics* *"Design and Anticipated Outcomes of the eMERGE-PGx Project: A Multicenter Pilot for Preemptive Pharmacogenomics in Electronic Health Record Systems" (Aug. 2014)*

eMERGE PGx Progress over 26 months

Aim	Starting Issues (June 2012)	Progress (August 2014)
1: Recruit / Collect Samples	How to identify & recruit target patients? How to identify actionable variants?	• Algorithm in use at 7 sites • **Enrollment 79% complete** - 2 Sites complete • Drug:Gene pair targets chosen; CPIC guidelines
1: PGRNseq sequencing	Which platform? How to run at multiple sites? How to call and collect variants?	• PGRNseq v.1 run at 5 sites + CIDR • Cross-site concordance excellent • **Variant calling from PGRNseq data 55% complete**
2: Clinical Variant Validation	How to validate?	• JHU custom assay developed and deployed; site CLIA validation also used • **Validation 47% complete** • Studying annotation variation
2: Return Results	What is EHR return?	• EHR integration at all sites • **Returned results 27% complete**
2. Patient and Clinician Education	What advice is provide to whom in what contexts?	• CDS developed for target drug: gene pairs • Infobutton project – CDS knowledge templates • MyResults.org developed for patient education
3. Variant and Phenotype Data Repository	What to do with variants of unknown significance?	• **All variants for ~ 5000 subjects archived in repository** and viewable in SPHINX (55% complete) • Associated phenotype data from site EMR systems

3. Functional and Association Studies	What discovery is possible in this data set?	• Hypothesis generation via SPHINX
		• Rare variants : phenotype traits association:
		  • SCN5A and KCNH2
		  • Lipid metabolism genes
		• PheWAS: Common and Binned Rare Variants

eMERGE PGx

Innovation & Future Opportunities

Innovation:

- Prospective genotyping genomic medicine implementation study
- Large (~9,000) cohort enables study of rare PGx variants
- Associated EHR-derived phenotype data

Unique Opportunities Delivered:

- Pharmacogenomics discovery - common and rare variants
- Penetrance, heritability, pathogenicity of rare genotypes
- Research on Clinical Implementation
  - Incidental findings implications
  - Process, ethical, and clinical implications of implementation models:
    - Variant discovery and clinical validation process models
    - Consent for variant deposition in EHR models
    - Rare variant investigation with and without intent to return results
    - Managing genotype re-interpretation over time
  - Utilization practices of CDS, patient portals, etc.
  - Patient responses to testing and tailored prescription

Genomic Medicine Site Updates

Cincinnati Children's Hospital Medical Center

CCHMC Genomics Pilot Progress To Date

- 147 of 200 planned parents enrolled to date
- 130 pediatric samples tested for CYP2D6
- 79 results returned to parents by Genetics APN via telephone
  - 100% completed telephone survey to date
    - 73% parents strongly agreed they could use result to improve how they care for their child
    - 81% parents strongly agreed their child's PCP could use result to improve how they care for their child
    - 42 of 72 parents with other children <18 years of age were extremely interested in having PGx testing for their other children
    - 62% stated their interest in PGx increased since learning result and completing the survey
  - 53 of 60 planned qualitative interviews completed to learn why parents responded to particular survey items

Boston Children's Hospital

BCH Genomics Pilot Progress To Date

- 24 enrolled, 21 surveys completed and 3 scheduled
- 19 interviews completed
- Recent IRB amendment approval allows us to call target population (instead of recruiting only through opt-in) to assess interest
- Expecting to substantially raise enrollment rates in coming months with this new recruitment ability to call eligible participants directly

Boston Children's Hospital

Cincinnati Children's Hospital Medical Center

Provider Responses

- CCHMC & BCH have IRB approvals to proceed with provider surveys.
- CCHMC is obtaining permissions from parents at 3 month follow up call to send child's provider CYP2D6 results. Currently we have permissions to send out to 38 providers.
- BCH has received PCP information from all participants to date.

