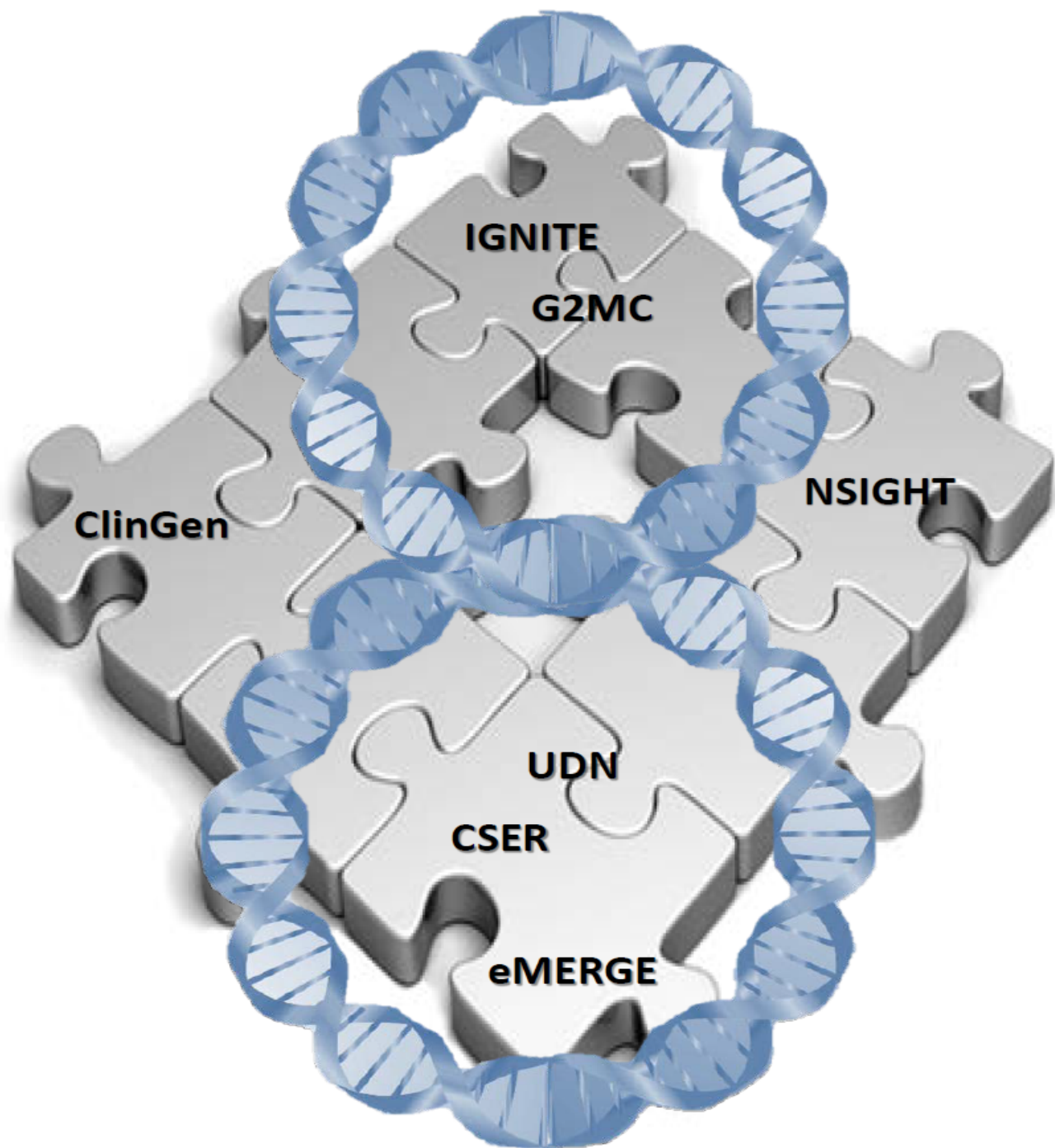


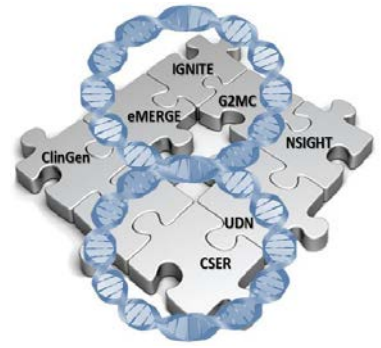
# **NHGRI**

## **Genomic Medicine Programs**



**Genomic Medicine VIII**  
**Bethesda, MD**  
**June 8-9, 2015**

# Genomic Medicine VIII: NHGRI's Genomic Medicine Portfolio



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- Clinical Sequencing Exploratory Research (CSER) including intramural ClinSeq
- Electronic Medical Records and Genomics Network (eMERGE)
- Genomic Medicine Meetings Program as a whole (GM MTGS)
- Global Genomic Medicine Collaborative (G2MC)
- Implementing Genomics into Practice (IGNITE)
- Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT)
- Undiagnosed Diseases Network (UDN)

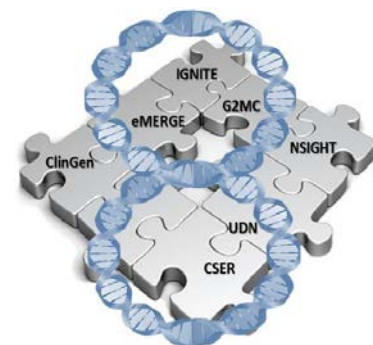
### RELATED PROGRAM SUMMARIES

- |          |                 |             |
|----------|-----------------|-------------|
| • AFMS   | • GTEX          | • NCI-MATCH |
| • CMG    | • H3AFRICA      | • PAGE      |
| • CPIC   | • HMORN         | • PCORnet   |
| • ENCODE | • IOM           | • PGRN      |
| • GAPH   | • LSAC          | • PhenX     |
| • GA4GH  | • ISCC          | • PMI       |
| • GGR    | • MVP           |             |
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### HOTEL AND TRAVEL LOGISTICS INFORMATION

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# Genomic Medicine VIII: NHGRI's Genomic Medicine Portfolio



June 8-9, 2015

Hilton - Washington DC / Rockville

1750 Rockville Pike, Rockville, MD 20852

(301) 468-1100

Monday, June 8<sup>th</sup>

**LOCATION:**

Hilton – Washington DC / Rockville Hotel

**WEBCAST:**

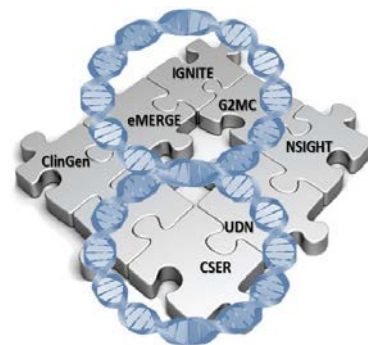
Genome TV - <http://www.genome.gov/GenomeTV/>

**TWITTER:**

#GenomicMed8

7:30 AM	Registration and Breakfast	Registration Table
8:30 AM	Welcome, Introductions, and Goals of the Meeting	Howard McLeod Eric Green
8:45 AM	Overview of NHGRI Genomic Medicine Programs	Teri Manolio
9:15 AM	<b>PANEL 1:</b> Key Unaddressed Evidence Gaps in Implementing Genomic Medicine	Geoff Ginsburg* Jonathan Berg Pierre Meulien Gurvaneet Randhawa
10:15 AM	BREAK	
10:45 AM	<b>PANEL 2:</b> Consistency of Interpretation of Variants Across Expert Labs / Groups, ClinVar Submissions?	Dan Roden* Gail Jarvik Robert Green
11:45 AM	<b>PANEL 3:</b> Changes in Evidence and Thus Updating Recommendations, Treatment	Howard Jacob* Heidi Rehm Sharon Plon Katrina Goddard
12:45 PM	Working Lunch	
1:30 PM	<b>PANEL 4:</b> Metrics of Progress and Measures of Impact Including Cost-Effectiveness, Outcomes to Value to Payers, Influencing Quality of Care Through Learning Healthcare Systems	Marc Williams* Warwick Anderson Erwin Bottinger Ruth Brenner

# Genomic Medicine VIII: NHGRI's Genomic Medicine Portfolio



June 8-9, 2015

Hilton - Washington DC / Rockville

1750 Rockville Pike, Rockville, MD 20852

(301) 468-1100

Monday, June 8<sup>th</sup> (Continued)

**LOCATION:**

Hilton – Washington DC / Rockville Hotel

**WEBCAST:**

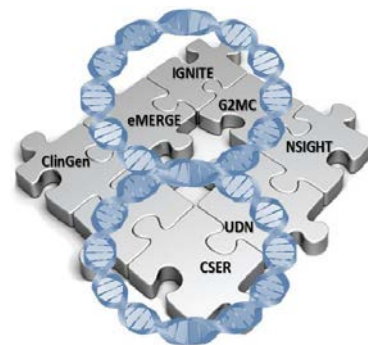
Genome TV - <http://www.genome.gov/GenomeTV/>

**TWITTER:**

#GenomicMed8

2:30 PM	<b>PANEL 5:</b> Enhancing Functionality of EHRs for Genomic Research, Including E-Phenotyping, Integrating Genomic Data, Transportable CDS, Privacy Threats	Rex Chisholm* Alexa McCray Chris Chute
3:30 PM	BREAK	
4:00 PM	<b>PANEL 6:</b> Increasing Diversity Among Patient Populations and Care Systems	Carol Bult* Cynthia Powell Vence Bonham Craig Hanis
5:00 PM	First Day Summary and Discussion	Teri Manolio Howard McLeod
6:00 PM	<b>ADJOURN</b> <ul style="list-style-type: none"><li>• All Attendees – On your own for dinner</li><li>• Genomic Medicine Working Group ONLY - See your email about evening details</li></ul>	

# Genomic Medicine VIII: NHGRI's Genomic Medicine Portfolio



June 8-9, 2015

Hilton - Washington DC / Rockville

1750 Rockville Pike, Rockville, MD 20852

(301) 468-1100

Tuesday, June 9<sup>th</sup>

**LOCATION:**

Hilton – Washington DC / Rockville Hotel Genome

**WEBCAST:**

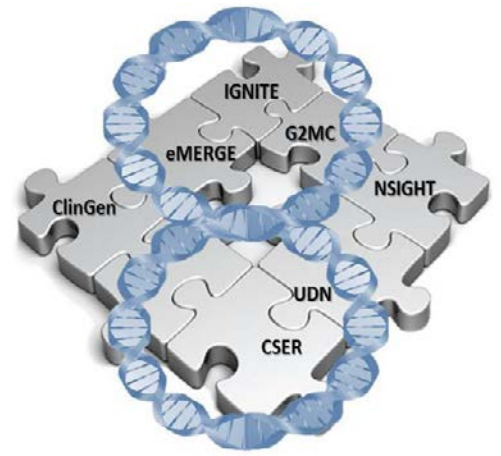
TV - <http://www.genome.gov/GenomeTV/>

**TWITTER:**

#GenomicMed8

7:30 AM	Breakfast	
8:30 AM	First Day Recap	Howard McLeod Teri Manolio
8:45AM	<b>PANEL 7:</b> Streamlining Clinical Workflow, Transportability to Other Systems, ClinVar Submissions?	Howard McLeod* Mike Gaziano Stephen Kingsmore Erin Ramos
9:45 AM	<b>PANEL 8:</b> Clinician Education (Especially Residents on Rotation, Genetic Counselors), Reporting Results to Clinicians	Mary Relling* Julie Johnson Bob Wildin Wendy Rubinstein
10:45 AM	BREAK	
11:15 AM	<b>PANEL 9:</b> Patient-Facing Information Tools, Counseling / Consent, Reporting Results to Patients	Laura Rodriguez* Steve Joffe Janet Williams William Lawrence
12:15 PM	WORKING LUNCH	
12:45 PM	Second Day Summary and Discussion	Howard McLeod Teri Manolio
1:30 PM	Next Steps	Teri Manolio Howard McLeod
2:30 PM	<b>ADJOURN</b>	

# Genomic Medicine VIII: NHGRI's Genomic Medicine Portfolio



## Glossary of Abbreviations

**AFMSA** – Air Force Medical Services Agency

**ClinGen** – Clinical Genomics Resource

**CMG** – Centers for Mendelian Genetics

**CPIC** – Clinical Pharmacogenetics Implementation Consortium

**CSER** – Clinical Sequencing Exploratory Research

**eMERGE Network** – Electronic Medical Records and Genomics Network

**ENCODE** – Encyclopedia of DNA elements

**G2MC** – Global Genomic Medicine Collaborative

**GA4GH** – Global Alliance for Genomics and Health

**GAPH** – GenomeCanada/Canadian Institutes of Health Research Genomics and Personalized Health

**GGR** – Genomics of Gene Regulation

**GS-IT** – Genome Sequencing Informatics Tools

**GTEx** – Genotype Tissue Expression Project

**H3Africa** – Human Health and Heredity in Africa

**HMORN** – Health Maintenance Organization Research Network

**IGNITE** – Implementing Genomics into Practice

**IOM** – Institute of Medicine

**ISCC** – Inter-Society Coordinating Committee for Practitioner Education in Genomics

**LSAC** – Large-Scale Genome Sequencing and Analysis Centers program

**MVP** – Million Veterans' Program

**NCI-ALCHEMIST** – Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials, genetically directed National Cancer Institute trial

**NCI-MATCH** – Molecular Analysis for Therapy Choice, genetically directed National Cancer Institute trial

**NHGRI GMWG** – NHGRI Genomic Medicine Working Group

**NSIGHT** – Newborn Sequencing in Genomic Medicine and Public Health

**PAGE** – Population Architecture using Genomics and Epidemiology

**PCORnet** – Patient-Centered Outcomes Research Network

**PGRN** – Pharmacogenetics Research Network

**PhenX** – Phenotypes and Exposures Toolkit

**PMI** – Precision Medicine Initiative

**UDN** – Undiagnosed Diseases Network

**USAF** – U.S. Air Force

# Goals and Programs

The Genomic Medicine Working Group convenes its next meeting in the GM series, GM VIII: "NHGRI's Genomic Medicine Programs." GM VIII has assembled leadership from NHGRI genomic medicine programs and representatives from other NIH ICs and external groups to examine the NHGRI genomic medicine portfolio in light of evolving scientific knowledge and opportunities.

Objectives for GM VIII are to:

1. Review NHGRI's ongoing genomic medicine portfolio and identify gaps and opportunities for collaborations among these programs
2. Identify related programs of other NIH Institutes/Centers or other funders and opportunities for collaborations with NHGRI programs
3. Identify research needs in genomic medicine for NHGRI and partner federal agencies to pursue
4. Enhance approaches to capturing and disseminating best practices for genomic medicine
5. Examine potential methods for assessing impact of programs

Focus Programs to be addressed directly in the agenda include:

- Clinical Genomics Resource (ClinGen) including NCBI's ClinVar
- Clinical Sequencing Exploratory Research (CSER) including intramural ClinSeq
- Electronic Medical Records and Genomics Network (eMERGE)
- Genomic Medicine Meetings program as a whole
- Global Genomic Medicine Collaborative (G2MC)
- Implementing Genomics into Practice (IGNITE)
- Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT)
- Undiagnosed Diseases Network (UDN)

Related Programs to inform the discussion, but not examine in depth, include:

- Big Data to Knowledge (BD2K) clinical subset
- Clinical Pharmacogenetics Implementation Consortium (CPIC)
- Encyclopedia of DNA elements (ENCODE)
- Genetically directed NCI trials including MATCH and ALCHEMIST
- Genotype Tissue Expression Project (GTEx)
- Genome Sequencing Informatics Tools (GS-IT)
- GenomeCanada/CIHR Genomics and Personalized Health (GAPH)
- Genomics of Gene Regulation (GGR)
- Global Alliance for Genomics and Health (GA4GH)
- Human Health and Heredity in Africa (H3Africa)
- HMO Research Network (HMORN) including HMO Collaboratory
- Institute of Medicine (IOM) Genomics Roundtable including EMR Action Collaborative
- Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC)
- Large-Scale Genome Sequencing program, including Centers for Mendelian Genetics

- Million Veterans' Program (MVP)
- Patient-Centered Outcomes Research Network (PCORnet)
- Pharmacogenetics Research Network (PGRN)
- Phenotypes and Exposures Toolkit (PhenX)
- Population Architecture using Genomics and Epidemiology (PAGE)
- Precision Medicine Initiative (PMI)
- U.S. Air Force Personalized and Precision Care



Objectives of major genomic medicine programs related to implementation of genomic medicine.

Objectives Related to Genomic Medicine Implementation	Focus Programs								Related Programs									
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC	AFMS	CMG	CPIC	GA4GH	GAPH	IOM	ISCC	LSAC	PAGE	PhenX
Improve genomic diagnostic methods	X	X	X							X								
Facilitate research in undiagnosed and/or Mendelian diseases	X		X							X								
Expand scale of genomic data available in newborns		X																
Advance understanding of disorders of newborns		X																
Research ethical/legal/social issues in genome sequencing		X	X											X				
Interpret sequence data in variety of clinical contexts			X	X														
Integrate genomic data into patient care			X	X	X				X					X				
Incorporate actionable variants into EMR, develop CDS			X	X	X				X					X				
Educate clinicians and patients on genomics in clinical care			X	X	X			X	X		X			X	X			X
Develop electronic phenotypes				X														X
Identify variants related to complex traits	X		X	X									X			X	X	
Characterize pharmacogenetic variants and use in care				X	X						X							
Assess outcomes of using genomic information in clinical care				X	X				X				X					
Assess penetrance of potentially actionable variants				X														
Translate implementation outside highly specialized centers					X	X												
Define and share processes of implementation, sustainability	X		X	X	X		X	X						X				
Share genotype/phenotype info through open databases						X						X						
Standardize clinical annotation and interpretation						X												X
Improve understanding of variation in diverse populations				X		X											X	
Assess actionability of genes and variants for clinical use						X					X							
Identify, address barriers to genomic medicine implementation				X			X	X	X									
Promote interaction and collaboration, reduce duplication	X					X	X	X		X		X		X	X			
Serve as clearinghouse, knowledge base for genomic medicine						X		X			X							
Use genomics to enable new drug development													X	X				
Create genomics-enabled learning health care systems				X	X									X				
Develop evidence base for clinical use of novel diagnostics													X					
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC		CMG	CPIC	GA4GH	GAPH	IOM	ISCC	LSAC	PAGE	PhenX

Barriers to genomic medicine implementation as identified by focus and related programs.

Barriers Identified	Focus Programs								Related Programs													
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC	CMG	CPIC	GAPH	GTEX	GS-IT	IOM	ISCC	LSAC	MVP	PAGE	PCORNet	PhenX	PGRN	
DATA/INFORMATION NEEDS																						
Evidence base for implement'n incl long-term outcomes			X	X			X	X						X								
Common data elements	X													X					X			
Development, validation of phenotypes				X															X			
Specific drug response phenotypes to add to trials																						X
Publicly available genotype/phenotype info						X			X			X										
Framework for classifying/curating actionable variants			X			X																
Unclear penetrance of actionable genes				X																		
Impact of variants in ancestrally diverse populations																		X				
RAPIDLY EVOLVING NATURE OF GENOMIC INFO																						
Evolving molecular testing panels					X																	
Changes in evidence and subsequent treatment					X																	
Division between discovery and implementation																X						
CLINICAL IMPLEMENTATION ISSUES																						
High cost of sequencing, data processing								X									X					
Targeted testing vs genome-scale sequencing			X																			
Limited use of standardized EMR terms, ontologies				X		X																
Concise, comprehensive, interoperable lab reports			X							X												
Integration of genomic data in learning healthcare system			X																			
Turnaround in clinically emergent settings			X																			
Use cases for genomic CDS development										X												
Limited usefulness and interoperability of CDS				X	X		X	X														
Rapidly evolving EMRs					X																	
Limited transportability of clinical workflows, protocols					X																	
Differing education needs across professional levels					X		X															
Returning incidental findings												X										
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM	G2MC	CMG	CPIC	GAPH	GTEX	GS-IT	IOM	ISCC	LSAC	MVP	PAGE	PCORNe	PhenX	PGRN	

Barriers Identified	Focus Programs								Related Programs													
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC	CMG	CPIC	GAPH	GTEX	GS-IT	IOM	ISCC	LSAC	MVP	PAGE	PCORNet	PhenX	PGRN	
<b>REGULATORY NEEDS</b>																						
Central IRB	X																					
Sharing identifiable data across collaborating sites	X																					
Privacy threats (FISMA compliance for UDN)	X			X																		
Regulations impeding return of results	X	X					X															
Need for cloud computing																X						
Reimbursement policies and regulations					X		X															
<b>OTHER</b>																						
Lack of centralized iPS cell repository												X										
Installing and using sequence analysis software												X										
Different tools for variant calling give different results												X										
Finding and interpreting CNVs and SVs												X										
Difficulty focusing on specific genes in massive BAMs												X										
Need secure systems enabling access by many users																X						
Harnessing social media and crowdsourcing methods																			X			
Increasing visibility and use of tools; tracking uptake																			X			
Need for bedside back to bench research							X															
Publication standards for rapid research results									X													
Worldwide ascertainment of Mendelian families									X													
	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC	CMG	CPIC	GAPH	GTEX	GS-IT	IOM	ISCC	LSAC	MVP	PAGE	PCORNet	PhenX	PGRN	

## **IMPACTFUL PUBLICATIONS – GENOMIC MEDICINE VIII MEETING**

**Enhanced CARE for RARE Genetic Diseases in Canada** (Kim Boycott and Alex MacKenzie)

**The clinical utility of whole-exome sequencing in the context of rare diseases – the changing tides of medical practice.**

Nguyen MT, Charlebois K, 2014-11-25, Clinical Genetics

Whole-exome sequencing (WES) carries the potential to facilitate the identification of disease causing genes. This is particularly relevant concerning rare diseases, which proves particularly difficult for physicians to diagnose. However, the complexity of this technology renders its applicability onto the clinical setting uncertain. Our study thus aims to understand physicians' perspectives regarding the clinical utility of WES, particularly for providing a diagnosis for patients with rare diseases.