The Children's Hospital of Philadelphia®

CHOP Updates

- 160 individuals with Autism have had results returned through Center for Autism Research for CNVs
- 1100 samples enrolled and DNA collected
- TPMT (Thiopurines) CDS protocol coming on line imminently (Almoguera *et al.* paper published in FiGs)
  - EHRI demo complete

The Children's Hospital of Philadelphia®

CHOP Updates

- CHOP-wide subcommittee formed for genomics EHR integration
- Health professional subsection for myresults.org
- Omeprazole and Abacavir next in line for EHR
- IRB has requested integration of ACMG recommendations into our current IRB protocol (obvious issues with controversial nature of the ACMG guidelines from the wider community)

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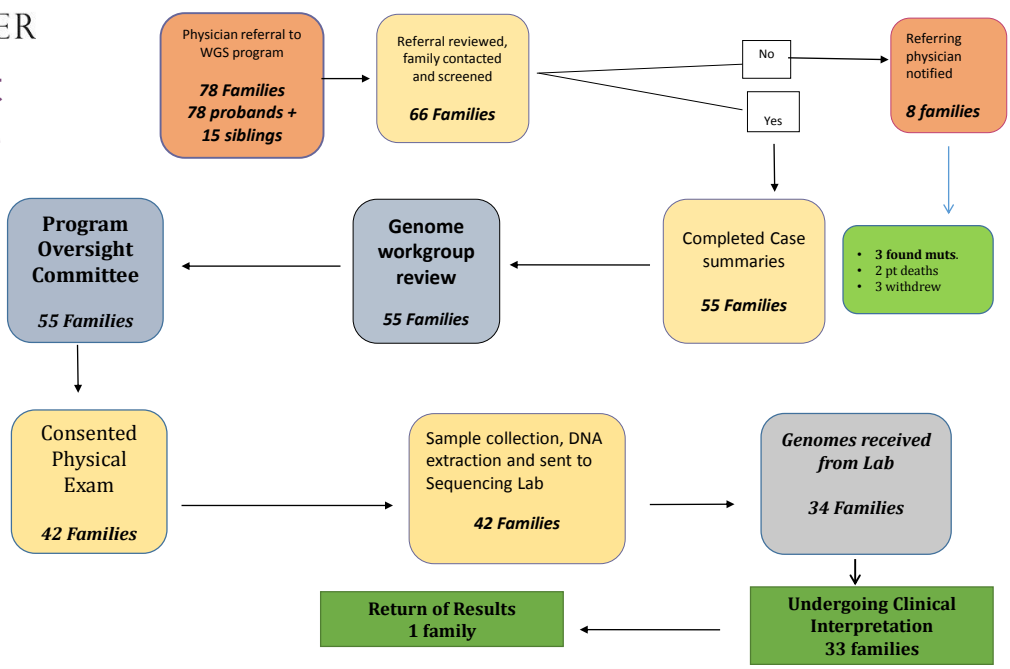
Project Update



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Results

- 30 families have had preliminary analysis of sequence data
  - 6 have been returned
- Have identified 6 definitely causal mutations
  - 3 have been returned (as well as one 'normal')
- Several other 'suspicious' findings undergoing additional analysis
- One case of a dual diagnosis
  - Siblings with ID and autism
  - One had Peter's anomaly (congenital malformation of the anterior chamber of the eye)
    - ❖De novo mutation identified in *PAX6* which explains the Peter's anomaly but not the ID
    - ❖Sibling without Peter's anomaly does not carry the mutation
    - ❖Cause of ID/autism not yet identified

GEISINGER

Research building on WGS

- Presentation of Dual Diagnosis in WGS at David W. Smith meeting July 2014
- Genetic Counseling Time Study
  - Published in Journal of Genetic counseling (Williams JL, Faucett WA, Smith-Packard B, Wagner M, Williams MS. An assessment of time involved in pre-test case review and counseling for a Whole Genome Sequencing Clinical Research Program. J Genet Counsel 2014 23: 516-521.)
- Genetic Counseling Impact Study (underway)
- PCORI-funded patient-facing genomic test report
  - Concluding qualitative research to construct report
  - Prospective pragmatic trial will begin early 2015

GHC/UW Project Update
Specific Aim 2:* Appropriate and effective integration of genomic information into clinical care and the EMR

- Participant observation of GHC Genomics Improvement Project – DONE
- Stakeholder needs assessment (leadership, patients, & provider)s– DONE
- Designing & testing CDS prototypes for carbamazepine, abacavir – IN PROGRESS
  - Interviews with patients (n=10) and providers (n=13) - DONE
    - Patients want access to results when relevant to care, especially via patient-facing tools (MyChart)
    - Providers want CDS beyond order-triggered alerts to improve visibility of genomic info, including active and passive "upstream decision support" early and throughout prescribing workflow
  - Collaborative development of prototypes - In PROGRESS
    - Worked with delivery system to redesign carbamazepine alert and create new abacavir alerts
    - Developed "provocative" prototypes to inform recommended CDS design principles based on needs of patients and providers
  - CDS deployment and usability testing - In PROGRESS
    - Deploying redesigned CDS
    - Small scale usability testing with select providers to identify iterative refinements

*UW/GH does not have a genomic medicine implementation project

PGx Accomplishments*

- In Year 2 we refined our selection criteria, identified subjects, plated samples and sent them for testing using the PGRN-Seq platform (300 to be tested by CIDR, 600 by the Nickerson lab at the University of Washington). PGRN sequencing is now complete and data received for all 900 samples to be tested for this site.
- In Year 3 we developed and refined our approach and consent materials to consent subjects for a second CLIA blood draw and the return of results. These materials have been approved by the IRB.
- We have selected a subset of 450 including all those who had a returnable finding and the balance of randomly chosen subjects who did not have a returnable finding. All 450 patients have been consented for a second sample to be collected for CLIA validation and return of results to themselves, their primary care provider and placement into the medical record.
- We met with our organization's Chief Information Officer and Medical Director for Clinical Informatics. We have a working plan for moving forward with EHR implementation for HLA/carbamazepine and HLA/Abacavir, using these as a test case for other drug/gene pairs that may be approved during the course of the project.
- We continue to work with our informatics leaders and the relevant review committees to facilitate ongoing assessment of additional pairs.

*UW/GH does not have a genomic medicine implementation project

AMD Genomic Medicine Pilot Aims

- To document why people elect not to enroll in a study to learn their genetic risk of AMD
- To understand how genetic data can be stored in the EPIC© electronic medical record so data are readily accessible and interpretable by health care professionals
- To document patient response to genetic testing and behavioral changes patients make after receiving information about genetic risk of AMD

Methods

- Recruitment through optometry
  - Patients aged 50-65 without AMD
  - Initially patients with a family history of AMD, then relaxed inclusion to include people without a known family history of AMD
- Blood draw and DNA extraction at Essentia
- Genotyping at ArcticDX, return of genetic risk score that includes 4 genes and smoking status
- Optometrist returned results
- Follow-up telephone interviews

Results

- Letters of invitation to 147 eligible individuals
  - 32 could not reach
  - 18 refusals (15%)
  - 101 participated (85%)
- Overwhelming support – all would be tested again
  - Most have family history of AMD
  - Most made changes, even if low genetic risk
    - Quit smoking, diet, exercise, brimmed hat, cholesterol check
- Currently conducting analysis in nVIVO