**Mutations in PNPLA6 are linked to photoreceptor degeneration and various forms of childhood blindness.**

Kmoch S, Majewski J, Cao S, Fahiminiya S, Ren H, MacDonald IM, Lopez I, Sun V, Keser V, Khan A, Stránecký V, Hartmannová H, Přistoupilová A, Hodaňová K, Piherová L, Kuchař L, Baxová A, Chen R, Barsottini OG, Pyle A, Griffin H, Splitt M, Sallum J, Tolmie JL, Sampson JR, Chinnery P, Banin E, Sharon D, Dutta S, Grebler R, Helfrich-Foerster C, Pedroso JL, Kretzschmar D, Cayouette M, Koenekoop RK, Care4Rare Canada

2015-01-09, Nature Communications

**Autism Spectrum Disorders: Genomes to Outcomes** (Stephen Scherer and Peter Szatmari)

**Autism spectrum disorder: advances in evidence-based practice**

Evdokia Anagnostou MD, Lonnie Zwaigenbaum MD, Peter Szatmari MD, Eric Fombonne MD, Bridget A. Fernandez MD, Marc Woodbury-Smith MD PhD, Jessica Brian PhD, Susan Bryson PhD, Isabel M. Smith PhD, Irene Drmic PhD, Janet A. Buchanan PhD, Wendy Roberts MD, Stephen W. Scherer PhD

Canadian Medical Journal, January 13 2014

In this review, we outline the current understanding of ASD and suggest best practices for primary care and specialized clinics based on evidence from randomized controlled trials (RCTs) or systematic reviews, if available.

## **Brain-expressed exons under purifying selection are enriched for de novo mutations in autism spectrum disorder**

Mohammed Uddin, Kristiina Tammimies, Giovanna Pellecchia, Babak Alipanahi, Pingzhao Hu, Zhuozhi Wang, Dalila Pinto, Lynette Lau, Thomas Nalpathamkalam, Christian R Marshall, Benjamin J Blencowe, Brendan J Frey, Daniele Merico, Ryan K C Yuen & Stephen W Scherer

Nature Genetics 46, 742–747 (2014)

A universal challenge in genetic studies of autism spectrum disorders (ASDs) is determining whether a given DNA sequence alteration will manifest as disease. Among different population controls, we observed, for specific exons, an inverse correlation between exon expression level in brain and burden of rare missense mutations. For genes that harbor de novo mutations predicted to be deleterious, we found that specific critical exons were significantly enriched in individuals with ASD relative to their siblings without ASD. Our results suggest that brain-expressed exons under purifying selection should be prioritized in genotype-phenotype studies for ASD and related neurodevelopmental conditions.

## **PACE-'Omics: Personalized, Accessible, Cost-Effective Applications of 'Omics Technologies** (Christopher McCabe and Tania Bubela)

### **Value-Engineered Translation: Developing Biotherapeutics That Align With Health-System Needs**

Tania Bubela, PhD, JD, and Christopher McCabe, PhD

<http://www.ajmc.com/journals/evidence-based-diabetes-management/2014/july-august-2014/Value-Engineered-Translation-Developing-Biotherapeutics-That-Align-With-Health-System-Needs#sthash.66MQ1q6U.dpuf>

AJMC July 21, 2014

Here we describe the Value-Engineered Translation (VET) framework that couples development decisions along the translational continuum with the production of a "reimbursable evidence dossier." It assists technology developers in comprehending the evidence requirements of healthcare payers, both public and private, in different markets. Concomitantly, it supports payers in evaluating a broader range of factors for novel bio-therapeutics that may address unmet healthcare needs. Finally it benefits the public and patients, who require better and more cost-effective therapeutics and diagnostics, by informing decisions on health insurance coverage and out-of-pocket expenses.

- See more at: <http://www.ajmc.com/journals/evidence-based-diabetes->

[management/2014/july-august-2014/Value-Engineered-Translation-Developing-Biotherapeutics-That-Align-With-Health-System-Needs#sthash.66MQ1q6U.Ackxl6oo.dpuf](http://management/2014/july-august-2014/Value-Engineered-Translation-Developing-Biotherapeutics-That-Align-With-Health-System-Needs#sthash.66MQ1q6U.Ackxl6oo.dpuf)

**Innovative Chemogenomic Tools to Improve Outcome in Acute Myeloid Leukemia** (Guy Sauvageau and Josée Hébert)

**Identification of small molecules that support human leukemia stem cell activity *ex vivo***

Caroline Pabst, Jana Krosi, Iman Fares, Geneviève Boucher, Réjean Ruel, Anne Marinier, Sébastien Lemieux, Josée Hébert & Guy Sauvageau

Nature Methods 11, 436–442 (2014)

Leukemic stem cells (LSCs) are considered a major cause of relapse in acute myeloid leukemia (AML). Defining pathways that control LSC self-renewal is crucial for a better understanding of underlying mechanisms and for the development of targeted therapies. However, currently available culture conditions do not prevent spontaneous differentiation of LSCs, which greatly limits the feasibility of cell-based assays. To overcome these constraints we conducted a high-throughput chemical screen and identified small molecules that inhibit differentiation and support LSC activity *in vitro*. Similar to reports with cord blood stem cells, several of these compounds suppressed the aryl-hydrocarbon receptor (AhR) pathway, which we show to be inactive *in vivo* and rapidly activated *ex vivo* in AML cells. We also identified a compound, UM729, that collaborates with AhR suppressors in preventing AML cell differentiation. Together, these findings provide newly defined culture conditions for improved *ex vivo* culture of primary human AML cells.

**Viral and Human Genetic Predictors of Response to HIV Therapies** (Richard Harrigan and Julio Montaner)

**Geographic and Temporal Trends in the Molecular Epidemiology and Genetic Mechanisms of Transmitted HIV-1 Drug Resistance: An Individual-Patient- and Sequence-Level Meta-Analysis.**

PLoS Med. 2015 Apr 7; 12(4):e1001810. doi: 10.1371/journal.pmed.1001810. eCollection 2015.

Rhee SY, Blanco JL, Jordan MR, Taylor J, Lemey P, Varghese V, Hamers RL, Bertagnolio S, Rinke de Wit TF, Aghokeng AF, Albert J, Avi R, Avila-Rios S, Bessong PO, Brooks JI, Boucher CA, Brumme ZL, Busch MP, Bussmann H, Chaix ML, Chin

BS, D'Aquin TT, De Gascun CF, Derache A, Descamps D, Deshpande AK, Djoko CF, Eshleman SH, Fleury H, Frange P, Fujisaki S, Harrigan PR, Hattori J, Holguin A, Hunt GM, Ichimura H, Kaleebu P, Katzenstein D, Kiertiburanakul S, Kim JH, Kim SS, Li Y, Lutsar I, Morris L, Ndembi N, Ng KP, Paranjape RS, Peeters M, Poljak M, Price MA, Ragonnet-Cronin ML, Reyes-Terán G, Rolland M, Sirivichayakul S, Smith DM, Soares MA, Soriano VV, Ssemwanga D, Stanojevic M, Stefani MA, Sugiura W, Sungkanuparph S, Tanuri A, Tee KK, Truong HH, van de Vijver DA, Vidal N, Yang C, Yang R, Yebra G, Ioannidis JP, Vandamme AM, Shafer RW.

Regional and subtype-specific mutational patterns of HIV-1 transmitted drug resistance (TDR) are essential for informing first-line antiretroviral (ARV) therapy guidelines and designing diagnostic assays for use in regions where standard genotypic resistance testing is not affordable. We sought to understand the molecular epidemiology of TDR and to identify the HIV-1 drug-resistance mutations responsible for TDR in different regions and virus subtypes.

**PEGASUS: Personalized Genomics for Prenatal Aneuploidy Screening Using Maternal Blood** (François Rousseau and Sylvia Langlois)

**Identification of trisomy 18, trisomy 13, and Down syndrome from maternal plasma.**

Gekas J1, Langlois S2, Ravitsky V3, Audibert F4, van den Berg DG5, Haidar H3, Rousseau F6.

Appl Clin Genet. 2014 Jul 7;7:127-31. doi: 10.2147/TACG.S35602. eCollection 2014.

Abstract

Current prenatal diagnosis for fetal aneuploidies (including trisomy 21 [T21]) generally relies on an initial biochemical serum-based noninvasive prenatal testing (NIPT) after which women who are deemed to be at high risk are offered an invasive confirmatory test (amniocentesis or chorionic villi sampling for a fetal karyotype), which is associated with a risk of fetal miscarriage. Recently, genomics-based NIPT (gNIPT) was proposed for the analysis of fetal genomic DNA circulating in maternal blood. The diffusion of this technology in routine prenatal care could be a major breakthrough in prenatal diagnosis, since initial research studies suggest that this novel approach could be very effective and could reduce substantially the number of invasive procedures. However, the limitations of gNIPT may be underappreciated. In this review, we examine currently published literature on gNIPT to highlight advantages and limitations. At this time, the performance of gNIPT is relatively well-documented only in high-risk pregnancies for T21 and trisomy 18. This additional screening test may be an

option for women classified as high-risk of aneuploidy who wish to avoid invasive diagnostic tests, but it is crucial that providers carefully counsel patients about the test's advantages and limitations. The gNIPT is currently not recommended as a first-tier prenatal screening test for T21. Since gNIPT is not considered as a diagnostic test, a positive gNIPT result should always be confirmed by an invasive test, such as amniocentesis or chorionic villus sampling. Validation studies are needed to optimally introduce this technology into the existing routine workflow of prenatal care.



# ***FOCUS PROGRAMS***

# Genomic Medicine VIII – Summary of Focus Program CLINGEN

Program Name and Website: Clinical Genome Resource, [www.clinicalgenome.org](http://www.clinicalgenome.org)

## PIs and Funded Sites:

U41 HG006834-01	Heidi L. Rehm, Ph.D., Christa L. Martin, Ph.D. David H. Ledbetter, Ph.D. Robert L. Nussbaum, M.D.	Brigham and Women's Hospital, Boston, MA Geisinger Health System, Danville, PA Geisinger Health System, Danville, PA University of California, San Francisco, CA
U01 HG007437-01	Jonathan S. Berg, M.D., Ph.D James P. Evans, M.D., Ph.D Michael S. Watson, Ph.D. David H. Ledbetter, Ph.D.	University of North Carolina, Chapel Hill, NC University of North Carolina, Chapel Hill, NC ACMG, Bethesda, MD Geisinger Health System, Danville, PA
U01 HG007436-01	Carlos D. Bustamante, Ph.D. Sharon E. Plon, M.D., Ph.D.,	Stanford University, Palo Alto, CA Baylor College of Medicine, Houston, TX
ClinVar	Melissa Landrum, Ph.D. Steve Sherry, Ph.D.	NCBI Intramural Program, Bethesda, MD

**Mission:** Building a genomic knowledge base to improve patient care

## Objectives:

1. Share genomic and phenotypic data through a central database for clinical and research use
2. Define the review level for ClinVar submissions and review expert panel applications
3. Standardize the clinical annotation and interpretation of genomic variants
4. Improve our understanding of variation in diverse populations to improve interpretation of genetic testing on a global scale
5. Develop machine-learning algorithms to improve the throughput of variant interpretation
6. Implement evidence-based expert consensus for curating genes and variants
7. Assess the action ability of genes and variants to support their use in clinical care systems
8. Disseminate the knowledge and resources for unrestricted use in the community

## Funding Period and FY14 Total:

FY13	FY14	FY15	FY16	Total*
\$5.8M	\$7.5M	\$7.5M	\$7.2M	\$28.0M

\* Co-funding from NCI & NICHD

## Current Intra-Program Working Groups:

1. **IT Standards & Data Submission:** Facilitate submission of data to ClinVar.
2. **Structural Variation:** Develop a dosage map of the human genome through gene curation, collect copy number data from clinical laboratories and public genomics efforts, and build tools to support standardization of copy number interpretation.
3. **Sequence Variation:** Recruit the submission of curated sequence variants to ClinVar and lead activities to improve the quality and utility of shared data.
4. **Phenotype:** Support the collection and submission of phenotypic data to ClinGen resources.
5. **Education, Engagement, and Access:** Foster community engagement in all aspects of the ClinGen project through education, outreach, and resource development.
6. **Consent and Disclosure Recommendations (CADRe):** Explore the ELSI issues relating to reporting actionability of particular variants.
7. **Gene Curation:** Develop evidence-based methods for evaluating gene-disease associations to inform the community on the strength of these associations for genes offered for testing.
8. **Actionability:** Identify those human genes that, when significantly altered, confer a high risk of serious disease that could be prevented or mitigated if the risk were known.
9. **Clinical Domains:** Create a comprehensive, standardized knowledge base of genes and variants relevant to the domains of *Cardiovascular Disease, Hereditary Cancer, Somatic Cancer, Inborn Errors of Metabolism, and Pharmacogenomics.*

10. **Informatics:** Coordinate the acquisition, analysis, and dissemination of ClinGen resource data.
11. **Data Model:** Provide a common set of definitions and consistent representation of core concepts, attributes, and terminology to support ClinGen & harmonize with relevant efforts.
12. **Electronic Health Record (EHR):** Aims to ensure that the ClinGen resource is designed to be accessible to providers and patients through electronic health record and related systems.

*Major Collaborations and Their Goals:*

- CSER: Facilitating ClinVar submissions, piloting pathogenicity calculator, cross-representation on ClinGen’s Somatic Cancer WG
- Cross-representation on many related (including the Global Alliance for Genomics and Health, DECIPHER, Matchmaker Initiative, IOM, ACMG, CPIC, Free-the-Data) to enhance communication and collaboration.

*Resources and Tools Produced:*

1. GenomeConnect: ClinGen’s patient portal ([available online](#))
2. Clinical validity framework ([available online](#))
3. Actionability scoring process and evidence summaries ([available online](#))
4. EHR web resources ([available online](#))

*Key Publications:*

1. Rehm HL, Berg JS, Brooks LD, Bustamante CD, Evans JP, Landrum MK, Ledbetter DH, Maglott DR, Martin CL, Nussbaum RL, Plon SE, Ramos EM, Sherry ST, Watson MS, on behalf of ClinGen. ClinGen: The Clinical Genome Resource. *In Press*.
2. Ramos EM, Din-Lovinescu C, Berg JS, et al., Williams MS., Characterizing Genetic Variants for Clinical Action. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* (special issue on implementation of genomic medicine), 166, No. 1, pp. 93-104. 2014.

*Major Obstacles or Needs Encountered:*

Major Needs	Approaches Implemented/Proposed to Overcome Obstacles
Consensus frameworks & robust curation environment for assessing clinical significance of genes & variants	Created a clinical validity matrix and detailed scoring process; Created semi-quantitative actionability metric; Informatics team is developing v1 of an online curation interface
Rich genotypic & phenotypic information in public repositories to inform curation	Exploring development of a controlled-access repository for case-level data
Consistent use of ontologies and disease terms	Selecting ontologies and term lists to use across ClinGen systems and ClinVar submissions

*NHGRI Program Officials:* Erin Ramos, Lisa Brooks, Carolyn Hutter, Ken Wiley

## Genomic Medicine VIII – Summary of Focus Program CSER

*Program Name and Website:* Clinical Sequencing Exploratory Research (CSER) Consortium,  
Website: <https://cser-consortium.org/>

### *PIs and Funded Sites (U-Grants and Coordinating Center)*

Sharon Plon, Will Parsons	Baylor College of Medicine (BCM)
Robert Green	Brigham and Women's Hospital
Ian Krantz, Nancy Spinner	Children's Hospital of Philadelphia (CHOP)
Levi Garraway, Pasi Janne	Dana Farber Cancer Institute (DFCI)/ Broad Institute
Greg Cooper, Rick Myers	HudsonAlpha
Katrina Goddard, Ben Wilfond	Kaiser Permanente
Arul Chinnaiyan	University of Michigan
James Evans, and others	University of North Carolina, Chapel Hill
Gail Jarvik	University of Washington
Gail Jarvik, and others	University of Washington (Coordinating Center)

*R-Grants:* 9 grants focused on return of results, funded by the Division of Genomics & Society

*NHGRI Intramural:* Les Biesecker, ClinSeq study

### *Objectives:*

1. Generate and interpret genomic sequence data on patients in a variety of clinical contexts;
2. Develop methods for integrating comprehensive genomic sequence data into patient care, including: a) generating and applying genomic sequence data within the clinical workflow; b) interpreting and translating sequence data for referring clinicians; and c) communicating sequencing results to the patient, provider and family.
3. Examine the ethical, legal, and psychosocial implications of bringing sequence data to the clinic. Identify the benefits and harms of genomic sequencing when applied in diverse clinical contexts.

### *Funding Period and FY14 Total: (U grants only)*

FY2011-FY2017. \$15.4M HG (\$2.9M NCI) in FY14

### *Current Intra-Program Working Groups:*

1. Actionability-Return of Results
2. Electronic Health Records (EHR)
3. Genetic Counselors
4. Informed Consent and Governance
5. Outcomes and Measures
6. Pediatrics
7. Phenotyping Measures and Analysis
8. Sequencing Standards
9. Tumor Sequencing

### *Major Collaborations and Their Goals:*

- eMERGE: share experience and lessons learned, identify priorities for (return of results, EHR)
- ClinGen: coordinate variant submission; provide scientific expertise (tumor, gene/variant WGs)
- Genome Sequencing Program (LSAC/CMG/GS-IT): joint meetings in 2012-2013

### *Resources and Tools Produced (representative sample):*

1. ClinVar deposition (N = 2171 completed or pending submissions)
2. TARGET database of cancer genes; PHIAL analysis platform (DFCI; PMID 24836576)
3. Software/platform for clinical exomes (BCM; PMID 24088041)
4. Proband pedigree app (<http://probandapp.com/>) (CHOP)
5. Dissemination of expertise, protocols and lessons learned via high visibility scientific conferences (ACMG, ASHG, NSGC, ASCO, AACR, ASBH) and expert consultations

### *Five Key Publications (3 CSER-wide, 2 single-site, from >140 publications):*

1. Amendola LM, et al. Actionable exomic incidental findings in 6503 participants: challenges of variant classification. Genome Res. 2015. PMID 25741865

2. Gallego CJ, et al. Next-Generation Sequencing Panels for the Diagnosis of Colorectal Cancer and Polyposis Syndromes: A Cost-Effectiveness Analysis. *J Clin Oncol*. 2015. PMID: 25940718
3. Gray SW, et al. Social and behavioral research in genomic sequencing: approaches from the CSER Consortium Outcomes and Measures Working Group. *Genet Med*. 2014. PMID: 24625446
4. McLaughlin HM, et al. A systematic approach to the reporting of medically relevant findings from whole genome sequencing. *BMC Med Genet*. 2014. PMID: 25714468
5. Shirts, et al. CSER and eMERGE: Current and Potential State of the Display of Genetic Information in the Electronic Health Record. *In press, JAMIA*.

**Major Obstacles or Needs Encountered:**

Major Obstacles or Needs	Approaches Implemented or Proposed to Overcome Obstacles
Define the clinical characteristics that signal when genome-scale sequencing vs. targeted testing approaches are effective in patient care.	Utilize the results across the diverse clinical settings in CSER to determine most appropriate test platform.
Address the cascade of information flowing from sequenced patients to patients and families, labs, and clinicians, with consideration of downstream challenges (e.g., privacy). Incorporate into a learning healthcare system and coordinate downstream effects of care delivery.	Coordination with other genomic medicine and learning healthcare efforts. Characterize the complexity learned from diverse clinical settings and identify best practices for implementation of clinical genomics.
Develop a framework for classifying and signing out variants. Address manual and automated curation resource needs; insufficient knowledge; changing knowledge requiring updating and reanalysis.	Development of resources to streamline curation for tumor and germline. Empirically assess variability in interpretation (variant "bake-off") and value of reanalysis.
Increase the evidence base for genomic testing by evaluating the long-term clinical, psychosocial and economic outcomes of primary and secondary findings. Do so across ethnic, socioeconomic, and clinical contexts.	Longitudinal follow-up with access to comprehensive outcome data. Dedicated recruitment and study of diverse patient populations. Identification of common and robust metrics.
Develop concise yet comprehensive laboratory reports for genomic results and integrate into EHR's to support high quality clinical care.	Development and dissemination of such reports tailored to diverse clinical settings.
Optimize informed consent, analysis and interpretation given inherent clinical time constraints, especially in setting of diseases with poor prognosis and short windows for action.	Assess and report on common themes across the CSER sites while commenting on the unique challenges of different clinical contexts.

**NHGRI Program Officials:** Lucia Hindorff, Carolyn Hutter (DGM); Jean McEwen, Dave Kaufman (DG&S). Charlisse Caga-Anan, Sheri Schully (NCI).