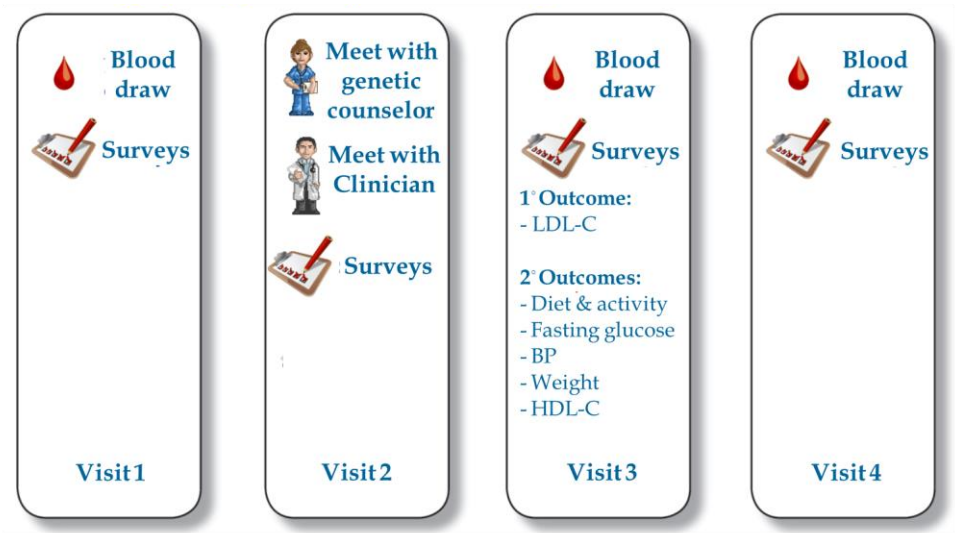
Project Update

MI-GENES outline

- 966 BioBank participants with intermediate CHD risk (5-20%)
- Screening genotyping of 28 CHD-associated SNPs
- Goal to recruit 100 with high, 50 intermediate, and 50 low GRS
- Blood draw and CLIA-certified genotyping of 28 CHD SNPs
- 1:1 Randomization, 100 FRS*GRS, 100 FRS
- Results placed in EHR
- Meet with genetic counselor and MD
- Follow up after 3 and 6 months
- Primary endpoint: LDL cholesterol at three months
- Secondary endpoints: fat intake, activity, weight, waist, BP, fasting blood sugar, total and HDL cholesterol

GRS = genetic risk score; FRS = Framingham risk score

Study progress (as of 8/29)



Completed n=215 | **Completed n=207** | **Completed n=201** | **n=76 125 to go**

Highlights

- 28 CHD SNPs genotyped in a CLIA lab
- Genetic risk score calculated
- 10-y CHD risk disclosed by a genetic counselor
- Shared decision-making with a physician
- Results placed in the EHR

Abstracts accepted for presentation

- **A genomic decision aid linked to the electronic health record to disclose CHD risk and enable shared decision-making (ASHG Oct 2014)**
- **Patient Perspectives on the Use of Electronic Health Records for Genomic Research: The MI-GENES Study (ASHG Oct 2014)**
- **Numeracy, Genetic Knowledge, and Perceived Risk for CHD in the MI-GENES Study (ASHG Oct 2014)**
- **The Effect of Disclosing CHD Genetic Risk on Shared-Decision Making (ASHG Oct 2014)**
- **Disclosing Genetic Risk for CHD: Effects on Perceived Personal Control and Genetic Counseling Satisfaction (AHA Nov 2014)**

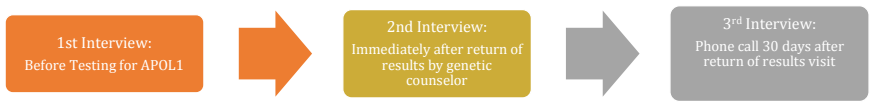
eMERGE Genomic Medicine Pilot Project: Apolipoprotein L1 (APOL1) Genetic Testing In African American Patients With Hypertension

Developed, validated and NYS/CLIA approved APOL1 G1/G2 risk allele genetic test

Performed interviews of hypertensive AA patients who underwent APOL1 genetic testing for kidney risk

Patient Interviews (N=26 completed):

- Eligibility criteria: African Ancestry, Mount Sinai biobank participant, + HTN - DM/CKD
- Questions about genomics, hypertension and kidney disease risk, management and consequences, APOL 1
- Three interviews



Primary Care Provider Interviews (N=15 completed):

- Eligibility criteria: Physician/ Physician Assistant at participating primary care site, at least 50% time caring for adult patients.
- Questions about genomics, kidney disease risk, management and consequences, Preferences and role of physician in testing and returning

Primary Care Provider Surveys (N=105 completed)

Results: Patient Interviews (baseline, post ROR, 30d post ROR)

- 100% came back for results
- Very few have had/know anyone who had genetic testing.
- Want genomics-light, action-heavy information (what results mean and what should be done next).
- No "decision regret" – knowledge = power to act
- Test= way to get patients and clinicians to do the right thing
- More focused on benefits to individual/community than risks to people of African Ancestry

Patient Participant Demographics	% (n=26)*
Mean age	54 yrs
APOL1 positive status	73% **
Female	73%
Income	
<$15,000	31%
$15,001-$30,000	38%
>$30,000	31%
Education	
< HS	8%
High school/GED	19%
Some college	42%
College/professional training	31%
Working full/part time	42%