## Genomic Medicine VIII – Summary of Focus Program eMERGE

**Program Name and Website:** Electronic Medical Records and Genomics (eMERGE) Network, <https://emerge.mc.vanderbilt.edu/>

### PIs and Funded Sites:

Hakon Hakonarson	Children’s Hospital of Philadelphia
John Harley, Isaac Kohane	Cincinnati Children’s Hospital Medical Center and Boston Children’s Hospital
Catherine McCarty, Murray Brilliant	Essentia Institute of Rural Health with Marshfield Clinic
David Carey, Marc Williams	Geisinger Health System
Eric Larson, Gail Jarvik	Group Health Cooperative with University of Washington
Iftikhar Kullo, Christopher Chute	Mayo Clinic
Erwin Bottinger	Icahn School of Medicine at Mount Sinai
Rex Chisholm, Maureen Smith	Northwestern University
Dan Roden	Vanderbilt University (Clinical Site)
Paul Harris	Vanderbilt University (Coordinating Center)

### Objectives:

1. Incorporate actionable genetic risk factors into electronic medical records (EMRs) for clinical research, clinical decision support, and clinical care
2. Develop, implement, and evaluate the process of clinician-patient education and community consultation for return of actionable genetic variants to EMRs
3. Develop and validate electronic phenotyping algorithms and define high-fidelity algorithms capable of classifying phenotypes of interest for genomic research using EMRs and biorepository samples
4. Identify genetic variants related to complex traits through association analyses
5. Characterize pharmacogenetic (PGx) variation and its phenotypic manifestations and use PGx variants to improve clinical care

### Funding Period and FY14 Total:

FY2008-FY2014, renewal pending, \$11.2M in FY14

### Current Intra-Program Working Groups:

1. Consent, Education, Regulation, and Consultation (CERC)
2. Electronic Health Records (EHR) Integration
3. Genomics
4. Phenotyping
5. Pediatrics
6. Return of Results
7. eMERGE-PGx Pharmacogenomics Initiative

### Major Collaborations and Their Goals:

- US Air Force Medical Service Personalized Medicine Program: adopt eMERGE genomic medicine implementation methods in military medical system
- ENCODE: explore phenotypic manifestations of functional variants
- CSER: share methods for RoR, EHR integration
- UK Biobank: share methods for outcome ascertainment through EHRs

### Resources and Tools Produced:

1. Model consent language
2. MyResults.org: Patient information about genetic results
3. PheKB: Validated e-phenotyping algorithms

4. eMERGE Record Counter
5. eleMAP: harmonize phenotype data
6. cTAKES: natural language processing system for information extraction from EMRs
7. SPHINX : A data exploring tool for genetics related drug response hypothesis generation
8. PheWAS Catalog: A catalog contains the PheWAS results for 3,144 single-nucleotide polymorphisms (SNPs) present in the NHGRI GWAS Catalog
9. Genomic Clinical Decision Support Artifact Repository (in development, go live June 2015)

**Five Key Publications:**

1. Gottesman O, et al. The Electronic Medical Records and Genomics (eMERGE) Network: Past, Present and Future. *Genet Med* 2013 Oct;15(10):761-71.
2. Jarvik GP, et al. Return of Genomic Results to Research Participants: The floor, the ceiling, and choices in-between. *Am J Hum Genet* 2014 94:818-826. This paper was chosen as one of the top 10 papers in 2014 by AJHG.
3. Denny JC, et al. Systematic comparison of phenome-wide association study of EMR data and genome-wide association study data. *Nat Biotechnol* 2013.
4. Denny JC, et al. Variants near FOXE1 are associated with hypothyroidism and other thyroid conditions. *Am J Hum Genet* 2011.
5. Loukides G et al., Anonymization of EMRs for validating genome-wide association studies. *PNAS* 2010.

**Major Obstacles or Needs Encountered:**

Major Obstacles or Needs	Approaches Implemented or Proposed to Overcome Obstacles
Increasing adoption of standardized EMR terms	Enhance collaborations with EMR vendors to promote interoperability
Assessing outcomes of genomic medicine implementation	Define process and health/clinical care outcomes, develop and disseminate assessment tools
Assessing penetrance of variants in actionable genes	Assay variants in well-phenotyped participants with adequate family history and outcome data
Providing interoperable genomic CDS	Standardize CDS tools and create CDS library
Reducing privacy threats	Define technical and policy protections proportional to threats posed by data sharing

*NHGRI Program Officials:* Rongling Li, Kenneth Wiley

## Genomic Medicine VIII – Summary of Focus Program G2MC

**Program Name and Website:** Global Genomic Medicine Collaborative (G2MC), [www.iom.edu/G2MC](http://www.iom.edu/G2MC)  
**Steering Committee Members:**

Marc Abramowicz	Université Libre de Bruxelles, Belgium
Fahd Al-Mulla	Kuwait University, Kuwait
Steven Bleyl	Intermountain Healthcare
Wasun Chantratita	Ramathibodi Hospital, Bangkok, Thailand
Vajira Dissanyake	University of Colombo, Colombo, Sri Lanka
Geoffrey Ginsburg	Duke University
Anne Kolbe	National Health Committee, Auckland, New Zealand
Bruce Korf	University of Alabama
Michiaki Kubo	RIKEN, Yokohama, Japan
Erkki Leego	University of Tartu, Tartu, Estonia
Gert Matthijs	University of Leuven, Leuven, Belgium
Yaakov Naparstek	Hadassah Hebrew University Hospital, Jerusalem, Israel
Irene Norstedt	Innovative Medicines Initiative, Brussels, Belgium
George Patrinos	University of Patras, Patras, Greece
Gad Rennert	Clalit National Personalized Medicine Program, Haifa, Israel
Robyn Ward	University of Queensland, St. Lucia, Australia
John Wong Eu Li	National University of Singapore, Singapore

**Objectives:** To improve global health by catalyzing the implementation of genomic tools and knowledge into health care delivery globally. Specifically, it is intended to:

1. Serve as nexus, clearinghouse, and knowledge base for genomic medicine activities globally;
2. Develop opportunities for global genomic medicine demonstration projects (implementation and outcomes research) and;
3. Capture and disseminate best practices for genomic medicine (in bioinformatics, education, evidence, pharmacogenomics, policy) across the global genomic medicine community.

**Funding Period and FY14 Total:** Not applicable

### Current Intra-Program Working Groups:

1. Communications
2. Clinician Education
3. Evidence Generation
4. Information Technology/bioinformatics
5. Pharmacogenomics
6. Policy

### Major Collaborations and Their Goals:

- Global Alliance for Genomics and Health (GA4GH), to promote clinical implementation of relevant outputs of GA4GH

### Resources and Tools Produced:

1. Workshop on Research Directions in Genetically Mediated Stevens Johnson Syndrome /Toxic Epidermal Necrolysis, March 2015, <https://www.genome.gov/27560487>

### Five Key Publications:

1. Manolio TA et al., Global implementation of genomic medicine: We are not alone. Science Translational Medicine, in press.



*Major Obstacles or Needs Encountered:*

<b>Major Obstacles or Needs</b>	<b>Approaches Implemented or Proposed to Overcome Obstacles</b>
Lack of evidence of impact of genomic medicine implementation	Promote research to fill evidence gaps
High cost of genomic testing	Continue research and development to drive costs downward
Need for clinician education and genomic clinical decision support (CDS)	Promote clinician education at variety of levels, tailored to multiple languages and cultures
Lack of interoperability of clinical care systems within and among countries	Assess model programs in nimble settings where implementation has worked, adapt as feasible

*NHGRI and IOM Staff:* Teri Manolio, Adam Berger, Meredith Hackmann

# Genomic Medicine VIII – Summary of Focus Program GM MTGS

*Program Name and Website:* NHGRI Genomic Medicine Meetings and Working Group (GMWG), <http://www.genome.gov/27549225>

## GMWG Members:

Carol Bult	Jackson Laboratory
Rex Chisholm	Northwestern University
Geoff Ginsburg	Duke University
Howard Jacob	HudsonAlpha Institute for Biotechnology
Mary Relling	St. Jude Children’s Research Hospital
Dan Roden	Vanderbilt University
Marc Williams	Geisinger Health System

**Objectives:** Assist in advising NHGRI on research needed to evaluate and implement genomic medicine

1. Review current progress, identify research gaps and approaches for filling them
2. Identify and publicize key advances
3. Plan genomic medicine meetings focusing on timely themes
4. Facilitate collaborations, coordination
5. Explore models for long-term infrastructure and sustainability of groups arising from genomic medicine meetings.

## Funding Period and FY14 Total:

FY2011-present, roughly \$80K in FY14

## Topics of Genomic Medicine Meetings 1-8:

1. Genomic Medicine Implementation in the U.S. (June 2011)
2. Forming Collaborations and Pilot Projects (December 2011)
3. Working with Implementation Stakeholders (May 2012)
4. Physician Education in Genomics (January 2013)
5. Working with Federal Stakeholders (May 2013)
6. Global Leaders in Genomic Medicine (January 2014)
7. Genomic Clinical Decision Support (October 2014)
8. NHGRI’s Genomic Medicine Portfolio (June 2015)

## Major Collaborations and Their Goals:

- National Academy of Medicine, Genomics Roundtable and Global Genomic Medicine Collaboration, to promote critical evaluation and sharing of approaches to implementing genomics in clinical care

## Resources and Tools Produced:

1. ClinAction Workshop, December 2011, leading to ClinGen solicitation and project, <http://clinicalgenome.org/>
2. Inter-Society Coordinating Committee for Practitioner Education in Genomics, <http://www.genome.gov/27554614>
3. Global Genomic Medicine Collaboration (G2MC) in collaboration with National Academy of Medicine, [www.iom.edu/G2MC](http://www.iom.edu/G2MC)
4. Workshop on Research Directions in Genetically Mediated Stevens Johnson Syndrome /Toxic Epidermal Necrolysis, March 2015, <https://www.genome.gov/27560487> , arising from G2MC

## Five Key Publications:

1. Manolio TA, et al. Implementing genomic medicine in the clinic: The future is here. *Genetics in Medicine* 2013; 15:258-67.

2. Ramos EM, et al., Characterizing genetic variants for clinical action. American Journal of Medical Genetics C Seminars in Medical Genetics 2014; 166:93-104.ClinAction
3. Manolio TA, Murray MF, for the Inter-Society Coordinating Committee on Practitioner Education in Genomics.. The growing role of professional societies in educating clinicians in genomics. Genetics in Medicine 2014; 16:571-72.
4. Manolio TA et al., Global implementation of genomic medicine: We are not alone. Science Translational Medicine, in press.

**Major Obstacles or Needs Encountered:**

<b>Major Obstacles or Needs</b>	<b>Approaches Implemented or Proposed to Overcome Obstacles</b>
Lack of evidence of impact of genomic medicine implementation	Promote research to fill evidence gaps
Lack of reimbursement for genomic testing	Work with payers and other stakeholders to identify information needed to support reimbursement
Need for clinician education and genomic clinical decision support (CDS)	Implement ISCC and research programs to provide genomic CDS
Restrictive regulatory policies poorly adapted to dynamic nature and scale of genomic interventions	Work with federal agencies to improve understanding and provide needed evidence
Need for bedside back to bench research pipeline for understanding genomic function and further applications	Promote collaborations among basic and applied programs, such as this GM8 meeting

**NHGRI Ex Officio Staff:** Eric Green, Teri Manolio, Laura Rodriguez

## Genomic Medicine VIII – Summary of Focus Program IGNITE

Program Name and Website: Implementing Genomics in Practice (IGNITE) Network, <http://www.ignite-genomics.org/>

### PIs and Funded Sites:

Erwin Bottinger, Carol Horowitz	Icahn School of Medicine at Mount Sinai
Josh Denny, Mia Levy	Vanderbilt University
Dave Flockhart, Paul Dexter	Indiana University
Geoff Ginsburg	Duke University
Julie Johnson	University of Florida
Toni Pollin	University of Maryland at Baltimore
Steve Kimmel	University of Pennsylvania (Coordinating Center)

### Objectives:

1. Develop methods for and evaluate feasibility of incorporating an individual's genomic information into his or her clinical care.
2. Integrate genomic information into the electronic medical record (EMR) and provide clinical decision support (CDS) for implementation of appropriate interventions or clinical advice.
3. Contribute to the evidence base regarding outcomes of incorporating genomic information into clinical care.
4. Define and share the processes of genomic medicine implementation, diffusion, and sustainability in diverse settings.

### Funding Period and FY14 Total:

FY2013-FY2017, \$5.7M in FY14

### Current Intra-Program Working Groups:

1. Common Measures
2. Dissemination, Outreach, Economics, and Sustainability (DOES)
3. Education
4. Provider and Payer Adoption (PPA)
5. Clinical Decision Support (CDS)
6. Clinical Validity and Utility (CVU)
7. Pharmacogenetics (PGx)
8. Publications

### Major Collaborations and Their Goals:

- eMERGE: share methods for implementation of genomic medicine and clinical decision support
- CYP2C19/Clopidogrel: perform multi-center analysis of outcomes of CYP2C19 testing for clopidogrel

Resources and Tools Produced: None to date

### Five Key Publications:

1. Kimmel, S. et al., **The Implementing Genomics in Practice Network (IGNITE): A Coordinated Effort to Study and Improve Implementation of Genomics in Clinical Practice.** Poster presentation at the American Society for Human Genetics Annual Meeting, San Diego CA, October 2014.
2. Levy, K et al., Prerequisites to Implementing a Pharmacogenomics Program in a Large Health-Care System. *Clinical Pharmacology & Therapeutics* 2014; 96:307-309.
3. Ginsburg, G. **Medical Genomics: Gather and use genetic data in health care.** *Nature* 2014; 508:451-3.
4. Orlando, L. et al., Implementing family health history risk stratification in primary care: Impact of guideline criteria on populations and resource demand. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 2014; 166:24-33.

5. Weitzel, K. et al., **Clinical pharmacogenetics implementation: Approaches, successes, and challenges**. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 2014; 166:56-67.

**Major Obstacles or Needs Encountered:**

<b>Major Obstacles or Needs</b>	<b>Approaches Implemented/Proposed to Overcome Obstacles</b>
Changing EHRs	Obtain substantial EHR team and resource commitment; purchase additional modules or build new programming to support HL7 connections with new EHR system
Site diversity – the same protocol doesn't work for all sites	Develop different protocols depending on the workflow of the site
Scalability and sustainability of genomic medicine	Work with payers to get reimbursement for genetic testing
Differing education and training needs for subgroups of professionals involved in clinical implementation; rotating staff	Develop different training modules; continuous education
Turnaround time for genomic results	Perform prospective genotyping, based on risk calculations
CMS/third party payers support of PGx and discrete testing versus PGx panels	Submit Current Procedural Terminology (CPT) Coding Change Request to the American Medical Association (AMA) for polypharmacy pharmacogenomics sequence analysis panels
Changes in evidence and thus changes in treatment	Update clinical decision support based on new clinical advisories
Developing applicable and useful CDS language that will be used in different clinical scenarios	Developed CDS working group to discuss and improve institutional CDS strategies based on clinical scenario
Migration to new molecular testing panels requires infrastructure evolution	Continuous iterative improvement in genomic results representation and opportunity to re-evaluate emerging standards for genomic health information

**NHGRI Program Officials:** Ebony Madden, Heather Junkins

## Genomic Medicine VIII – Summary of Focus Program INSIGHT

Program Name and Website: Newborn Sequencing In Genomic medicine and public Health (NSIGHT), <http://www.genome.gov/27558493>

### PIs and Funded Sites:

Principal Investigator	Institution	Title
Robert Green and Alan Beggs	Brigham and Women's Hospital	Genome Sequence-Based Screening for Childhood Risk and Newborn Illness
Stephen Kingsmore	Children's Mercy Hospital	Clinical and Social Implications of 2-day Genome Results in Acutely Ill Newborns
Steven Brenner, Barbara Koenig, Puiyan Kwok, Jennifer Puck	University of California, San Francisco	Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening
Cynthia Powell and Jonathan Berg	University of North Carolina at Chapel Hill	NC NEXUS, North Carolina Newborn Exome Sequencing for Universal Screening

### Objectives:

1. Acquisition and analysis of genomic datasets that expand considerably the scale of data available for analysis in the newborn period.
2. Perform clinical research that will advance understanding of specific disorders identifiable via newborn screening through promising new DNA-based analysis
3. Conduct research related to the ethical, legal and social implications (ELSI) of the possible implementation of genomic sequencing of newborns

### Funding Period and FY14 Total:

FY2013-FY2017, \$4.73 in FY14 (\$2.366M each from NHGRI and NICHD)

Source	FY13	FY14	FY15	FY16	FY17	Total
NHGRI	\$2.355M	\$2.366M	\$2.365M	\$2.361M	\$2.368M	\$11.815M
NICHD	\$2.355M	\$2.366M	\$2.365M	\$2.361M	\$2.368M	\$11.815M
TOTAL	\$4.71M	\$4.73M	\$4.73M	\$4.72M	\$4.74M	\$23.63M

### Current Intra-Program Working Groups:

1. Common Data Elements (CDE)
2. Ethical, Legal and Social Implications (ELSI)

**Major Collaborations and Their Goals:** None to date

**Resources and Tools Produced:** None to date

**Five Key Publications:** None to date

### Major Obstacles or Needs Encountered:

Major Obstacles or Needs	Approaches Implemented/Proposed to Overcome Obstacles
Regulation around return of genomic data to participants	NHGRI in discussions with the FDA
Creation of Common Data Element lists	Database of elements for studies to use across NHGRI or NIH

**NHGRI Program Officials:** Anastasia Wise, Tiina Urv (NICHD), Joy Boyer, Lucia Hindorff, Jeffery Schloss, Lu Wang

## Genomic Medicine VIII – Summary of Focus Program UDN

*Program Name:* Undiagnosed Disease Network, <https://commonfund.nih.gov/Diseases/index>

*PIs and Funded Sites:*

### Coordinating Center

Zak Kohane, Rachel Ramoni, and Alexa McCray Harvard Medical School

### Sequencing Cores

Christine Eng Baylor College of Medicine

Howard Jacob Medical College of Wisconsin w/ Illumina

### Clinical Sites

Brendan Lee Baylor College of Medicine

Vandana Shashi and David Goldstein Duke University w/Columbia University

Joseph Loscalzo Harvard Teaching Hospitals (including Boston Children’s Hospital, Brigham and Women’s Hospital and Massachusetts General)

Euan Ashley, Jonathan Bernstein and Paul Graham Fisher Stanford University

Eric Vilain, Katrina Dipple, Stanley Nelson and Christina Palmer University of California, Los Angeles

John Phillips and John Newman Vanderbilt University Medical Center

### Objectives:

1. Improve the level of diagnosis and care for patients with undiagnosed diseases through common protocols designed by a large community of investigators
2. Facilitate research into the etiology of undiagnosed diseases by collecting and sharing high quality clinical and laboratory data.
3. Create an integrated and collaborate community across clinical sites and among laboratory and clinical investigators.

*Funding Period and FY14 Total:* FY2013-FY2017: FY14 total \$19.6 M

### Current Intra-Program Working Groups:

1. Billing Working Group
2. Biorepository and Biospecimen Working Group
3. Clinical Protocols Working Group
4. Economics Working Group
5. Genetic Counseling & Testing Working Group
6. Sequencing Working Group
7. Technology Working Group

*Major Collaborations and Their Goals:* None to date

*Resources and Tools Produced:* None to date

*Five Key Publications:* None to date

### Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:

Major Obstacles and Needs	Approaches Considered or Proposed to Overcome Obstacles
Establishment of a Central IRB	Language in FOAs, central IRB specified up front
Sharing of identifiable data	Development of language to share with community
FISMA compliance	Language in FOAs, clear path for initiatives with intramural components
Regulation around return of genomic data to participants	NHGRI in discussions with the FDA
Matching patients to themselves	Considering use of GUID

*NHGRI Program Officials:* Anastasia Wise

# ***RELATED PROGRAMS***



## Genomic Medicine VIII – Summary of Related Program AFMS

Program Name and Website: AFMS Personalized Medicine Program

<https://kx2.afms.mil/kj/kx2/PC2ZGenomicMedicine/Pages/home.aspx>

### PIs and Funded Sites:

<b>Intramural Collaborators</b>	
Debra Niemeyer	USAF 59 <sup>th</sup> Medical Wing
Col Michael Grinkemeyer	USAF 711 <sup>th</sup> Human Performance Wing
Capt Mauricio De Castro	USAF 81 <sup>st</sup> Medical Group
Zygmunt Galdzicki	Uniformed Services University of the Health Sciences
<b>Extramural Collaborators</b>	
Michael Christman	Coriell Institute
Deepak Voora	Duke University
Allison Vordestrasse	Duke University
Andrew Dewan	Yale University
<b>University Affiliated Research Center (UARC)</b>	
Ruth Vogel	Johns Hopkins Applied Physics Lab
Chris Bradburne	Johns Hopkins Applied Physics Lab
Lucy Carruth	Johns Hopkins Applied Physics Lab
Bart Paulhamus	Johns Hopkins Applied Physics Lab

### Objectives:

1. Develop/facilitate necessary infrastructure and environment for the development of personalized medicine within the AFMS
2. Harvest information on the medical application of genomic medicine, as well as determine Air Force relevancy for further investigation
3. Translate genomic discoveries into new clinical practices for Airmen and their beneficiaries
4. Address educational gaps for patients and providers
5. Determine the clinical value of utilizing genetic risk information in patient care

### Funding Period and FY14 Total:

FY2011-FY2018, renewal under consideration: FY14 total \$14.8M

### Current Intra-Program Working Groups:

1. Precision Care Advisory Panel (PCAP)
  - Provides recommendations on the advancement of personalized medicine by bringing together a broadly-developed and engaged coalition of researchers, clinicians, educators, counselors, and policy specialists.
  - Provides policy, scientific, and operational recommendations and approaches for the Military Health System in concert with federal efforts to support clinical genetic screening, counseling, and health care services for Service Members and beneficiaries.
2. Genomic Research Working Group (GRWG)
  - GRWG brings together Air Force Genomics Researchers to discuss current and future research projects.
  - Current GRWG membership includes:
    - AFMSA/SG5P Research and Innovations
    - USAF 59<sup>th</sup> Medical Wing
    - USAF 711<sup>th</sup> Human Performance Wing
    - USAF 81<sup>st</sup> Medical Group

3. Center for Clinical Laboratory Medicine (CCLM) within the Defense Health Agency develops Clinical Laboratory Improvement Amendments (CLIA) comparable regulations and administers the Clinical Laboratory Improvement Program (CLIP); AFMS participation is within the Lab Joint Working Group
4. Provider Education Panel designs educational resources for Military Health System (MHS) healthcare providers

**Major Collaborations and Their Goals:**

1. Electronic Medical Records and Genomics (eMERGE) Network: <https://emerge.mc.vanderbilt.edu/>
2. Implementation, Adoption, and Utility of Family History in Diverse Care Settings: [http://www.ignite-genomics.org/ignite\\_duke.html](http://www.ignite-genomics.org/ignite_duke.html)

**Resources and Tools Produced:**

1. Requirements have been established for the AFMS Digital Biobank. A prototype is currently in development; prototype completion is scheduled for 2016.
2. Consideration of telegenetics resource to ensure the necessary tools and resources are made available to patients and providers.

**Five Key Publications:**

1. Diseati L. *et al* (2015). Common Genetic Risk for Melanoma Encourages Preventive Behavior Change. *J Pers Med*. 2015 Feb 17;5(1):36-49. doi: 10.3390/jpm5010036.

# Genomic Medicine VIII – Summary of Related Program CMG

Program Name and Website:

Centers for Mendelian Genomics, <http://www.mendelian.org/>

## PIs and Funded Sites (U-Grants and Coordinating Center)

Richard Lifton (contact PI), Murat Gunel, Mark Gerstein, Shrikant Mane	Yale University Center for Mendelian Genomics (YCMG)
David Valle (contact PI), Jim Lupski	Baylor-Hopkins Center for Mendelian Genomics (BHCMG)
Deborah Nickerson (contact PI), Michael Bamshad, Jay Shendure	University of Washington Center for Mendelian Genomics (UWCMG), Coordinating Center of Centers for Mendelian Genomics

## Objectives:

1. Discover as many “causal genes” for Mendelian disorders as possible at the funded centers
2. Improve success rates, costs, and efficiency for causal gene discovery
3. Enable others to discover more causal genes through resource sharing
4. Coordinate with other researchers and programs worldwide on disorders to be studied and resource development

**Funding Period and FY14 Total: (U grants only)** - FY2012-FY2019. \$9.48M HG and \$1.97M HL in FY14

## Current Intra-Program Working Groups:

- Community Engagement/Inquiry Response
- Regulatory Review
- Data Analysis/Data Release
- Phenotype Review
- “Solve” Rate
- Rapid Publication

## Major Collaborations and Their Goals:

- Genome Sequencing Program (LSAC/CMG/GS-IT): joint meetings in 2012-2013
- GA2GH - Matchmaker Exchange for project coordination

## Resources and Tools Produced (representative sample):

1. phenoDB (<https://phenodb.org/>)
2. GeneMatcher (<https://genematcher.org/>)
3. ALOFT (<https://www.github.com/gersteinlab/aloft>)
4. Mendelian Phenotype Variant Comparison Tool: <http://mpvct.gs.washington.edu>
5. PRIMUS (Pedigree Reconstruction and Identification of a Maximally Unrelated Set (<https://primus.gs.washington.edu/primusweb/>))
6. Sequence datasets in dbGaP (<https://www.ncbi.nlm.nih.gov/gap>)
7. Causal variant information in ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>; to be scaled up)

## Five Key Publications (from >170 publications):

1. Bamshad MJ, et al. The Centers for Mendelian Genomics: A new large-scale initiative to identify the genes underlying rare Mendelian conditions. AJMG. 2012. PMID: 22628075

## Major Obstacles or Needs Encountered:

Major Needs	Approaches Implemented/to be Implemented to Meet the Needs
Worldwide ascertainment and phenotypic characterization of families with Mendelian conditions	Continuous solicitation efforts; phenoDB for collection, storage, and analysis of phenotypic features; Project Coordination (e.g., Matchmaker Exchange)
Improvement of success rates for discovering causal genes/variants	Improvement of study designs; Improvement of sequencing quality and costs; Improvement of analysis methods; Project coordination

Maximizing the accessibility and usefulness of publically released genomic data	Submitting causal variant information to ClinVar; Release allele frequencies and associated high level phenotype information for easy access (pilot effort ongoing)
Rapid publication of research results on peer-reviewed journals	Establishing minimum publication requirement with journals (exploratory stage)

*NHGRI Program Officials:* Lu Wang (DGSci), Chris Wellington (DGSci), Nicole Lockhart (DG&S)

# Genomic Medicine VIII – Summary of Related Program CPIC

**Program Name and Website:** Clinical Pharmacogenetics Implementation Consortium (CPIC), <https://www.pharmgkb.org/page/cpic>

## PIs and Funded Sites:

Mary Relling	St. Jude Children's Research Hospital
Teri Klein	Stanford University

## Objectives:

The goal of the Clinical Pharmacogenetics Implementation Consortium (CPIC) is to accelerate implementation of research discoveries in pharmacogenomics into the clinic. A key assumption of CPIC is that the genetic test results are already available. CPIC does not take a position on when tests should be ordered, but rather how they should be used.

1. Create, curate, and update CPIC gene/drug guidelines for all gene/drug groupings that are clinically actionable; expand the guidelines to include definitive clinical recommendations for non-actionable drugs linked to otherwise actionable genes.
  - freely available, peer-reviewed, updatable guidelines
  - include comprehensive tables to translate genotype information to phenotype to facilitate
  - clinical decision support (CDS) in electronic health records (EHRs)
2. Enhance access to and input into guidelines by external groups such as NIH's Pharmacogenomics Research Network, NIH's Genomic Medicine Working group, AHRQ's [www.guidelines.gov](http://www.guidelines.gov), NIH's Genetic Test Registry, PubMed, FDA, ClinGen, IOM's Genomic Medicine Roundtable, professional societies, and EHR vendors by systematically evaluating community usage of CPIC guidelines on a quantitative, qualitative, and ongoing basis to respond to the community and make enhancements as needed.

## Funding Period and FY14 Total:

FY2012-FY2015, renewal under consideration: FY14 total \$410,000/year direct

## Current Intra-Program Working Groups:

- CPIC Informatics Working Group <https://www.pharmgkb.org/page/cpicinformatics>
- CPIC Steering Committee <https://www.pharmgkb.org/page/cpic>

## Major Collaborations and Their Goals:

- PharmGKB ([www.pharmgkb.org](http://www.pharmgkb.org))
- NHGRI's Genomic Medicine Working group <http://www.genome.gov/27549220>
- AHRQ's National Guidelines Clearinghouse [www.guidelines.gov](http://www.guidelines.gov)
- NCBI's Genetic Test Registry <http://www.ncbi.nlm.nih.gov/gtr/>
- ClinGen's Pharmacogenomic Domain Working Group <http://www.clinicalgenome.org/about/working-groups/>
- IOM's Roundtable on Translating Genomic-Based Research for Health <https://www.iom.edu/Activities/Research/GenomicBasedResearch.aspx>
- ASHP <http://www.ashp.org/menu/PracticePolicy/PolicyPositionsGuidelinesBestPractices/BrowsebyDocumentType/EndorsedDocuments.aspx>
- Genetics/genomics Competency Center <http://g-2-c-2.org/>
- Emerge-PGx <http://www.genome.gov/27540473> (informal connections through CPIC Informatics Working Group)

## Resources and Tools Produced:

1. CPIC guidelines <https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC>
2. Gene/drug list <https://www.pharmgkb.org/cpic/pairs>
3. List of pharmacogenetic variants <https://www.pharmgkb.org/cpic/alleles>
4. CPIC Term Standardization for Clinical Pharmacogenetic Test Results Project <https://www.pharmgkb.org/page/cpicTermProject>

## Five Key Publications:

1. Caudle KE, Klein TE, Hoffman JM, Muller DJ, Whirl-Carrillo M, Gong L, McDonagh EM, Sangkuhl K, Thorn CF, Schwab M, Agundez JA, Freimuth RR, Huser V, Lee MT, Iwuchukwu OF, Crews KR, Scott SA, Wadelius M, Swen JJ, Tyndale RF, Stein CM, Roden D, Relling MV, Williams MS, Johnson SG. Incorporation of pharmacogenomics into

- routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Current drug metabolism*. 2014;15(2):209-17. PubMed PMID: 24479687
2. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clinical pharmacology and therapeutics*. 2011;89(3):464-7. PMID: 21270786
  3. Relling MV, Gardner EE, Sandborn WJ, Schmiegelow K, Pui CH, Yee SW, Stein CM, Carrillo M, Evans WE, Klein TE, Clinical Pharmacogenetics Implementation C. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clinical pharmacology and therapeutics*. 2011;89(3):387-91. PubMed PMID: 21270794
  4. Scott SA, Sangkuhl K, Stein CM, Hulot JS, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR, Clinical Pharmacogenetics Implementation C. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clinical pharmacology and therapeutics*. 2013;94(3):317-23. PMID: 23698643
  5. Johnson JA, Gong L, Whirl-Carrillo M, Gage BF, Scott SA, Stein CM, Anderson JL, Kimmel SE, Lee MT, Pirmohamed M, Wadelius M, Klein TE, Altman RB, Clinical Pharmacogenetics Implementation C. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clinical pharmacology and therapeutics*. 2011;90(4):625-9. PubMed PMID: 21900891

**Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:**

<b>Major Obstacles and Needs</b>	<b>Approaches Considered or Proposed to Overcome Obstacles</b>
Lack of standardization of test results hindering EHR vendor-ready solutions	CPIC Term Standardization for Clinical Pharmacogenetic Test Results Project
<u>Limited set of use cases for genomic clinical decision support (CDS)</u>	<u>CPIC provides vendor agnostic resources to facilitate implementation of CDS in EHRs</u>

**NIH Program Officials:** Rochelle Long (NIGMS); Teri Manolio (NHGRI)

# Genomic Medicine VIII – Summary of Related Program ENCODE

**Program Name and Website:** Encyclopedia of DNA Elements (ENCODE)

Project Website: <https://www.encodeproject.org/>

NHGRI Website: <https://www.genome.gov/encode/>

## PIs and Funded Sites:

<b>Production Centers</b>	
Bradley Bernstein	Broad Institute of MIT and Harvard
Thomas Gingeras	Cold Spring Harbor Laboratory
Brenton Graveley	University of Connecticut Health Center
Richard Myers	HudsonAlpha Institute for Biotechnology
Bing Ren	LICR/University of California, San Diego
Michael Snyder	Stanford University
John Stamatoyannopoulos	University of Washington, Seattle
<b>Data Centers</b>	
Michael Cherry	Stanford University
Zhiping Weng	University of Massachusetts Medical School
<b>Computational Analysis</b>	
Peter Bickel	University of California
David Gifford	Massachusetts Institute of Technology
Sunduz Keles	University of Wisconsin, Madison
Robert Klein	Mount Sinai School of Medicine
Jonathan Pritchard	Stanford University
Xinshu Xiao	University of California, Los Angeles

## Objectives:

1. Identify all of the candidate functional elements in the human and mouse genomes by employing high-throughput, genome-wide experimental and computational methods
2. Make the catalog of candidate functional elements freely available to the biomedical community
3. Implement standards to ensure high-quality data and develop novel algorithms to facilitate analysis
4. Improve high-throughput methods to identify functional elements
5. Develop new methods to improve interpretation and analysis of ENCODE data
6. Combine ENCODE data with related functional data from other projects to drive new biological insights
7. Use ENCODE data to improve on the analysis of disease mapping studies to identify causal variants

**Funding Period and FY14 Total:** FY2003-FY2015, renewal under consideration: FY14 total \$26.2M

## Current Intra-Program Working Groups:

1. Analysis Working Group
  - 1.1 ENCODE and GWAS Working Group
  - 1.2 ENCODE and Cancer Working Group
  - 1.3 3D Nucleome Working Group
  - 1.4 Regulation Working Group
2. Human Resources Working Group
3. Mouse Working Group
4. Data Release and Publications Working Group
5. Outreach Working Group
6. Functional Characterization/Validation Working Group
7. Binding Working Group
8. RNA Working Group
9. DNase Working Group

**Major Collaborations and Their Goals:**

1. Common Fund Epigenomics Project (Lead IC: NIEHS and NIDA)
  - i. Project description: <https://commonfund.nih.gov/epigenomics/>
  - ii. Data portal: <http://www.roadmapepigenomics.org/>
2. International Human Epigenome Consortium (IHEC): <http://www.ihec-epigenomes.org/>
3. Genotype-Tissue Expression (GTEx): <https://commonfund.nih.gov/GTEx/index>
4. Electronic Medical Records and Genomics (eMERGE) Network: <https://emerge.mc.vanderbilt.edu/>

**Resources and Tools Produced:**

1. ENCODE Consortium Data Portal: <https://www.encodeproject.org/>
2. ENCODE tutorials: <http://www.genome.gov/27553900>

**Five Key Publications:**

See: <https://www.encodeproject.org/publications> for links to ENCODE-funded publications and to community publications from groups not funded by ENCODE, including several hundred human disease studies ([https://www.encodeproject.org/search/?type=publication&published\\_by=community&categories=human%20disease](https://www.encodeproject.org/search/?type=publication&published_by=community&categories=human%20disease)).

1. Maurano, M.T., et al (2012) Systematic localization of common disease-associated variation in regulatory DNA. Science 337(6099):1190. [doi: 10.1126/science.1222794](https://doi.org/10.1126/science.1222794)
2. Schaub MA, Boyle AP, Kundaje A, Batzoglou S, Snyder M. (2012) Linking disease associations with regulatory information in the human genome. Genome Res. 22(9):1748. [doi: 10.1101/gr.136127.111](https://doi.org/10.1101/gr.136127.111)
3. Boyle, A.P., et al (2012) Annotation of functional variation in personal genomes using RegulomeDB. Genome Res. 22(9):1790. [doi: 10.1101/gr.137323.112](https://doi.org/10.1101/gr.137323.112)
4. Ward, L.D., and Kellis, M. (2012) HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. Nucleic Acids Res. 40(Database issue):D930. [doi: 10.1093/nar/gkr917](https://doi.org/10.1093/nar/gkr917)
5. The ENCODE Project Consortium (2012) An integrated encyclopedia of DNA elements in the human genome. Nature 489(7414): e11247. [doi:10.1038/nature11247](https://doi.org/10.1038/nature11247)

**Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:**

Major Obstacles and Needs	Approaches Considered or Proposed to Overcome Obstacles
None known at this time	

**NHGRI Program Officials:** Elise Feingold, Dan Gilchrist, Mike Pazin



## Genomic Medicine VIII – Summary of Related Program GA4GH

**Program Name and Website:** Global Alliance for Genomics and Health, <http://genomicsandhealth.org/>

**Steering Committee Members:**

David Altshuler	Vertex Pharmaceuticals
Martin Bobrow	University of Cambridge
Kathryn North	Murdoch Children's Research Institute
Dixie Baker	Martin, Blanck and Associates
Richard Durbin	Wellcome Trust Sanger Institute
Paul Flicek	European Bioinformatics Institute
Peter Goodhand	Global Alliance for Genomics and Health
David Haussler	University of California, Santa Cruz
Thomas Hudson	Ontario Institute for Cancer Research
Kazuto Kato	Osaka University
Bartha Knoppers	Centre of Genomics and Policy
Brad Margus	A-T Children's Project
Elizabeth Nabel	Brigham and Women's Hospital
Charles Sawyers	Memorial Sloan Kettering Cancer Center

**Objectives:** To accelerate progress in human health by helping to establish a common framework of harmonized approaches to enable effective and responsible sharing of genomic and clinical data, and by catalyzing data sharing projects that drive and demonstrate the value of data sharing.

**Funding Period and FY14 Total:**

**Current Intra-Program Working Groups:**

1. Clinical Working Group
2. Data Working Group
3. Regulatory and Ethics Working Group
4. Security Working Group

**Major Collaborations and Their Goals:**

1. BRCA Challenge: to pool data on variants from current sequencing efforts, coupled with phenotype data, as an international data sharing resource to improve identification of clinically actionable variants.
2. Matchmaker Exchange: to allow researchers and clinicians working in both germline and cancer to discover samples with a given rare genotype or Member.
3. Beacon Project: to test the willingness of international sites to share genetic data in the simplest of all technical contexts.

**Resources and Tools Produced (selected, see <http://genomicsandhealth.org/our-work/current-initiatives> for more complete list):**

1. Constitution of the Global Alliance for Genomics and Health
2. Catalog of Activities – eHealth, Mendelian
3. Genomics API
4. Matchmaker Exchange API
5. Metadata Specification
6. Consent Policy and Tools
7. Framework for Responsible Sharing of Genomic and Health-Related Data
8. Policy Template
9. Privacy and Security Policy

**Five Key Publications:**

1. White Paper: Creating a Global Alliance to Enable Responsible Sharing of Genomic and Clinical Data
2. Knoppers BM. Framework for responsible sharing of genomic and health-related data. *The HUGO Journal* 2014, 8:3. <http://www.thehugojournal.com/content/8/1/3>. doi:10.1186/s11568-014-0003-1.

## Genomic Medicine VIII – Summary of Related Program GAPH

**Program Name and Website:** 2012 Large-Scale Applied Research Project Competition in Genomics and Personalized Health (GAPH), <http://www.genomecanada.ca/en/portfolio/research/2012-competition.aspx>

### Projects, Lead Centres, Project Leader(s):

<b>Project</b>	<b>Lead Genome Centre/Co-Lead Centre</b>	<b>Project Leader(s)</b>
<a href="#">Autism Spectrum Disorders: Genomes to Outcomes</a>	Ontario Genomics Institute	Scherer, Stephen Szatmari, Peter
<a href="#">Biomarkers for Pediatric Glioblastoma through Genomics and Epigenomics</a>	Genome Quebec	Jabado, Nada Majewski, Jacek
<a href="#">Clinical Implementation and Outcomes Evaluation of Blood-based Biomarkers for COPD Management</a>	Genome British Columbia	Sin, Don Ng, Raymond
<a href="#">Early Detection of Patients at High Risk of Esophageal Adenocarcinoma</a>	Ontario Genomics Institute	Stein, Lincoln Godfrey, Tony
<a href="#">Enhanced CARE for RARE Genetic Diseases in Canada</a>	Ontario Genomics Institute	Boycott, Kym Mackenzie, Alex
<a href="#">IBD Genomic Medicine Consortium (iGenoMed): Translating Genetic Discoveries into a Personalized Approach to Treating Inflammatory Bowel Diseases</a>	Genome Quebec	Rioux, John Bitton, Alain
<a href="#">Innovative Chemogenomic Tools to Improve Outcome in Acute Myeloid Leukemia</a>	Genome Quebec	Sauvageau, Guy Hébert, Josée
<a href="#">PACE-'Omics: Personalized, Accessible, Cost-Effective Applications of 'Omics Technologies</a>	Genome Alberta	McCabe, Christopher Bubela, Tania
<a href="#">PEGASUS: Personalized Genomics for Prenatal Aneuploidy Screening Using Maternal Blood</a>	Genome Quebec, Genome Br. Columbia	Rousseau, Francois Langlois, Sylvie
<a href="#">Personalized Cancer Immunotherapy</a>	Genome Quebec	Perreault, Claude Roy, Denis-Claude
<a href="#">Personalized Medicine in the Treatment of Epilepsy</a>	Genome Quebec	Cossette, Patrick Minassian, Berge Michaud, Jacques
<a href="#">Personalized Medicine Strategies for Molecular Diagnostics and Targeted Therapeutics of CVD</a>	Genome Quebec	Tardif, Jean-Claude Dubé, Marie-Pierre
<a href="#">Personalized Risk Stratification for Prevention and Early Detection of Breast Cancer</a>	Genome Quebec	Simard, Jacques Knoppers, Bartha
<a href="#">Personalized Treatment of Lymphoid Cancer: British Columbia as Model Province</a>	Genome British Columbia	Connors, Joseph Marra, Marco
<a href="#">Reducing Stroke Burden with Hospital-Ready Biomarker Test for Rapid TIA Triage</a>	Genome British Columbia	Penn, Andrew Borchers, Christoph
<a href="#">The Microbiota at the Intestinal Mucosa-Immune Interface: A Gateway for Personalized Health</a>	Ontario Genomics Institute	Stintzi, Alain Mack, David
<a href="#">Viral and Human Genetic Predictors of Response to HIV Therapies</a>	Genome British Columbia	Harrigan, Richard Montaner, Julio

**Objectives:** To demonstrate how genomics-based research can contribute to a more evidence-based approach to health and improving the cost-effectiveness of the health-care system. Specifically:

1. To develop an evidence base on how to assess and, where appropriate, integrate innovative diagnostics (including laboratory diagnostics and medical imaging) into health policy and practice.

2. To stimulate the discovery, validation, and translation of biomarkers, targets and genomic signatures for risk prevention and for diseases, which have the potential to improve the outcomes of therapeutic interventions by selecting tailoring of treatment choices to individual patient characteristics?
3. To foster the development and validation of diagnostics based on such biomarkers, targets and genomic signatures, and of innovative devices for the application to patient practice.