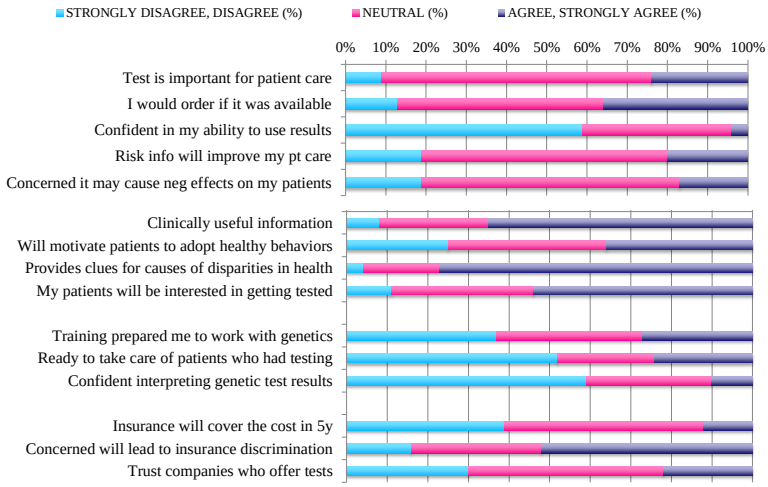
** Purposefully selected from biobank to oversample positives

Results: Primary Care Provider Interviews (n=15)

- Not trained, not comfortable or knowledgeable in genetic testing.
- Want information to enhance patient communication and to make sure it's easy to communicate.
- Would test if results would change their practice… and if easy to do (i.e. EMR enabled guidelines
- View genetic testing/counseling as potential motivator (and cutting edge)
- Comfortable with connection between ancestry and genomics, but concerned may lead to stigma or increase patient mistrust

Mount Sinai

Primary Care Provider Survey Results: Knowledge Towards Kidney Disease And Apolipoprotein L1



Demographics (N= 105)	Participants % (n)
Average Age	36 yrs. old (age 26-72)
Gender*	
Male	40% (38)
Female	60% (58)
Ethnicity**	
Black/African American	10% (11)
Caucasian/White	51% (53)
Hispanic/Latino	8% (8)
Asian	25% (26)
Mixed race or Other	6% (6)
Position	
Attending (Family & Internal Medicine)	46% (48)
Resident	48% (51)
Nurse Practitioner	6% (6)

Northwestern Medicine

NU Genomic Medicine Pilot: Structure

Consultation
- Physician Advisory Committee
- Patient Advisory Committee

EHRI
- Structural design
- Content; fact sheets, BPAs, Infobutton

IRB
- Returning results to biobank participants
- How to handle incidental findings

Laboratory
- Logistics
- Integrate with CDS

Northwestern Medicine

Participant Selection and Enrollment

- Target population identified: NUgene biobank participants
  - Hemochromatosis homozygotes , compound heterozygotes (impact upon medical care)
    - C282Y/C282Y – 13, H63D/H63D – 57, C282Y/H63D – 45
  - FVL and Prothrombin homozygotes/carriers (minimal impact on medical care without other risk factors)
    - FVL Homozygotes – 3, FVL Heterozygotes – 141
    - PTT Homozygotes – 1, PTT Heterozygotes – 80
    - FVL/PTT Compound Heterozygotes – 4
  - Hemochromatosis carriers, negative results for HH, FVL, PTT
- Status of project
  - Patient and physician consultation-ongoing (Manuscripts in progress)
  - Presentation to physicians in General Internal Medicine (GIM)
  - GIM physicians consented
  - NUgene participants identified and contacted-reconsent and enrollment ongoing
  - No results returned yet-see laboratory issues (next slide)

Northwestern Medicine

Laboratory and EHRI

- Laboratory
  - Hospital-based molecular diagnostics laboratory (Northwestern Memorial Hospital)
  - Difficulty integrating into current lab workflow (change of operating procedures)-resolved
  - Laboratory not set up to bill for research-resolved
  - Timing and release of results and CDS-requires some development from Powerchart team, working to resolve timeline for development
- EHRI
  - Time to develop CDS was much reduced since similar procedures already developed for PGx
  - EPIC IT teams have experience with CDS implementation; need to add Powerchart teams since laboratory uses Powerchart
  - BPAs written for HH, FVL, PTT
  - BPA's trigger logic created
  - Patient and physician facts sheets completed for HH, FVL, PTT