**Funding Period and FY14 Total:** FY2013-FY2016: \$149.8M (GenomeCanada, Canadian Institute for Health Research, regional genome centres, others), ~\$37.5M in FY14

**Current Intra-Program Working Groups:** *Learning Network in the process of being developed and will be funded by Genome Canada*

**Major Collaborations and Their Goals:** *Informatics Infrastructure for Genomics and Health (aligned with the Global Alliance for Genomics and Health and funded by Genome Canada and CIHR).*

**Resources and Tools Produced:** TBD

**Five Key Publications:** (to be added)

**Major Obstacles or Needs Encountered:**

<b>Major Obstacles or Needs</b>	<b>Approaches Implemented or Proposed to Overcome Obstacles</b>
Develop receptor capacity for technology pull (capacity for clinical and translational research)	Engage with the regional health authorities and provincial ministries of health (those that pay for health care delivery in Canada) to understand their needs and priorities
Involve the private sector	Create forums where industry players can be exposed to what is happening inside the projects
Educate and train healthcare professionals to be proficient users of the technology	CIHR to fund training networks as part of their Patient Oriented Research initiative
Ensure information systems are state of the art and harmonize e-patient records	Engage with the major actors in health informatics infrastructure development (in Canada several players are involved and the scene is fragmented). Align Canada more with the Global Alliance for Genomics and Health (Genome Canada and CIHR to fund specific activities to “:get our act together”
Increase the role of patients and advocacy groups in demanding evidence based medicine	Involve patients and advocacy groups within our projects (this is not done systematically as yet)
Apply robust technology assessments focused on improvement of clinical outcomes and economic benefit analyses	Create a learning network across the 17 project in the GAPH portfolio to create robust methodologies for HTA that develop concrete “value propositions”. Genome Canada will fund such a network that is in the process of being put together

## Genomic Medicine VIII – Summary of Related Program GGR

**Program Name and Website:** Genomics of Gene Regulation (GGR), <http://www.genome.gov/27561317>

### PIs and Funded Sites:

#### Projects (5):

Alexander Hoffmann, Ph.D. and Douglas Black, Ph.D.	University of California, Los Angeles
Christina Leslie, Ph.D. and Alexander Rudensky, Ph.D.	Memorial Sloan Kettering Cancer Center
Jeremy Luban, M.D. and Manuel Garber, Ph.D.	University of Massachusetts Medical School
Timothy Reddy, Ph.D.	Duke University
Michael Snyder, Ph.D.	Stanford University

#### Data Center, ENCODE DCC:

J. Michael Cherry	Stanford University
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### Objectives:

The goal of the Genomics of Gene Regulation (GGR) project is to develop better methods to construct predictive, accurate gene regulatory network models using genomic data. The ability to make accurate predictions from gene regulatory networks could support genomic medicine and precision medicine, by providing us one more tool to understand the consequences of genetic variation.

**Funding Period and FY14 Total:** FY15-17; FY14 total is \$0

**Current Intra-Program Working Groups:** None

**Major Collaborations and Their Goals:** No collaborations at this time

**Resources and Tools Produced:** None at present

**Five Key Publications:** None at present

### Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:

Major Obstacles and Needs	Approaches Considered or Proposed to Overcome Obstacles
NONE	

**NHGRI Program Director:** Mike Pazin

# Genomic Medicine VIII – Summary of Related Program GS-IT

Program Name and Website: **Genome Sequencing Informatics Tools (GS-IT)**

GS-IT Program: <http://www.genome.gov/27546195>

iSeqtools Portal: <http://iseqtools.org>

## PIs and Funded Sites:

Eric Banks	Broad Institute
Steve McCarroll	Harvard Medical School
Ali Torkamani	The Scripps Research Institute
Gabor Marth	University of Utah
Goncalo Abecasis	University of Michigan
Li Ding	Washington University in St. Louis
Ting Chen, Ewa Deelman	University of Southern California

## Objectives:

1. Develop researcher friendly sequence analysis tools and software for a broad community of scientist who rely on genomics
2. Access to these tools is democratized to provide easy access to useful analysis software to independent researchers
3. Invest in existing tools of known utility to make them robust, reliable, easy to use, and well-supported for easy adoption by researchers
4. Development of innovative strategies on the cloud to aid researchers achieve their goals
5. Deployment of interactive visualization methods to further democratize access to sequence analysis tools and software

**Funding Period and FY14 Total:** FY2012 - FY2016, \$4 M in FY14

**Current Intra-Program Working Groups:** Cloud Working Group

## Major Collaborations and Their Goals:

- Pilots with data producers
  - Centers for Mendelian Genomics – complex indels
  - Undiagnosed Disease Program – data sharing

## Resources and Tools Produced:

Overview at iSeqTools Portal: <http://iseqtools.org>

Most relevant to genomic medicine:

1. SG-ADVISER CNV: copy-number variant annotator/interpreter: <https://genomics.scripps.edu/ADVISER/>
2. GenomeSTRIP CNV: copy-number variant predictor pipeline: <http://www.broadinstitute.org/software/genomestrip/>
3. IOBIO: web-based, real-time, genomic analysis (see video: <http://iobio.io>)
4. CombineVariants GKNO pipeline: Accurate, graph-based merging and evaluation of variant calls: <http://gkno.me/>
5. Large-scale cloud-enabled sequence processing: GATK, GotCloud, GKNO, GenomeVIP

## Five Key Publications:

1. Erikson, G. A., Deshpande, N., Kesavan, B. G. & Torkamani, A. "SG-ADVISER CNV: copy-number variant annotation and interpretation" *Genet. Med.* (2014) [Torkamani]
2. Handsaker, R. E. *et al.* "Large multiallelic copy number variations in humans" *Nat. Genet.* **47**, 296–303 (2015) [McCarroll]
3. Miller, C. A., Qiao, Y., DiSera, T., D'Astous, B. & Marth, G. T. "bam.iobio: a web-based, real-time, sequence alignment file inspector" *Nat. Methods* **11**, 1189 (2014) [Marth]
4. Jun, G., Wing, M.K., Abecasis, G.R., Kang, H.M. An efficient and scalable analysis framework for variant extraction and refinement from population scale DNA sequence data" *Genome Research* (2015) doi: 10.1101/gr.176552.114 [Abecasis]
5. Van der Auwere G. A. *et al.* "From FastQ data to high-confidence variant calls: The Genome Analysis Toolkit Best Practices pipeline" *Current Protocols in Bioinformatics* (2013) doi: 10.1002/0471250953.bi1110s43 [Banks]

*Major Obstacles or Needs Encountered:*

<b>Major Obstacles or Needs</b>	<b>Approaches Implemented/Proposed to Overcome Obstacles</b>
Challenge for researchers to install and use genome sequence analysis software with large-scale data.	Three-pronged approach to combine robust software engineering, good support of users, and innovation using cloud and app frameworks.
Different tools for variant calling do not produce the same results and it is hard to know what are the true SNVs.	The best, most reliable predictions for a particular gene can be selected using local graph realignment (see GKNO CombineVariants)
Finding and interpreting CNVs and SVs is even more challenging than SNVs.	Powerful new tools for detecting and annotating pathogenic impact of CNVs and SVs.
Researchers often want to focus on a gene or sets of genes of interest but are forced to contend with massive BAM files.	The IOBIO app framework provides rapid, interactive visualizations and is easy to create new lightweight, intuitive apps for analysis.

*NHGRI Program Official:* Heidi Sofia (PO) and Alex Lee (Analyst)

# Genomic Medicine VIII – Summary of Related Program GTEx

Program Name and Website: Genotype Tissue Expression Project (GTEx), <https://commonfund.nih.gov/GTEx/index>

## PIs and Funded Sites:

<b>Biospecimen Source Sites</b>	
John Lonsdale and Jeffery Thomas	National Disease Res Interchange
Harold Magazine and Mark Kartub	Science Care, Inc.
Barbara Foster	Roswell Park Cancer Institute
<b>Comprehensive Biospecimen Resource</b>	
Scott Jewell	Van Andel Research Institute
<b>Comprehensive Data Resource</b>	
Nancy Roche	Leidos Biomedical Research, Inc.
<b>Laboratory, Data Analysis and Coord Center</b>	
Kristin Ardlie and Gad Getz	Broad Institute
<b>Enhancing GTEx (RFA-RM-12-009)</b>	
Joshua Akey	University of Washington
Andrew Feinberg	Johns Hopkins University
Manolis Kellis	MIT
Jin Billy Li	Stanford University
Brandon Pierce	The University of Chicago
Michael Snyder and Hua Tang	Stanford University
John Stamatoyannopoulos	University of Washington
Barbara Stranger	The University of Chicago
<b>Statistical Meth (RFA-RM-09-006 &amp; RN-12-019)</b>	
Jun Liu	Harvard University
Christopher Brown and Barbara Englehardt	University of Pennsylvania
Donald Conrad	Washington University
Nancy Cox and Dan Nicolae	The University of Chicago
Emmanouil Dermitzakis, Carlos Bustamante, Roderic Guigo, Mark McCarthy	University of Geneva
Chiara Sabatti	Stanford University
Matthew Stephens	The University of Chicago
Fred Wright and Andrew Nobel	North Carolina State University

## Objectives:

1. Provide a comprehensive atlas of human gene expression and a list of cis- and trans- eQTLs across multiple human tissues.
2. Establish a researcher-accessible tissue bank for future genomic studies and a data portal for accessing summary data.
3. Develop a standardized post-mortem biospecimen collection, storage, and analysis pipeline.
4. Explore the effectiveness of the donor consent process to address concerns and expectations of participants in the study.

**Funding Period and FY14 Total:** FY10-FY17, \$20 million per year

## Current Intra-Program Working Groups:

1. Analysis Working Group (AWG)
2. 13 AWG subgroups: eQTLs, Sex Bias and Sex specificity Analyses, Rare Regulatory Variants, Genotype, LOF, transcriptome, GWAS, Functional and Network Analysis, Imprinting, ASE, Benchmarking, RNA editing, Pathogen.

3. Enhanced GTEx (eGTEx) WG
4. Principal Investigator/Program Officer WG
5. Publication WG

**Major Collaborations and Their Goals:**

- Encyclopedia of DNA Elements (ENCODE), <https://www.encodeproject.org/>; collection of 4 donors using GTEx infrastructure
- Single Cell Analysis Program (SCAP), <https://commonfund.nih.gov/Singlecell/index>; using single cell analysis on GTEx brain tissues

**Resources and Tools Produced:**

1. GTEx Consortium Data Portal: <http://www.gtexportal.org/home/>
2. dbGaP: [http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000424.v4.p1](http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000424.v4.p1)

**Five Key Publications:**

1. The GTEx Consortium. The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. Science. 8 May 2015; Vol 348 no. 6235 pp 648-660. DOI: 10.1126/science.1262110.
2. Melé et al. The human transcriptome across tissues and individuals. Science. 8 May 2015; Vol 348 no. 6235 pp 660-665. DOI: 10.1126/science.aaa0355
3. Rivas et al. Effect of predicted protein-truncating genetic variants on the human transcriptome. Science. 8 May 2015; Vol 348 no. 6235 pp 666-669. DOI: 10.1126/science.1261877.
4. Baran et al. The landscape of genomic imprinting across diverse adult human tissues. Genome Research. 8 May 2015. DOI: 10.1101/gr.192278.115
5. Pierson et al. Sharing and specificity of co-expression networks across 35 human tissues. 2015. PLOS Comput Biol. 11(5):e1004220.

**Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:**

<b>Major Obstacles and Needs</b>	<b>Approaches Considered/Proposed to Overcome Obstacles</b>
Data is controlled access	Ability to re-contact next-of-kin to request open access authorization
Lack of centralized iPS cell repository	Changed consent to allow iPS cell creation and comparison with matching tissues
Return of incidental findings (IF) affecting organ recipients and/or family members	Creation of a committee to evaluate return of IF to organ recipients. Guidelines on returning genomic results relevant to family members.

**NHGRI Program Officials:** Simona Volpi and Jeff Struewing



# Genomic Medicine VIII – Summary of Related Program H3AFRICA

Program Name and Website: Human Heredity and Health in Africa (H3Africa) <http://h3africa.org/>

## PIs and Funded Sites:

<b>Clement Adebamowo</b>	<b>Institute of Human Virology, Abuja, Nigeria</b>
Dwomoa Adu and Akinlolu Ojo	University of Ghana Medical School, Accra, Ghana and University of Michigan, Ann Arbor, Michigan, U.S.A.
Gabriel Anabwani; Moses Joloba; Adeodata Kekitiinwa; Graeme Mardon; Wata Mpoloka; and Oathokwa Nkomazana	Botswana-Baylor Children's Clinical Centre of Excellence, Gaborone, Botswana; Makerere University College of Health Sciences, Kampala, Uganda; Baylor College of Medicine Children's Foundation, Kampala, Uganda; Baylor College of Medicine, Houston, Texas, U.S.A.; University of Botswana Faculty of Biological Sciences, Gaborone, Botswana; and University of Botswana Faculty of Health Sciences, Gaborone, Botswana
Mayowa Ojo Owolabi and Bruce Ovbiagele	University of Ibadan, Ibadan, Nigeria and Medical University of South Carolina, Charleston, South Carolina, U.S.A.
Michele Ramsay and Osman Sankoh	University of Witwatersrand & NHLS, Johannesburg, South Africa and International Network for the Demographic Evaluation of Populations and Their Health in Developing Countries (INDEPTH), Accra, Ghana
Enock Matovu	Makerere University, Kampala, Uganda
Bongani Mayosi	University of Cape Town, Cape Town, South Africa
Ayesha Motala	University of KwaZulu-Natal, Durban, South Africa
<b>Dissou Affolabi</b>	<b>National Hospital for Tuberculosis and Pulmonary Diseases, Cotonou, Benin</b>
Gobena Ameni	Addis Ababa University, Addis Ababa, Ethiopia
Christian Happi	Redeemer's University, Redemption City, Nigeria
<b>Guida Landoure</b>	<b>University of Bamako, Bamako, Mali</b>
Mark Nicol	University of Cape Town, Cape Town, South Africa
Hugh-George Patterton	University of the Free State, Bloemfontein, South Africa
Dan Stein and Raj Ramesar	University of Cape Town, Cape Town, South Africa
Ambroise Wonkam	University of Cape Town, Cape Town, South Africa
Getnet Tadele	Addis Ababa University, Addis Ababa, Ethiopia
Alice Matimba, Lovemore Gwanzura and Rugare Kangwende,	University of Zimbabwe College of Health Sciences, Harare, Zimbabwe and Africa University Clinical Research Centre, Mutare, Zimbabwe
Keymanthri Moodley	Stellenbosch University Tygerberg Campus
Jantina de Vries	University of Cape Town, Cape Town, South Africa
Nicola Mulder	University of Cape Town, Cape Town, South Africa
Ute Jentsch	Wits Health Consortium (Pty) Ltd, Johannesburg, South Africa
Alash'le Abimiku	Institute of Human Virology, Abuja, Nigeria
Moses Joloba	Makerere University College of Health Sciences, Kampala, Uganda

## Objectives:

To facilitate a contemporary research approach to the study of genomics and environmental determinants of common diseases with the goal of improving the health of African populations. To accomplish this, the H3Africa Initiative aims to contribute to the development of the necessary expertise among African scientists, and to establish networks of African investigators.

#### *Funding Period and FY14 Total:*

FY12-FY16 (FY18 for Biorepositories); \$67,737,884 (plus \$15,000,000+ from Wellcome Trust)

#### *Major Collaborations and Their Goals:*

- This initiative is collaboration between NIH Common Fund, Wellcome Trust, and the African Society of Human Genetics

#### *Five Key Publications:*

1. Research capacity. Enabling the genomic revolution in Africa. H3Africa Consortium, Science. 2014 Jun 20;344(6190):1346-8. PMID: 24948725
2. Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. Gire SK, Goba A, Andersen KG, Sealfon RS, Park DJ, Kanneh L, Jalloh S, Momoh M, Fullah M, Dudas G, Wohl S, Moses LM, Yozwiak NL, Winnicki S, Matranga CB, Malboeuf CM, Qu J, Gladden AD, Schaffner SF, Yang X, Jiang PP, Nekoui M, Colubri A, Coomber MR, Fonnies M, Moigboi A, Gbakie M, Kamara FK, Tucker V, Konuwa E, Saffa S, Sellu J, Jalloh AA, Kovoma A, Koninga J, Mustapha I, Kargbo K, Foday M, Yillah M, Kanneh F, Robert W, Massally JL, Chapman SB, Bochicchio J, Murphy C, Nusbaum C, Young S, Birren BW, Grant DS, Scheffelin JS, Lander ES, Happi C, Gevao SM, Gnirke A, Rambaut A, Garry RF, Khan SH, Sabeti PC. Science. 2014 Sep 12;345(6202):1369-72. PMID: 25214632
3. A call for policy action in sub-Saharan Africa to rethink diagnostics for pregnancy affected by sickle cell disease: differential views of medical doctors, parents and adult patients predict value conflicts in Cameroon. Wonkam A, Hurst S. OMICS. 2014 Jul;18(7):472-80. PMID: 24754796
4. The H3Africa policy framework: negotiating fairness in genomics. de Vries J, Tindana P, Littler K, Ramsay M, Rotimi C, Abayomi A, Mulder N, Mayosi BM. Trends Genet. 2015 Mar;31(3):117-9. doi: 10.1016/j.tig.2014.11.004. Epub 2015 Jan 15. PMID: 25601285
5. A quick guide for building a successful bioinformatics community. Budd A, Corpas M, Brazas MD, Fuller JC, Goecks J, Mulder NJ, Michaut M, Ouellette BF, Pawlik A, Blomberg N. PLoS Comput Biol. 2015 Feb 5;11(2):e1003972. PMID: 25654371

*NHGRI Program Officials:* Jennifer Troyer, Ken Wiley, Ebony Madden, Mark Guyer, Jeff Struewing

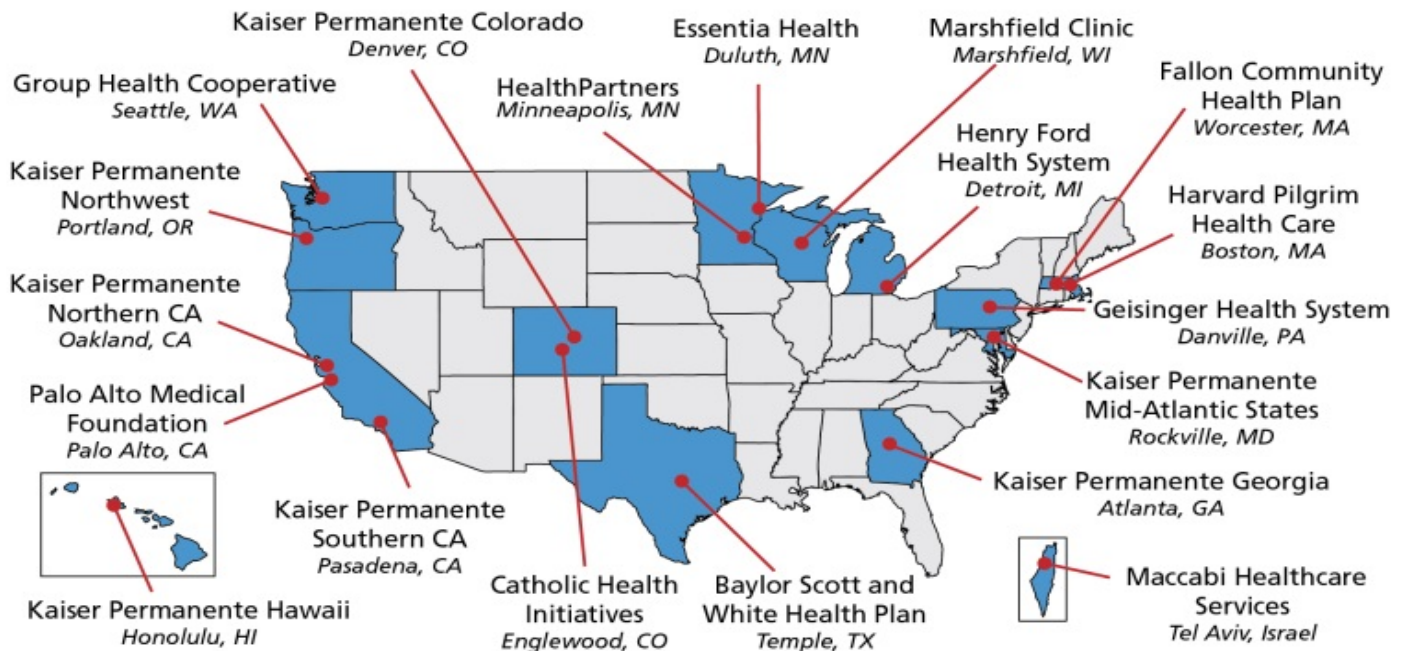
## Genomic Medicine VIII – Summary of Related Program HMORN

*Program Name and Website:* HMO Research Network (Will be renamed the Health Care Systems Research Network in August 2015) <http://www.hmoresearchnetwork.org/en/>

### *Pls and Funded Sites:*

The HMORN is composed of health care delivery systems that are involved in health services research. It is funded through contributions of member sites. It does not have any grant funding as an entity, in fact is not even incorporated as an entity. For grants and contracts it functions more as a clearinghouse where an HMORN site will take the lead and involve other sites based in desired expertise and willingness to participate. Very little (if any) of the research portfolio facilitated by the HMORN is relevant to basic science discovery research and understanding. However, several members are also members of NHGRI funded networks like eMERGE, so there is some experience with this from some sites.

## HMO Research Network Members



### *Objectives:*

1. Fostering multidisciplinary research collaboration
2. Disseminating information about the research interests, resources, and capabilities of our sites and researchers
3. Sharing methodologies, best practices, and consultative expertise across research centers
4. Leveraging our unique assets, especially defined populations and comprehensive data

*Funding Period and FY14 Total:* N/A

### *Current Intra-Program Working Groups:*

At present only the Genomic Medicine Scientific Interest Group is of specific interest to NHGRI activities. The mission of the Genomics SIG is to bring together HMORN researchers working in genomics to facilitate collaboration and research on the translation of genomic technologies into clinical practice to improve the health of our members. Over 40 individuals currently belong to the SIG with almost all HMORN sites represented.

### *Major Collaborations and Their Goals:*

1. Electronic Medical Records and Genomics (eMERGE) Network: <https://emerge.mc.vanderbilt.edu/> (4 HMORN members participate in the network, Essentia Health, Group Health Cooperative, Marshfield Clinic and Geisinger Health System)
2. There are no other currently funded efforts in genomics that have been brokered through the HMORN.
3. Currently exploring collaboration with the NHGRI genomic medicine working group.

### **Resources and Tools Produced:**

1. The Virtual Data Warehouse (VDW). The VDW is a series of dataset standards and automated processes in place at each of the HMORN sites. The VDW allows SAS programs written at one HMORN Site to be run against all the others quickly, and with a minimum of site-specific customization.  
<http://www.hmoresearchnetwork.org/en/About/Data/>  
[http://www.hmoresearchnetwork.org/en/Tools%20&%20Materials/VDW/VDWScientists/HMORN\\_VDW-Questions-and-Answers.pdf](http://www.hmoresearchnetwork.org/en/Tools%20&%20Materials/VDW/VDWScientists/HMORN_VDW-Questions-and-Answers.pdf)
2. Centralized IRB policies and governance. The HMORN has an IRB ceding process to support streamlined review. A Standard Operating Procedure (SOP) documents policies and procedures for ceded IRB review of research between HMORN sites. The SOP covers data-only, epidemiologic, and health services research performed in the HMORN for which participant informed consent and HIPAA authorization may or may not be required. The HMORN's IRB ceding process cannot be used for prospective biomedical research studies of human participants involving drugs, devices or biologics. <http://www.hmoresearchnetwork.org/en/Tools%20&%20Materials/IRB/>
3. We are in the process of developing a catalogue of biospecimen resources, consents and genomic research projects at each of the HMORN sites. Current estimates of resources: Over 300,000 samples are currently available across the HCSRNHMORN. Projected enrollment efforts across HCSRNHMORN sites over the next 5 years is anticipated to provide over 1,000,000 samples connected to health-related and genomic data.

### **Five Key Publications:**

1. Steiner JF, Paolino AR, Thompson EE, Larson EB. Sustaining Research Networks: the Twenty-Year Experience of the HMO Research Network. EGEMS (Wash DC). 2014 Jun 9;2(2):1067. eCollection 2014. PMC4371441
2. Paolino AR, Lauf SL, Pieper LE, Rowe J, Vargas IM, Goff MA, Daley MF, Tuzzio L, Steiner JF. Accelerating regulatory progress in multi-institutional research. EGEMS (Wash DC). 2014 Jul 10;2(1):1076. doi: 10.13063/2327-9214.1076. eCollection 2014. PMC4371517
3. Ross TR, Ng D, Brown JS, Pardee R, Hornbrook MC, Hart G, Steiner JF. The HMO Research Network Virtual Data Warehouse: A Public Data Model to Support Collaboration. EGEMS (Wash DC). 2014 Mar 24;2(1):1049. doi: 10.13063/2327-9214.1049. eCollection 2014. PMC4371424
4. Holmes JH, Brown J, Hennessy S, Lane K, Langer RD, Lazarus R, O'Connor PJ, Strom BL, Platt R. Developing a distributed research network to conduct population-based studies and safety surveillance. AMIA Annu Symp Proc. 2008 Nov 6:973. PMID: 18999251

### **Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:**

At present genomic medicine research is in the early stages of exploration by the HMORN. Our next step is to have representatives of the NHGRI Genomic Medicine Working Group present to the HMORN Genomic SIG to begin to determine if there is value in collaboration. We think the HMORN sites could be a good test bed for testing the generalizability of genomic medicine implementation projects funded by NHGRI. Also, since most HMORN sites have payers as part of the system, this could be a venue to carry forward some of the action items from the GM 3 Payers meeting.

# Genomic Medicine VIII – Summary of Related Program IOM

Program Name and Website:

## IOM Roundtable on Translating Genomic-Based Research for Health

<https://www.iom.edu/Activities/Research/GenomicBasedResearch.aspx>

### Roundtable Members:

Geoffrey Ginsburg, Duke University, *Co-Chair*  
Sharon Terry, Genetic Alliance, *Co-Chair*

Robert B. Darnell, The Rockefeller University  
Mary V. Relling, St. Jude Children's Research Hospital  
David L. Veenstra, University of Washington  
Naomi Aronson, BC BS  
Euan Angus Ashley, AHA  
Paul R. Billings, Life Technologies  
Bruce Blumberg, Kaiser Permanente  
Philip J. Brooks, NCATS  
John Carulli, Biogen IDEC  
Ann Cashion, NINR  
Michael J. Dougherty, ASHG  
W. Gregory Feero, JAMA  
Andrew N. Freedman, NCI  
Jennifer L. Hall, ISCTR  
Richard J. Hodes, NIA  
Katherine Johansen Taber, AMA  
Muin J. Khoury, CDC

Gabriela Lavezzari, PhRMA  
Thomas Lehner, NIMH  
Debra Leonard, CAP  
Elizabeth Mansfield, FDA  
Laura K. Nisenbaum, Eli Lilly and Company  
Robert M. Plenge, Merck  
Victoria M. Pratt, AMP  
Ronald Przygodzki, VA  
Nadeem Sarwar, Eisai, Inc.  
Joan A. Scott, HRSA  
Sam Shekar, Northrop Grumman  
Michael S. Watson, ACMG  
Daniel Wattendorf, USAF  
Catherine A. Wicklund, NSGC  
Robert S. Wildin, NHGRI  
Janet K. Williams, AAN

### Objectives:

The Roundtable on Translating Genomic-Based Research for Health provides both a mechanism and a venue for interested parties from government, academia, industry, and other stakeholder groups to explore and implement strategies for improving health through the translation of genomics and genetics research findings into medicine, public health, education, and policy. The primary purpose of the Roundtable is to foster dialogue across sectors and among stakeholders, and to identify, illuminate, and develop potential solutions for critical scientific and policy issues related to the translation of genomic discoveries. Since its establishment in 2007, the Roundtable has organized and hosted 25 meetings and 21 public workshops and published 20 workshop summary reports. Through its meetings and workshops, the Roundtable has provided strategic thinking around some of the most paramount issues facing the field of genomics including: return of incidental results from genome sequencing; drivers for system-wide adoption of genomic medicine programs; challenges and opportunities for integrating genomic information in the electronic medical record; ethical considerations in conducting genomics research; data sharing; the use of genomic sequencing information in health care decision making; current DNA sample collection practices; genomics as an enabler of a new drug development pipeline paradigm; improving graduate education and continuing health professional education in genetics; and creating genomics-enabled learning health care systems as a means to drive research and patient care.

**Funding Period and FY14 Total:** N/A

### Current Working Groups:

The work of the **Implementation Group** seeks to enable the use of genomic information for the benefit of individuals and communities for wellness, health care, and/or research.

The **Evidence for Policy and Practice Group** aims to enable stakeholder decision making by identifying evidence gaps, prioritizing translational research, and exploring innovative mechanisms of evidence generation.

The role of the **Discovery Group** is to facilitate actionable translation of genetic knowledge into discovery of novel and targeted therapeutics.

### Major Collaborations and Their Goals:

1. **Displaying and Integrating Genetic Information Through the EHR (DIGITizE).**
  - Mission: To enable the standardized representation of genetic and genomic information in the electronic health record through a collaborative, multi-stakeholder approach that will ensure interoperability and usability of the data in the clinic and for research applications.
  - <https://www.iom.edu/DIGITIZE>
2. **Global Genomic Medicine Collaborative (G2MC).**
  - Mission: To identify opportunities and foster global collaborations for enabling the demonstration of value and the effective use of genomics in medicine.
  - <https://www.iom.edu/G2MC>

### Selected List of Resources and Tools Produced:

1. DIGITizE- minimum list of data elements for somatic and germline genetic test reports, model for data flow across the EHR information ecosystem, provider and EHR vendor implementation guides for pharmacogenomic use cases, and formation of pilot project partner units for phase I of use case implementation.
2. Roundtable Discussion Paper Series: Analytic Validity of Genomic Testing, Variant Validity (Selected vs. General Population); Clinical Utility: Informing Treatment Decisions by Changing the Paradigm; Evaluating the Clinical Utility of Genomic Variants Derived from Next-Generation Sequencing for Opportunistic Disease Screening and Risk Assessment: Evidence Gaps and Priorities; The Cost-Effectiveness of Clinical Sequencing, Return of Anticipated and Incidental Results from Next-Generation Sequencing: Implications for Providers and Patients; Return of Anticipated and Incidental Results from Next-Generation Sequencing: Implications for Providers and Patients; and Implementation of Pharmacogenomics: Evidence Needs.

### Five Key Publications:

1. [Genomics-Enabled Learning Health Care Systems: Gathering and Using Genomic Information to Improve Patient Care and Research](#) (2015)
2. [Assessing Genomic Sequencing Information for Health Care Decision Making](#) (2014)
3. [Improving the Efficiency and Effectiveness of Genomic Science Translation](#) (2014)
4. [Integrating Large-Scale Genomic Information into Clinical Practice](#) (2011)
5. [Generating Evidence for Genomic Diagnostic Test Development](#) (2011)
6. (For a complete list, see: <https://www.iom.edu/Reports.aspx?Activity={E731F2C3-E58F-4524-99DC-AFAF029998BD}>)

### Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:

Major obstacles exist to implementing genomic medicine, including the existence of significant gaps in the evidence base that inhibit stakeholder decision-making and an absence of genomic data standards to represent genetic information within the EHR. The Roundtable working groups and Action Collaboratives are focusing their efforts on addressing these and other issues to provide insight on possible solutions to overcome them.

**IOM Program Staff:** Adam Berger, Sarah Beachy, and Meredith Hackmann

# Genomic Medicine VIII – Summary of Related Program ISCC

Bob Wildin, MD; GHB Chief, DPCE, NHGRI; NIH Co-chair of ISCC

## Overview of the ISCC

The purpose of the Inter-Society Coordinating Committee for Practitioner Education in Genomics (ISCC, <http://www.genome.gov/27554614>) is to facilitate interactions among professional societies that will enhance their efforts to increase the understanding and expertise of practitioners in applying genomic results to clinical care. The committee is charged with improving genomic literacy of physicians and other practitioners and enhancing the practice of genomic medicine (that is, using an individual patient's genomic results in their clinical care) through sharing of educational approaches and joint identification of educational needs.

In its start-up phase, the ISCC focused primarily on physicians and dentists. The membership has since expanded to include nurses, pharmacists, and genetic counselors. The committee is open to expanding its membership to include more allied health practitioner groups, such as nurse practitioners and physician assistants.

The ISCC is currently supported by NHGRI staff and volunteers. Approaches to sustainability are under evaluation. The ISCC is led by a team of two healthcare professional co-chairs, one from NHGRI and the other from among the member organizations.

Current Co-Chairs: [Bob Wildin, MD](#)  
(January 2015 – present) Chief, Genomic Healthcare Branch, Division of Policy, Communications, and Education, National Human Genome Research Institute

[Ann Karty, MD](#)  
Medical Director for Continuing Medical Education, American Academy of Family Physicians

## Evolution of the ISCC and Products

The ISCC was formed in February 2013 in response to a recommendation from the NHGRI Genomic Medicine Working Group (<http://www.genome.gov/27549220>). The committee began as the Inter-Society Coordinating Committee for *Physician* Education in Genomics. The committee's membership has expanded to include professional societies for dentists, nurses, pharmacists, and genetic counselors and thus became the Inter-Society Coordinating Committee for *Practitioner* Education in Genomics.

ISCC leadership and members value the dissemination of foundational knowledge, resource information, and work products developed by ISCC working groups. The committee has published the following two journal articles in *Genetics in Medicine* (impact factor = 6.435). ISCC working groups are encouraged to create manuscripts highlighting their achievements.

1. Korf, B. et al. (2014). Framework for development of physician competencies in genomic medicine: report of the Competencies Working Group of the Inter-Society Coordinating Committee for Physician Education in Genomics. *Genetics in Medicine*, 16(11): 804-809.
2. Manolio, T., Murray, M., for the Inter-Society Coordinating Committee for Practitioner Education in Genomics. (2014). The growing role of professional societies in educating clinicians in genomics. *Genetics in Medicine*, 16(8): 571-572.

## Meetings

Meetings are held approximately semi-annually. The ISCC has held four in-person meetings and planning is underway for the January 14, 2016 event. The meetings provide an opportunity for members to exchange information, have group discussions, formulate opportunities for workgroup focus, hear about innovations in provider education, and network. Minutes and materials from each in-person meeting are posted on the website. There are also monthly conference calls for networking and progress updates.

## Working Groups

The ISCC initial four commissioned working groups has grown to seven. Each working group plays a key role in engaging medical professional societies, collecting and reviewing existing specialty-specific educational products

and competencies, and proposing strategies for establishing cross-specialty standards for resident training and practicing physician education programs in genomic-based medicine.

Working Group	Description and Activities
<b>Case Studies</b> <i>Chairs: Reed Pyeritz, Wendy Rubinstein</i>	Produced two highly structured, peer-reviewed cases as well as a Case Study template designed to guide development of new instructive cases: Mitochondrial DNA Mutation A1555G and Aminoglycoside-induced Hearing Loss, and Utilizing Family History to Identify Lynch Syndrome. The cases and template are posted on the ISCC website.
<b>Competencies (work completed)</b>	Published five EPAs that comprise a basic set of genomic skills: Family History; Genomic Testing; Treatment Based on Genomic Results; Somatic Genomics; and Microbial Genomic Information. EPAs are “entrustable professional activities” defined by medical educators as “... those professional activities that together constitute the mass of critical elements that operationally define a profession.”
<b>Education for Insurer Staff</b> <i>Chair: Suzanne Belinson, Bob Wildin</i>	Explores the genomics educational needs of staff that process providers’ authorization requests for genetic and genomic testing with insurance companies. Plans a pilot educational webinar series to provide staff with knowledge for efficient throughput and resource management, followed by expansion to several of the largest insurers.
<b>Educational Products</b> <i>Chair: Kristin Weitzel, Jean Jenkins</i>	Members identify and peer-review submitted genomic education resources and map them to provider competencies. They are then disseminated through the Genetics and Genomics Competency Center website (G2C2, <a href="http://g-2-c-2.org/">http://g-2-c-2.org/</a> ), started in 2004 and housing >900 educational resources. The G2C2 Physician’s portal, with 77 resources, was launched June 2014.
<b>Specialty Boards</b> <i>Chair: Miriam Blitzer, Jean Jenkins</i>	Evaluate and encourage sharing interaction between Specialty Societies and Specialty Boards to increase representation of genomic-medicine evaluation in specialty board exams and maintenance of certification activities.
<b>Innovative Approaches to Education</b> <i>Chair: Richard Haspel, Teri Manolio</i>	Explore ways to further innovative provider educational programs, such as flipped classroom, developed by a current ISCC member to be replicated with other ISCC members’ specialties and provider groups. Exemplar: <a href="http://www.pathologylearning.org/trig/resources">http://www.pathologylearning.org/trig/resources</a> .
<b>Language of Genomics</b> <i>Chair: Suzanne Belinson, Carla Easter</i>	Influence provider-patient communications by studying the largely scientific structure of genomics language and offering alternative constructions and imagery that is commonly consumable by patients. This group involves the industry partner Blue Cross Blue Shield Association.



## Genomic Medicine VIII – Summary of Related Program LSAC

**Program Name and Website:** The Large-Scale Genome Sequencing and Analysis Centers (LSAC) program is one of four components of the larger NHGRI Genome Sequencing Program (<http://www.genome.gov/10001691>), which also includes the Centers for Mendelian Genomics (CMG), the Clinical Sequencing Exploration Centers (CSER), and the Genome Sequencing Informatics Tools (GS-IT) program.

### PIs and Funded Sites:

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**LSAC:**

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Richard Gibbs/Eric Boerwinkle	Baylor College of Medicine
Eric Lander/Stacey Gabriel	Broad Institute of MIT and Harvard
Richard Wilson	Washington University, St. Louis

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### Objectives:

1. All four GSP elements were initiated together, based on scientific considerations that were evident four or five years ago, with the strategic intent to cover multiple areas related to discovery, community use, and clinical use of sequence data.
2. The scope and purpose of the LSAC component is to provide large-scale genome sequence datasets and analyses in pursuit of multiple long-term goals of high significance to a broad range of the biomedical research community. These include:
  - identifying somatic mutations associated with cancer
  - characterizing variation underlying complex disease,
  - pursuing questions about basic genomic variation and how it relates to biology and disease
  - exploring basic questions in comparative and evolutionary genomics through sequencing many organismal genomes
  - adding value to model organism research by providing reference genome sequences,

These “discovery” projects are carried out in collaboration with independent study investigators and through collaborations with other IC’s on multiple concurrent projects (see below); part of the purpose of the LSAC program is to identify and foster these collaborations towards the general scientific program goals.

3. An additional key LSAC goal is to advance the state of the art in genomic sequencing through technological and methodological improvements, including improvements in analysis and project design; cost and quality improvements; developing novel applications, etc.

### Funding Period and FY14 Total:

- FY2011-2015; FY14 total \$77M (LSAC), not including supplements from collaborating IC’s. The entire GSP will be restructured in 2016 (see GSP website for new solicitations).

### Current Intra-Program Working Groups:

- All active working groups are in the context of the LSAC Projects (see below); LSAC members also participate in some intra-GSP working groups

### Major Collaborations and Their Goals:

*Below are listed several prominent, large collaborative projects undertaken by the LSAC. All are collaborations to which the LSAC contributes genome sequencing capacity and project design and analysis expertise. A detailed list of all projects (including sub-projects)—both collaborative and not--- can be found at <http://www.genome.gov/27557963>*

1. The Cancer Genome Atlas (with NCI); LSAC was the primary provider of data for TCGA, and partners for study design and analysis. (<http://cancergenome.nih.gov/>)
2. The 1000 Genomes Project (with multiple international collaborators; <http://www.1000genomes.org/>)
3. The Alzheimer’s Disease Sequencing Project (ADSP; with NIA) <https://www.niagads.org/adsp/content/home>
4. The Autism Sequencing Consortium (ASC; with NIMH); [http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study\\_id=phs000298.v2.p2](http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000298.v2.p2)
5. The T2D-Genes Consortium (with NIDDK; <http://t2d-genes.sph.umich.edu/>)

6. The TOP-Med consortium (direct co-funding from NHLBI; <https://www.nhlbiwgs.org/>)
7. The Genome Reference Consortium <http://www.ncbi.nlm.nih.gov/projects/genome/assembly/grc/>

*Resources and Tools Produced:*

- See Projects and detailed Project list; datasets (for case/control; references, etc.) are available

*Five Key Publications:*

1. The ENCODE Project Consortium (2012) An integrated encyclopedia of DNA elements in the human genome. Nature 489(7414): e11247. [doi:10.1038/nature11247](https://doi.org/10.1038/nature11247)
2. The ENCODE Project Consortium (2011) A User's Guide to the Encyclopedia of DNA Elements (ENCODE). PLoS Biol 9(4): e1001046. [doi:10.1371/journal.pbio.1001046](https://doi.org/10.1371/journal.pbio.1001046)
3. ENCODE Project Consortium, *et al* (2007) Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature Jun 14;447(7146):799-816. [doi:10.1038/nature0587](https://doi.org/10.1038/nature0587)
4. The ENCODE Project Consortium (2004) the ENCODE (ENCyclopedia Of DNA Elements) Project. Science Oct 22; 306:636-640).

*Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:*

<b>Major Obstacles and Needs</b>	<b>Approaches Considered or Proposed to Overcome Obstacles</b>
Drawing too bright a line between discovery and clinical efforts is likely to miss significant opportunities in both areas.	Building direct continuity or collaboration between clinical and discovery efforts; routing clinical participants into discovery research programs (including broad consent for general research use); improved clinical phenotyping data for use in discovery projects; improved data repositories/records/informatics tools/etc. to encourage ready uptake and use of clinical data in research discovery efforts, and conversely rapid uptake of variant discovery results by clinical data resources; many of these are features of some proposals for "Precision Medicine".

*NHGRI Program Officials:* Adam Felsenfeld (LSAC); Lu Wang (CMG); Carolyn Hutter (TCGA and CSER); Lucia Hindorff (CSER); Heidi Sofia (GS-IT).

# Genomic Medicine VIII – Summary of Related Program MVP

## Program Name and Website:

Million Veteran Program (MVP) - <http://www.research.va.gov/mvp/>

## PIs and Funded Sites:

### VA Central Office

Timothy O’Leary, M.D., Ph.D.; Sumitra Muralidhar, Ph.D.; Ronald Przygodzki, Ph.D.; Grant Huang, Ph.D., M.P.H.; James Breeling, M.D.; Jennifer Moser, Ph.D., Kendra Schaa, Kristina Hill

### MVP Steering Committee and Subcommittees

**Steering Committee:** John Concato, M.D., M.S., M.P.H., Co-Chair; J. Michael Gaziano, M.D., M.P.H., Co-Chair; Rayan Al Jurdi, M.D.; James L. Breeling, M.D.; Louis Fiore, M.D., M.P.H., ex-officio; John B. Harley, M.D., Ph.D.; Elizabeth Hauser, Ph.D.; Grant Huang, M.P.H., Ph.D. Ex-Officio; Phil Tsao, Ph.D.; Janet D. Crow, ORD Liaison; Philip D. Harvey, Ph.D.; Timothy J. O’Leary, M.D., Ph.D., Ex-Officio; Stephen G. Waxman, M.D., Ph.D.; Peter W. F. Wilson, M.D.

**Access Policy Subcommittee:** John, Concato, M.D., M.S., M.P.H., (Chair); Sumitra Muralidhar, Ph.D. (VACO Liaison); Michael Hart, M.D.; Fred Wright, M.D.; John (Tom) Callaghan M.D., Ph.D.; J. Michael Gaziano, M.D., M.P.H.; Saiju Pyarajan, Ph.D.; Carl Grunfeld, M.D., Ph.D.

**Chemical Analysis Subcommittee:** Philip Tsao, Ph.D. (Chair); Steven Schichman, M.D., Ph.D.; Saiju Pyarajan, Ph.D.; Chris Corless, M.D., Ph.D.; Robert Lundsten; Jenny Moser, Ph.D.; Sunil Ahuja, M.D.