Genomic Medicine Implementation at Vanderbilt

PREDICT - **P**harmacogenomic **R**esource for **E**nhanced **D**ecisions **i**n **C**are & **T**reatment

- 4 drug-genome interactions implemented
- Prospective and Just-in-time test ordering
- Illumina Veracode ADME 34 genes, 184 variants (*platform currently in transition*)
- 14,650 patients have been tested

PCMI – **P**ersonalized **C**ancer **M**edicine **I**nitiative

- SNaPShot
  - Cancer-specific: lung, melanoma, breast, colorectal
  - ~40 variants in 6-8 genes
- ~4000 tumor specimens tested to date

PREDICT - Pharmacogenomic Resource for Enhanced Decisions in Care & Treatment

- 14,650 patients have been tested in routine clinical care
- 4 drug-genome interactions currently implemented
- Prospective and Just-in-Time test ordering
- Illumina Veracode ADME panel test for 34 genes, 184 variants (*platform currently in transition*)
- Validation study demonstrates that **PREDICT Prognostic Model outperforms** random sampling and simple prediction rules in identifying patients most likely to benefit from genotyping (Schildcrout et al., 2014, submitted)
- **Pilot expansion of PREDICT** to Meharry/Nashville General, Nashville VA, and Aurora Healthcare (Wisconsin) started through NHGRI's IGNITE Consortium (PIs: Josh Denny and Mia Levy)

Challenges in Genomic Medicine Implementation: Billing and Reimbursement

- Reimbursement landscape for genetic tests is slowly improving . . .
  - Private insurers increasingly recognizing PGx as *medically necessary,* e.g. CYP2C19 and clopidogrel
  - CPT 2015 includes CPT codes for some panel-based tests (but not PGx . . . yet?)
- But significant challenges remain.
  - CPT code ≠ reimbursement
  - Continued uncertainty around CMS and private insurer reimbursement policies for many drug-gene pairs (e.g. CYP2D6)
  - Uncertain impact of FDA regulation of laboratory developed tests (LDTs) on

INSTRUCTIONS FOR EXPENSE REIMBURSEMENT

The eMERGE Coordinating Center will reimburse your travel-related expenses. This includes flight, hotel (including internet access), taxi fare, meals, etc. However, because we are federally funded, we cannot reimburse expenses for alcohol.

Vanderbilt's travel reimbursement policy requires your **original receipts**. We will not be able to return your receipts, so we recommend that you make and keep a copy for your records. Since the Coordinating Center (not Vanderbilt's Finance Dept.) will be reimbursing you, there is no Travel Expense Report form to fill out as described in the accompanying pdf. All we require is that your original receipts include the information below.

All receipts should show:

- Date
- Amount of payment
- Method of payment (i.e. cardholder's name and card number's last four digits)
- Your name (if this isn't already on the receipt, just sign the back)
- Item or description of service (if not already on the receipt, write on the back or attach the receipt to a sheet of paper that has a description)

Put all your receipts in one envelope, and mail to the address below. **Please include your Social Security Number and preferred mailing address** (the one to which your check should be sent) in your materials; this is required to complete the reimbursement forms.

Adam Hardebeck
2525 West End Ave.
6th Floor Suite
Nashville, TN USA 37203

Special instructions for reimbursement

(In other words, if these details aren't on the receipts, you *may* be asked to submit more information, including a copy of the credit card statement showing these charges.)

If possible, **hotel** receipts should include the daily breakdown of charges.

The **flight** receipts should include the itinerary; if you paid online, the airlines may have emailed your receipt as a payment confirmation with itinerary. In this case, the email confirmation may be an acceptable original receipt if it includes your credit card information (cardholder's name and card number's last four digits).

We recommend mailing us your receipts within 10 days after the event. Checks will generally be mailed within two weeks after their arrival at Vanderbilt. Please contact Adam Hardebeck at adam.hardebeck@vanderbilt.edu or (615) 343-8477 if you have any questions.

If a **group meal** is included for full reimbursement, a list of attendees must accompany it. If the person is only paying for their portion of the bill, please indicate that on the receipt, and write the reimbursable amount beside the total on the receipt.