**Recruitment Subcommittee:** Rayan Al Jurdi, M.D. (Chair); Jennifer Deen, Hermes Florez, M.D., Ph.D., M.P.H.; Amy Kilbourne, Ph.D., M.P.H.; Frank Lederle, M.D.; Kendra Schaa, ScM, C.G.C. (ORD Liaison); Ralph Heussner; Stephen Herring.

**Phenotyping and Epidemiology Subcommittee:** J. Michael Gaziano, M.D., M.P.H. (Chair); Jenny Moser, Ph.D.; Seth Eisen, M.D., M.Sc.; David Gagnon, M.D., Ph.D.; Saiju Pyarajan, Ph.D.; Jonathan Nebeker, M.D., M.S.; Denise Hynes, Ph.D., M.P.H., R.N.; Matthew Samore, M.D.

### Boston Coordinating Center (MAVERIC)

J. Michael Gaziano, M.D., M.P.H.; Stacey Whitbourne, Ph.D., Jennifer Deen; Colleen Shannon, M.P.H.; Kelly Cho, Ph.D.; Xuan-Mai Nguyen, Ph.D.; David Gagnon, M.D., Ph.D.; Donald Pratt; Lindsay Hansen, M.P.A.; Keri Hannagan, M.P.H.; Derrick Morin

### West Haven Coordinating Center (CERC)

John Concato, M.D., M.P.H.; Mihaela Aslan, Ph.D.; Peter Guarino, Ph.D.; Daniel Anderson; Rene LaFleur; Lesley Mancini, M.B.A.; John Russo; Cindy Cushing; Vales Jean-Paul; Fred Sayward; Louis Piscitelli; Donna Cavaliere

### VA Central Biorepository - Boston

Mary Brophy, M.D., M.P.H.; Donald Humphries, Ph.D.; Geetha Sugumaran, Ph.D.; Deborah Govan; Christine Govan

### Genomic Information System for Integrated Sciences (GenSIS) - Boston

Louis Fiore, M.D., M.P.H.; Saiju Pyarajan, Ph.D.; Tony Chen, Ph.D.; Edmund Peirce; Paul Hseih, Ph.D.; Luis Selva, Ph.D.; Beth Katcher; Robert Hall, M.P.H.; Weijia Mo; Felicia Fitzmeyer; Anahit Aleksanyan

### MVP Information Center – Canandaigua, NY

Annie Correa; Melissa Juhl; George Barzac III; Liam Cerveney; Anne Van Patten; Jonathan Martinez; Eileen Loh-Fontier; Jessica Marino

### MVP Local Site Investigators

VA HEALTHCARE SYSTEM UPSTATE NEW YORK: Laurence Kaminsky, Ph.D. NEW MEXICO VA HEALTHCARE SYSTEM: Jose Canive, M.D. ATLANTA VA MEDICAL CENTER: Farooq Amin, M.D. VA MARYLAND HEALTH CARE SYSTEM: Alan Shuldiner, M.D.; Miriam Smyth, Ph.D. BAY PINES VA HEALTHCARE SYSTEM: Rachel Mcardle, Ph.D.; Theodore Strickland, M.D., M.P.H., F.C.A.P. EDITH NOURSE ROGERS MEMORIAL VETERANS HOSPITAL: John Wells, Ph.D. BIRMINGHAM VA MEDICAL CENTER: Louis Dell’Italia, M.D.; Jasvinder Singh, M.D., M.P.H. VA BOSTON HEALTHCARE SYSTEM: Ildiko Halasz, M.D. VA WESTERN NEW YORK HEALTHCARE SYSTEM: Junzhe Xu, M.D.; Ali A. El Solh, M.D., M.P.H. CENTRAL TEXAS VETERANS HEALTH CARE SYSTEM: Keith Young, Ph.D. RALPH H. JOHNSON VA MEDICAL CENTER: Mark Hamner, M.D. CINCINNATI VA MEDICAL CENTER: John B. Harley, M.D., Ph.D. LOUIS STOKES CLEVELAND VA MEDICAL CENTER: Eric Konicki, M.D.; Curtis Donskey, M.D. WM. JENNINGS BRYAN DORN VA MEDICAL CENTER: Kathryn Sue Haddock, R.N., Ph.D. VA NORTH TEXAS HEALTH CARE SYSTEM: Padmashri Rastogi, M.D. VA EASTERN COLORADO HEALTH CARE SYSTEM: Robert Keith, M.D. DURHAM VA MEDICAL CENTER: William Yancy, M.D. N. FL/S. GA VETERANS HEALTH

SYSTEM: Peruvemba Sriram, M.D. HAMPTON VA MEDICAL CENTER: Marinell Mumford, Ph.D.; Pran Iruvanti, D.O., Ph.D. EDWARD HINES, JR. VA HOSPITAL: Salvador Gutierrez, M.D. MICHAEL E. DEBAKEY VA MEDICAL CENTER: Rayan Al Jurdi, M.D.; Laura Marsh, M.D. RICHARD ROUDEBUSH VA MEDICAL CENTER: John Callaghan, M.D., Ph.D.; Thomas Sharp, M.D. KANSAS CITY VA MEDICAL CENTER: Prashant Pandya, D.O.; Thomas Demark, M.D. VA EASTERN KANSAS HEALTH CARE SYSTEM: Mary Oehlert, Ph.D. CENTRAL ARKANSAS VETERANS HEALTH CARE SYSTEM: K. David Straub, M.D., Ph.D.; Sue Theus, Ph.D. VA LOMA LINDA HEALTHCARE SYSTEM: Ronald Fernando, M.D. VA LONG BEACH HEALTHCARE SYSTEM: Timothy Morgan, M.D. VA GREATER LOS ANGELES HEALTH CARE SYSTEM: Agnes Wallbom, M.D., M.S. WILLIAM S. MIDDLETON MEMORIAL VETERANS HOSPITAL: Robert Striker, M.D., Ph.D. VA MAINE HEALTHCARE SYSTEM: Ray Lash, M.D., F.A.C.P. VA MEDICAL CENTER MANCHESTER: Nora Ratcliffe, M.D. VA NEW YORK HARBOR HEALTHCARE SYSTEM: Scott Sherman, M.D., M.P.H. MEMPHIS VA MEDICAL CENTER: Richard Childress, M.D.; Marshall Elam, M.D., Ph.D. MIAMI VA HEALTH CARE SYSTEM: Hermes Florez, M.D., Ph.D. CLEMENT J. ZABLOCKI VA MEDICAL CENTER: Jeff Whittle, M.D., M.P.H. MINNEAPOLIS VA HEALTH CARE SYSTEM: Frank A. Lederle, M.D. VA TENNESSEE VALLEY HEALTHCARE SYSTEM: Adriana Hung, M.D., M.P.H.; Jeffrey Smith, M.D., Ph.D. CENTRAL WESTERN MASSACHUSETTS HEALTHCARE SYSTEM: Kristin Mattocks, Ph.D., M.P.H. ORLANDO VA MEDICAL CENTER: Kenneth Goldberg, M.D.; Adam Golden, M.D. VA PALO ALTO HEALTH CARE SYSTEM: Philip Tsao, Ph.D. PHILADELPHIA VA MEDICAL CENTER: Darshana Jhala, M.D.; Kyong-Mi Chang, M.D. PHOENIX VA HEALTH CARE SYSTEM: Samuel Aguayo, M.D. VA PITTSBURGH HEALTH CARE SYSTEM: Elif Sonel, M.D.; Gretchen Haas, Ph.D. PORTLAND VA MEDICAL CENTER: David Cohen, M.D. RICHMOND VA MEDICAL CENTER: Michael Godschalk, M.D. W.G. (BILL) HEFNER VA MEDICAL CENTER: Robin Hurley, M.D. VA SALT LAKE CITY HEALTH CARE SYSTEM: Laurence Meyer, M.D., Ph.D.; Vickie Venne, M.S. SOUTH TEXAS VETERANS HEALTH CARE SYSTEM: Sunil Ahuja, M.D.; Jacqueline Pugh, M.D. VA SAN DIEGO HEALTHCARE SYSTEM: Gwen Anderson, Ph.D., R.N. VA CARIBBEAN HEALTHCARE SYSTEM: Carlos Rosado-Rodriguez, M.D.; William Rodriguez, M.D. VA PUGET SOUND HEALTH CARE SYSTEM: Edward Boyko, M.D.; Karin Nelson, M.D. OVERTON BROOKS VA MEDICAL CENTER: Ronald Washburn, M.D. ST. LOUIS VA HEALTH CARE SYSTEM: Michael Rauchman, M.D. JAMES A. HALEY VETERANS' HOSPITAL: Stephen Mastorides, M.D.; Lauren Deland, R.N., M.P.H. SOUTHERN ARIZONA VA HEALTH CARE SYSTEM: Ronald Schiffman, M.D.; Stephen Thomson, M.D. TUSCALOOSA VA MEDICAL CENTER: Lori Davis, M.D.; Patricia Pilkinton, M.D. WASHINGTON DC VA MEDICAL CENTER: Ayman Fanous, M.D. VA CONNECTICUT HEALTH CARE SYSTEM: Daniel Federman, M.D. WHITE RIVER JUNCTION VA MEDICAL CENTER: Brooks Robey, M.D.

### **Objectives:**

The main objective of MVP is to improve understanding of how genetic characteristics, behaviors, and environmental factors combine to affect health. Ultimately, the intent is to enhance the care of the Veteran patient population by providing a framework for scientifically valid and clinically relevant genomic medicine. Veterans who volunteer provide a blood sample for biobanking and responses to questionnaires; they also consent to allow access to clinical data from VA electronic health records and other sources such as NDI, CMS and DOD, and to being re-contacted by MVP staff for (potential) further data collection or future studies.

**Funding Period and FY14 Total:** Continuously funded since 2010

**Current Intra-Program Working Groups:** See Committee structure above.

### **Major Collaborations and Their Goals:**

The establishment of the resources and several funded test projects are conducted largely by VA Investigators and other employees and others at affiliated academic institutions. Two large-scale test projects are in the area of mental health.

### **Resources and Tools Produced:**

- MVP baseline and lifestyle questionnaire
- Automated sample processing facility
- Automated biospecimens storage facility
- Data base with 380,000 enrollees
- Phenomics core
- Informatics core

**Five Key Publications:** Design paper submitted

*Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:*

<b>Major Obstacles and Needs</b>	<b>Approaches Considered or Proposed to Overcome Obstacles</b>
Low cost sequencing and other omics	Contract or collaboration
Low cost processing of sequence data	Contract or collaboration
Upgraded internal HPC secured in VA	Contract
Cloud computing environment	Hosted by outside vender via contract
System to enable access by many users	Built by internal informatics team and/or contracted

*NCI Program Officials:* VA Program Official: Dr. Tim O’Leary, CRADO, VA Central Office, Washington, DC

## Genomic Medicine VIII – Summary of Related Program NCI-ALCHEMIST

Program Name and Website: ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) ([http://dctd.cancer.gov/MajorInitiatives/NCI-sponsored\\_trials\\_in\\_precision\\_medicine.htm](http://dctd.cancer.gov/MajorInitiatives/NCI-sponsored_trials_in_precision_medicine.htm))

PIs and Funded Sites: up to 2400 clinical sites thru National Clinical Trials Network, led by ECOG-ACRIN (Bob Comis MD), ALLIANCE (Monica Bertagnolli MD) Two CLIA accredited lab sites for sequencing EGFR and for FISH for ALK translocation; Center for Cancer Genomics and TCGA Sequencing and Characterization centers for exploratory genomics (whole exome, RNA seq, whole genome)

### Objectives:

Observational trial for those 85% or so that do not have activating EGFR mutations or ALK rearrangements. This research trial studies genetic testing in screening patients with stage IB-IIIa non-small cell lung cancer that has been or will be removed by surgery. Studying the genes in a patient's tumor cells may help doctors select the best treatment for patients that have certain genetic changes. If patients have EGFR activating mutations or ALK rearrangements they will be offered participation in the relevant randomized phase 3 trial of standard treatment with or without the relevant targeted treatment:

- Screen 6000-8000 patients
- Epidemiology/exposure questionnaire
- reprofile at relapse
- collection of plasma for ctDNA
- Public resource for research community with genomic characterization tied to detailed clinical annotation, epidemiologic data, long term outcome data (Genomic Data Commons)

**Funding Period and FY14 Total:** *not a grant, but uses several grants and contract*

**Current Intra-Program Working Groups:** Steering committee; IDSC

**Major Collaborations and Their Goals:**

NCTN; NCORP (NCI supported clinical trials groups) NCI supported cancer centers

**Resources and Tools Produced:** none to date

### Five Key Publications:

1. Gerber DE, Oxnard GR, Govindan R. ALCHEMIST: Bringing genomic discovery and targeted therapies to early-stage lung cancer. *Clin Pharmacol Ther.* 2015 May;97(5):447-50
2. Abrams J, Conley B, Mooney M et al. National Cancer Institute's Precision Medicine Initiatives for the new National Clinical Trials Network. *Am Soc Clin Oncol Educ Book.* 2014:71-6. doi: 10.14694/EdBook\_AM.2014.34.71.

### Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:

Major Obstacles and Needs	Approaches Considered or Proposed to Overcome Obstacles
NONE	

**NCI Program Officials:** Jeff Abrams MD; Shakun Malik MD; & Meg Mooney MD

## Genomic Medicine VIII – Summary of Related Program NCI-MATCH

Program Name and Website: NCI-MATCH (Molecular analysis for therapy choice) will be posted to [clinicaltrials.gov](http://clinicaltrials.gov) once activated ([http://dctd.cancer.gov/MajorInitiatives/NCI-sponsored\\_trials\\_in\\_precision\\_medicine.htm](http://dctd.cancer.gov/MajorInitiatives/NCI-sponsored_trials_in_precision_medicine.htm))

PIs and Funded Sites: up to 2400 clinical sites thru National Clinical Trials Network, led by ECOG-ACRIN (Bob Comis MD) Four CLIA accredited lab sites for NGS: Yale (Jeff Sklar MD), MDAnderson CancerCenter (Stan Hamilton MD), Massachusetts General Hospital (A. John Iafrate MD) and the Molecular Characterization Laboratory at the Frederick National Laboratory for Cancer Research (PM Williams PhD)

### Primary Objective:

- To evaluate the proportion of patients with objective response (OR) to targeted study agent(s) in patients with advanced refractory cancers/lymphomas.

### Secondary Objectives

- To evaluate the proportion of patients alive and progression free at 6 months of treatment with targeted study agent in patients with advanced refractory cancers/lymphomas.
- To evaluate time until death or disease progression.
- To identify potential predictive biomarkers beyond the genomic alteration by which treatment is assigned or resistance mechanisms using additional genomic, RNA and protein-based assessment platforms.

**Funding Period and FY14 Total:** *not a grant, but uses several grants and contracts*

### Current Intra-Program Working Groups:

Steering committee; Agents/Genes working group; Samples/sequencing working group; Informatics working group; Incidental findings/ethics working group; Imaging working group; Regulatory working group

### Major Collaborations and Their Goals:

NCTN; NCORP (NCI supported clinical trials groups) NCI supported cancer centers

**Resources and Tools Produced:** *none to date*

### Five Key Publications:

1. Conley BA, Doroshow JH. Molecular analysis for therapy choice: NCI MATCH. [Semin Oncol](#). 2014 Jun;41(3):297-9.
2. Kummar S, Williams PM, Lih C-H et al. Application of molecular profiling in clinical trials for advanced metastatic cancer. [J Natl Cancer Inst](#). 2015; 107(4) online

### Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:

Major Obstacles and Needs	Approaches Considered or Proposed to Overcome Obstacles
NONE	

**NCI Program Officials:** *Barbara Conley MD; Jeff Abrams MD; & Alice Chen MD*

## Genomic Medicine VIII – Summary of Related Program PAGE

*Program Name and Website:* Population Architecture using Genomics and Epidemiology (PAGE) Consortium, <https://pagestudy.org/>

### *PIs and Funded Sites:*

Christopher Haiman, Loic Le Marchand	University of Southern California / Multiethnic Cohort Study
Ruth Loos	Mount Sinai School of Medicine / Institute for Personalized Medicine (IPM) BioMe Biobank
Kari North	University of North Carolina, Chapel Hill / Genetic Epidemiology of Causal Variants Across the Life Course (CALiCo)
Charles Kooperberg	Fred Hutchinson Cancer Research Center/ Women's Health Initiative
Tara Matisse, Steve Buyske	Rutgers University / Coordinating Center
Kim Doheny, Jane Romm	Centers for Inherited Disease Research (genotyping)

### *Objectives:*

1. Examine putative causal genetic variants across approximately 100,000 African Americans, Asian Americans, American Indians, European Americans, Hispanic Americans, and Native Hawaiians from four studies representing seven large U.S.-based cohorts with extensive data on a range of traits and disease relevant to human health (PAGE 1).
2. Provide support for investigators to sample and assess genomic variation from over 50,000 well-phenotyped individuals of non-European (EA) ancestry and disseminate the resulting data to form a population resource that will expand understanding of ancestral differences in genomic disease associations (PAGE 2).

*Funding Period and FY14 Total:* FY2008-FY2016, \$7.47M (FY2014)

### *Current Intra-Program Working Groups:*

1. Analysis
2. Anthropometrics
3. Array design and samples
4. CHD/ECG
5. Clinically relevant variants
6. Hypertension/kidney
7. Inflammation
8. Lifestyle/reproduction
9. Lipids
10. Type 2 diabetes

### *Major Collaborations and Their Goals:*

- Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA): design of MEGA array (see below)

### *Resources and Tools Produced:*

1. Multi-Ethnic Genotyping Array (MEGA): Illumina genotyping array featuring common and rare variation selected for ancestrally diverse populations ([http://www.cidr.jhmi.edu/supported/20140729\\_MEGA\\_CustomerFAQ\\_to%20\(3\)\\_EDITED\\_JMR.pdf](http://www.cidr.jhmi.edu/supported/20140729_MEGA_CustomerFAQ_to%20(3)_EDITED_JMR.pdf))
2. dbGaP submissions (<http://www.ncbi.nlm.nih.gov/gap?term=PAGE%5BStudy%20Name%5D>)

### *Five Key Publications:*

1. Matisse TC, et al. The Next PAGE in understanding complex traits: design for the analysis of Population Architecture Using Genetics and Epidemiology (PAGE) Study. 2011; Am J Epidemiol 174, 849-859. PMID 21836165.
2. Gong, J, et al. Fine Mapping and Identification of BMI Loci in African Americans. 2013; Am J Hum Genet; 93(4):661. PMID 24094743.
3. Carlson CS, et al. Generalization and dilution of association results from European GWAS in populations of non-European ancestry: the PAGE study. 2013; PLoS Biol. 11(9):e1001661. PMID 24068893.
4. Park SL, et al. Association of the FTO obesity risk variant rs8050136 with percentage of energy intake from fat in multiple racial/ethnic populations: the PAGE study. 2013; Am J Epidemiol. 178(5):780. PMID 23820787.
5. Buyske S, et al. Evaluation of the metabochip genotyping array in African Americans and implications for fine mapping of GWAS-identified loci: the PAGE study. 2012; PLoS One 7, e35651. PMID 22539988.



*Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:*

<b>Major Obstacles and Needs</b>	<b>Approaches Considered/Proposed to Overcome Obstacles</b>
Integrate ancestrally diverse individuals into genomic medicine research	Focus on recruiting, analyzing, and communicating with diverse individuals and their healthcare providers. Build on extant collections of well-characterized and ancestrally diverse cohorts for personalized medicine research.
Improve identification and interpretation of clinically relevant variants for ancestrally diverse individuals	Be aware of differences in allele frequencies of clinically relevant variants among ancestral populations, and highlight when such frequencies are not known.
Facilitate collection and standardization of large-scale phenotyping data derived from heterogeneous sources	Learn from and contribute to existing phenotype harmonization efforts. Broaden efforts to harmonize phenotypes across multiple modalities (e.g, mHealth, EHR, surveys). Facilitate collaboration among large cohorts with heterogeneous sources of phenotype data.

*NHGRI Program Officials:* Lucia Hindorff

# Genomic Medicine VIII – Summary of Related Program PCORnet

## Program Name and Website:

PCORnet (PCORI funded initiative): <http://www.pcornet.org/>

Includes 11 Clinical Data Research Networks (CDRNs), 18 Patient Powered Research Networks (PPRNs), and a Coordinating Center (Harvard, Duke; CO-PIs Richard Platt and Adrian Hernandez)

## PIs and Funded Sites:

### CDRNs:

CDRN Name	Lead Organization	Principal Investigator
ADVANCE	Oregon Community Health Information Network	Jennifer DeVoe
CAPriCORN	The Chicago Community Trust	Terry Mazany
Great Plains Collaborative	University of Kansas Medical Center	Lemuel Waitman
Louisiana Clinical Data Research Network	Louisiana Public Health Institute	Anjum Khurshid
Mid-South CDRN	Vanderbilt University	Russell Rothman
NYC-CDRN	Weill Medical College of Cornell University	Rainu Kaushal
PEDSNet	The Children's Hospital of Philadelphia	Christopher Forrest
PORTAL	Kaiser Foundation Research Institute	Elizabeth McGlynn
pSCANNER	University of California, San Diego	Lucila Ohno-Machado
PZATH	University of Pittsburgh	Rachel Hess
SCIHLS	Harvard University	Kenneth Mandl

### PPRNs:

Organization	PI	Condition	Proposed PPRN Population Size
Accelerated Cure Project for Multiple Sclerosis	Robert McBurney	Multiple Sclerosis	20,000
American Sleep Apnea Association	Susan Redline	Sleep Apnea	50,000
Cincinnati Children's Hospital Medical Center	Peter Margolis	Pediatric Crohn's Disease and Ulcerative Colitis	15,000
COPD Foundation	Richard Mulanski	Chronic Obstructive Pulmonary Disease	50,000
Crohn's and Colitis Foundation of America	R. Ballour Sartor	Inflammatory Bowel Disease (Crohn's disease and ulcerative colitis)	30,000
Global Healthy Living Foundation	Seth Ginsberg	Arthritis (rheumatoid arthritis, spondyloarthritis), musculoskeletal disorders (osteoporosis), and inflammatory conditions (psoriasis)	50,000
Massachusetts General Hospital	Andrew Nierenberg	Major Depressive Disorder (MDD) and Bipolar Disorder (BP)	50,000
Univ of California, San Francisco	Mark Pletcher	Cardiovascular health	100,000
University of South Florida	Rebecca Sutphen	Hereditary Breast and Ovarian Cancer (HBOC)	17,000

Organization	PI	Condition	Proposed PPRN Population Size
ALD Connect, Inc	Florian Eichler	Adrenoleukodystrophy	3,000
Arbor Research Collaborative for Health	Bruce Robinson	Primary Nephrotic Syndrome (Focal Segmental Glomerulosclerosis [FSGS], Minimal Change Disease [MCD], and Membranous Nephropathy [MN] Multiple Sclerosis	1,250
Duke University	Laura Schanberg	Juvenile Rheumatic Disease	9,000
Epilepsy Foundation	Janice Beulow	Aicardi Syndrome, Lennox-Gastaut Syndrome, Phelan-McDermid Syndrome, Hypothalamic Hamartoma, Dravet Syndrome, and Tuberous Sclerosis	1,500
Genetic Alliance, Inc	Sharon Terry	Alstrom syndrome, Dyskeratosis congenital, Gaucher disease, Hepatitis, inflammatory breast cancer, Joubert syndrome, Klinefelter syndrome and associated conditions, Metachromatic leukodystrophy, Pseudoxanthoma elasticum (PXE), Psoriasis	50- 50,000
Immune Deficiency Foundation	Kathleen Sullivan	Primary Immunodeficiency Diseases	1,250
Parent Project Muscular Dystrophy	Holly Peay	Duchenne and Becker muscular dystrophy	4,000
Phelan-McDermid Syndrome Foundation	Megan O'Boyle	Phelan-McDermid Syndrome	737
University of Pennsylvania	Peter Merkel	Vasculitis	500

## Objectives:

1. **Create** a secure national research resource that will enable teams of health researchers, patients, and their partners to work together on researching questions of shared interest
2. **Utilize** multiple rich data sources to support research, such as electronic health records, insurance claims data, and data reported directly by patients
3. **Engage** patients, clinicians & health system leaders throughout the research cycle from idea generation to implementation
4. **Support** observational and interventional research studies that compare how well different treatment options work for different people
5. **Enable** external partners to collaborate with PCORI-funded networks
6. **Sustain** PCORnet resources for a range of research activities supported by PCORI and other sponsors

## Funding Period and FY14 Total:

PCORI has committed over \$250 million to date towards PCORnet including:

### PHASE I: Initial 18 months (January 2014-July 2015)

11 CDRNs at \$7 million each = \$77 million

18 PPRNs at \$1 million each = \$18 million

Coordinating Center at ~ \$12 million

### PHASE II: 36 months (~ July 2015-July 2018)

13 CDRNs at ~\$8.75 million each = \$114 million

22 PPRNs at ~\$1 million each = \$22 million  
 Coordinating Center at ~ \$14 million

**TRIALS**

ADAPTABLE (ASA TRIAL): \$14 million  
 Obesity Observational Trials: \$9 million

**Major Collaborations and Their Goals:**

1. FDA Mini-Sentinel/Sentinel Network: Similar common data model and participation of CDRNs in Sentinel network.
2. Emerge: Sharing Computable phenotypes on the PheKB website
3. CTSA Consortium: Use of IRBshare, ACTA, REDCap, and other CTSA consortia tools

**Resources and Tools Produced:**

1. Development of PCORnet Common Data Model
2. Tools for electronic identification and contact of patients using REDCap including e-consent, and electronic survey via web or mobile technology
3. Integration of PROMIS measures into REDCap
4. Development of network-wide policies related to datasharing, IRB, and contracting

**Five Key Publications:**

1. Fleurence RL, Curtis LH, Califf RM, Platt R, Selby JV, Brown JS. Launching PCORnet, a national patient-centered clinical research network. *Journal of the American Medical Informatics Association : JAMIA*. 2014;21(4):578-582. doi:10.1136/amiajnl-2014-002747.
2. [PCORnet PPRN Consortium](#), [Daugherty SE<sup>1</sup>](#), [Wahba S<sup>1</sup>](#), [Fleurence R<sup>1</sup>](#), Patient-powered research networks: building capacity for conducting patient-centered clinical outcomes research. *J Am Med Inform Assoc*. 2014 Jul-Aug;21(4):583-6. doi: 10.1136/amiajnl-2014-002758. Epub 2014
3. Waitman LR, Aaronson LS, Nadkarni PM, Connolly DW, Campbell JR. The Greater Plains Collaborative: a PCORnet Clinical Research Data Network. *Journal of the American Medical Informatics Association : JAMIA*. 2014;21(4):637-641. doi:10.1136/amiajnl-2014-002756.
4. Rosenbloom, S. T., Harris, P., Pulley, J., Basford, M., Grant, J., DuBuisson, A., & Rothman, R. L. (2014). The Mid-South Clinical Data Research Network. *Journal of the American Medical Informatics Association : JAMIA*, 21(4), 627–632. doi:10.1136/amiajnl-2014-002745
5. Kho AN, Hynes DM, Goel S, et al. CAPriCORN: Chicago Area Patient-Centered Outcomes Research Network. *Journal of the American Medical Informatics Association : JAMIA*. 2014;21(4):607-611. doi:10.1136/amiajnl-2014-002827.

**Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:**

Major Obstacles and Needs	Approaches Considered or Proposed to Overcome Obstacles
Linkage of clinical EHR data to biorepository data	Use of de-identified data linkage (ex. BioVu). Need to address patient consent/privacy issues. Cost of additional genomic data.
Transformation of biorepository data into standardized data for PCORnet common data model	
Validation of phenotypes	Sharing of computable phenotypes via PheKB

## Genomic Medicine VIII – Summary of Related Program PGRN

Program Name and Website: Pharmacogenomics Research Network (PGRN),  
<http://pgrn.org/display/pgrnwebsite/PGRN+Home>

### PIs and Funded Sites:

Kenneth E. Thummel, Ph.D. and Wylie Burke, M.D. Ph.D.	NWAP: Pharmacogenetics in Rural and Underserved Population
Mark J. Ratain, M.D., Nancy J. Cox, Ph.D. M. Eileen Dolan, Ph.D.	PAAR: Pharmacogenomics of Anticancer Agents Research Group
Mary V. Relling, Pharm.D.	PAAR4Kids: Pharmacogenomics of Anticancer Agents Research in Children
Alan R. Shuldiner, M.D.	PAPI-2: Pharmacogenomics of Anti-Platelet Intervention-2 (PAPI-2) Study
Ronald M. Krauss, M.D.	PARC: Pharmacogenomics and Risk of Cardiovascular Disease
Dan M. Roden, M.D.	PAT: Pharmacogenomics of Arrhythmia Therapy
Julie A. Johnson, Pharm.D., Rhonda Cooper-DeHoff, Pharm.D.	PEAR: Pharmacogenomic Evaluation of Antihypertensive Responses
John R. Kelsoe, M.D.	PGBD: Pharmacogenomics of Mood Stabilizer Response in Bipolar Disorder
Scott T. Weiss, M.D., M.S., <a href="#">Kelan G. Tantisira</a> , M.D.	PHAT: Pharmacogenetics of Asthma Treatment
Soumya Raychaudhuri, M.D., and Michael Brenner, M.D.	PhRAT: Pharmacogenomics of Rheumatoid Arthritis Therapy
Kathleen M. Giacomini, Ph.D.	PMT: Pharmacogenetics of Membrane Transporters
Caryn Lerman, Ph.D., and Rachel Tyndale, Ph.D.	PNAT: Pharmacogenetics of Nicotine Addiction Treatment
Richard M. Weinshilboum, M.D., and Liewei Wang, M.D., Ph.D.	PPII: Pharmacogenetics of Phase II Drug Metabolizing Enzymes
Wolfgang Sadée, Dr.rer.nat.	XGEN: Expression Genetics in Drug Therapy

### Objectives:

The PGRN is a network of scientific groups whose vision is to lead discovery and advance translation in genomics, to enable safer and more effective drug therapies. It has been supported since 2000 by the NIH. Its objectives are to:

- Conduct studies in basic, translational, and clinical science to advance the scientific vision
- Develop novel experimental methods and tools to solve pharmacogenomic problems
- Share data and, where feasible, biological samples in collaborations
- Foster cross-disciplinary teams for discovery and dissemination of new information
- Build effective partnerships and alliances with key stakeholders outside the PGRN
- Engage related disciplines to advance the application of pharmacogenomic knowledge
- Work together to make the network become more than the sum of the parts

**Funding Period and FY14 Total:** FY2000-FY2015, renewal under consideration: the network is undergoing transition; see the [PGRN Transition Plans](#)

### Current Intra-Program Working Groups:

- P-STAR – PGRN Statistical Analysis Resource
- PG-POP – PharmacoGenomic discovery and replication in very large patient POPulations
- PHONT – PGRN Ontology Network Resource
- Deep Sequencing Resources: BCM-HGSC (Baylor), UW-NEXTGEN – University of Washington, WU-NGS – Washington University

### Major Collaborations and Their Goals:

- PharmGKB – Pharmacogenomics Knowledge Base [www.pharmgkb.org/index.jsp](http://www.pharmgkb.org/index.jsp)
- PGRN-CGM – Pharmacogenomics Research Network & Center for Genomic Medicine Global Alliance (with RIKEN Center for Genomic Medicine) <http://pgrn.org/display/pgrnwebsite/PGRN-CGM+Profile>

- CPIC—Clinical Pharmacogenetics Implementation Consortium <https://www.pharmgkb.org/page/cpic>

**Resources and Tools Produced:**

1. PharmGKB – Pharmacogenomics Knowledge Base [www.pharmgkb.org/index.jsp](http://www.pharmgkb.org/index.jsp)
2. Translational Scholar Career Awards: <http://www.nigms.nih.gov/Research/SpecificAreas/PGRN/CTSAscholars/Pages/default.aspx>
3. Research in Progress Seminars: <http://pgrn.org/display/pgrnwebsite/PGRN-RIPS+Schedule>
4. Projects: PGRNSeq/PGxSeq Project; Translational Pharmacogenetics Project; Polygenic Modeling Project; RNA Seq Project <http://pgrn.org/display/pgrnwebsite/Network-wide+Projects>

**Five Key Publications:**

1. Diouf B, Crews KR, Lew G, Pei D, Cheng C, Bao J, Zheng JJ, Yang W, Fan Y, Wheeler HE, Wing C, Delaney SM, Komatsu M, Paugh SW, McCorkle JR, Lu X, Winick NJ, Carroll WL, Loh ML, Hunger SP, Devidas M, Pui C-H, Dolan ME, Relling MV, Evans WE. Association of an Inherited Genetic Variant with Vincristine-Related Peripheral Neuropathy in Children with Acute Lymphoblastic Leukemia. *JAMA*. 2015 Feb 24;313(8):815-23. PMID: 25710658
2. Perera MA, Cavallari LH, Limdi NA, Gamazon ER, Konkashbaev A, Daneshjou R, Pluzhnikov A, Crawford DC, Wang J, Liu N, Tatonetti N, Bourgeois S, Takahashi H, Bradford Y, Burkley BM, Desnick RJ, Halperin JL, Khalifa SI, Langaee TY, Lubitz SA, Nutescu EA, Oetjens M, Shahin MH, Patel SR, Sagreiya H, Tector M, Weck KE, Rieder MJ, Scott SA, Wu AH, Burmester JK, Wadelius M, Deloukas P, Wagner MJ, Mushiroda T, Kubo M, Roden DM, Cox NJ, Altman RB, Klein TE, Nakamura Y, Johnson JA. Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study. *Lancet*. 2013 Aug 31;382(9894):790-6. PMID: 23755828
3. International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, Eriksson N, Gage BF, Kimmel SE, Lee MT, Limdi NA, Page D, Roden DM, Wagner MJ, Caldwell MD, Johnson JA. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med*. 2009 Feb 19;360(8):753-64. PMID: 19228618
4. Mangravite LM, Engelhardt BE, Medina MW, Smith JD, Brown CD, Chasman DI, Mecham BH, Howie B, Shim H, Naidoo D, Feng Q, Rieder MJ, Chen YD, Rotter JI, Ridker PM, Hopewell JC, Parish S, Armitage J, Collins R, Wilke RA, Nickerson DA, Stephens M, Krauss RM. A statin-dependent QTL for GATM expression is associated with statin-induced myopathy. *Nature*. 2013 Oct 17;502(7471):377-80. PMID: 23995691
5. Long RM, Berg JM. What to expect from the pharmacogenomics research network. *Clin Pharmacol Ther*. 2011 Mar;89(3):339-41. PMID: 21326260

**Major Obstacles and Needs that Might be Facilitated by Genomic Medicine Research:**

Major Obstacles and Needs	Approaches Considered or Proposed to Overcome Obstacles
Ensuring that large clinical studies and trials, as well as cohorts being developed, are suitable for pharmacogenomics analysis.	The PGRN wants to provide specific, detailed guidance focused on drugs and drug response phenotypes to major national and international efforts that intend to create biospecimen banks and work with EMRs.

**NIH Program Official:** Rochelle Long (NIGMS) and program directors at other institutes, NIH

# Genomic Medicine VIII – Summary of Related Program PhenX

**Program Name and Website:** Consensus Measures for Phenotypes and eXposures (PhenX), <https://www.phenx.org>

## PIs and Funded Sites:

Carol Hamilton

RTI International

## Objectives:

1. Create a public and freely available web-based catalog of well-established, low-burden, standard measures and protocols for use in biomedical studies.
2. Encourage use of standard measures and establish common data elements to help researchers effectively collaborate, share data, and conduct cross-study analysis.
3. Enhance PhenX Toolkit content by identifying measures in new research domains (Rare Genetic Conditions, Obesity, Pregnancy and Pediatrics) and engage expert review panels to revisit existing measures to ensure they are still useful.
4. Extend PhenX capabilities through use of social media, inclusion of protocols in languages other than English, and extend mode of administration to include web-based data collection.
5. Collaborate with other groups that are producing collections of common data elements, e.g. PROMIS and NINDS CDE Program.
6. Engage and educate the scientific community through educational webinars and presentations at scientific conferences, workshops, and through publications.

## Funding Period and FY14 Total:

- FY2007-FY2014, \$3.2M in FY14 (\$1.2M from NHGRI; co-funding from NIDA and supplement funds provided by NHLBI, NIMH, and TRSP).

## Current Intra-Program Working Groups:

1. Obesity
2. Rare Genetic Conditions
3. Trans-NIH Collaborations adding depth to the PhenX Toolkit
  - a. Tobacco Regulatory Research (NIH Tobacco Regulatory Science Program supplement)
    - i. Areas of emphasis: social/cognitive, biobehavioral, agent, vector, environment
  - b. Mental Health Research (NIMH supplement)
    - i. Areas of emphasis: suicide, PTSD
  - c. Substance Abuse and Addiction (NIDA supplement)
    - i. Areas of emphasis: substance use, risk factors, community/comorbidities/outcomes
  - d. Sickle Cell Disease (NHLBI supplement)
    - i. Areas of emphasis: cardiovascular, pulmonary, and renal complications, neurology, quality of life and health services

## Major Collaborations and Their Goals:

- dbGaP: Mapping PhenX measures to all completed studies deposited in dbGaP. Mappings will enable easier identification of dbGaP studies that include similar measures/variables.
- REDCap: In collaboration with REDCap, PhenX is developing REDCap Instrument Zip files for all PhenX measures/protocols. This feature will improve visibility and uptake of PhenX measures by CTSA and other REDCap users.
- Genetic Alliance: A crowdsourcing effort aimed at getting clinicians to provide information about the use of PhenX measures for specific rare genetic conditions.
- NIH ICs: See "Intra-Program WGs" for more details about our partnerships across the NIH.

## Resources and Tools Produced:

1. [www.phenxtoolkit.org](http://www.phenxtoolkit.org): A database for standard measures related to complex diseases
2. [www.phenx.org](http://www.phenx.org): A web portal that provides information about the project, and supports project participants

## Five Key Publications:

1. Stover, P. J., Harlan, W., Hammond, J., Hendershot, T., & Hamilton, C. M. (2010). PhenX: a toolkit for interdisciplinary genetics research. *Current Opinion in Lipidology*, 21, 136–140.

2. Hamilton, C. M., Strader, L. C., Pratt, J., Maiese, D., Hendershot, T., Kwok, R., Hammond, J., Huggins, W., Jackman, D., Pan, H., Nettles, D., Beaty, T., Farrer, L., Kraft, P., Marazita, M., Ordovas, J., Pato, C., Spitz, M., Wagener, D., Williams, M., Junkins, H., Harlan, W., Ramos, E. & Haines, J. (2010) The PhenX Toolkit: Get the Most From Your Measures. *American Journal of Epidemiology*. 2011 Aug 1;174(3):253-60.
3. Pan, H., Tryka, K., Vreeman, D., Huggins, W., Phillips, M., Mehta, J., Phillips, J., McDonald, C., Junkins, H., Ramos, E. & Hamilton, C. M. (2012) Using PhenX Measures to Identify Opportunities for Cross-Study Analysis. *Human Mutation*, 33(5), 849-857.
4. McCarty, C.A., Berg, R., Rottscheit, C.M., Waudby, C.J., Kitchner, T., Brilliant, M., Ritchie, M.D. (2014) Validation of PhenX measures in the personalized medicine research project for use in gene/environment studies. *BMC Medical Genomics*, 7(3), doi:10.1186/1755-8794-7-3
5. McCarty, C.A., Huggins, W., Aiello, A.E., Bilder, R.M., Hariri, A., Jernigan, T.L., Newman, E., Sanghera, D.K., Strauman, T.J., Zeng, Y., Ramos, E.M., Junkins, H.A. (2014) PhenX RISING: real world implementation and sharing of PhenX measures. *BMC Medical Genomics*, 7(16), doi: 10.1186/1755-8794-7-16.

**Major Obstacles or Needs Encountered:**

<b>Major Obstacles or Needs</b>	<b>Approaches to Overcome Obstacles</b>
Identifying best approaches for harnessing social media and crowdsourcing methods	Piloting crowdsourcing projects; Considering developing a moderated "wiki" to obtain feedback on value and use of PhenX measures
Increasing visibility and use of PhenX measures	PhenX protocols available for upload to REDCap; Include PhenX protocols in languages other than English
Tracking use of PhenX measures in on-going studies	Implemented "Register Your Study" to identify studies using PhenX and allow PIs opportunities for cross-study collaboration
Monitoring PhenX Toolkit traffic and community awareness	Regularly monitor website statistics; challenging to gauge PhenX uptake through publications and citations

**NHGRI Program Officials:** Erin Ramos

# Genomic Medicine VIII – Summary of Related Program PMI

**Program Name and Website:** Precision Medicine Initiative, <http://www.nih.gov/precisionmedicine/>

## Precision Medicine Initiative Working Group:

Richard Lifton (co-chair)	Yale University
Bray Patrick-Lake (co-chair)	Duke University
Kathy Hudson (co-chair)	National Institutes of Health
Estaban Gonzalez Burchard	University of California, San Francisco
Tony Coles	Yumanity Therapeutics
Rory Collins	University of Oxford
Andrew Conrad	Google X
Josh Denny	Vanderbilt University
Susan Desmond-Hellman	Gates Foundation
Eric Dishman	Intel
Kathy Giusti	Multiple Myeloma Research Foundation
Sekar Kathiresan	Massachusetts General Hospital
Sachin Kheterpal	University of Michigan
Shiriki Kumanyika	University of Pennsylvania
Spero Manson	Colorado School of Public Health
P. Pearl O'Rourke	Partners Health Care System
Richard Platt	Harvard Pilgrim Health Care Institute
Jay Shendure	University of Washington
Sue Siegel	Ventures & Healthymagination
Robert Califf (ex officio)	Food and Drug Administration
Karen DeSalvo (ex officio)	Office of the National Coordinator for Health IT
Jo Handelsman (ex officio)	White House Office of Science and Technology Policy
Tim O'Leary (ex officio)	Department of Veterans Affairs
Terry Rauch (ex officio)	Defense Medical Research and Development Program

## Objectives:

1. Create a large research cohort of one million or more participants who choose to share many types of data (e.g., biomedical, behavioral, and lifestyle) to advance research
2. Use this research cohort to discover and quantify factors that contribute to illness, and test approaches that can preserve health and treat disease
3. Incorporate rapidly evolving technology into the cohort design
4. Involve participants in the planning, building, and management of the cohort
5. Identify and address gaps in existing policies on data privacy, security, and misuse that must be filled to support the PMI cohort

**Funding Period and FY14 Total:** FY2016 (proposed): \$130M

## Current Intra-Program Working Groups:

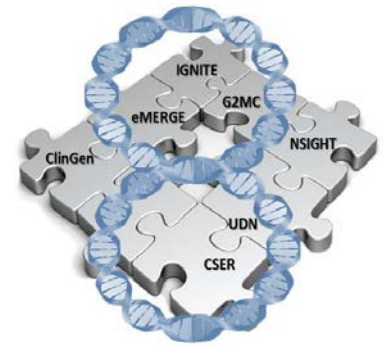
1. Cohorts and Epidemiology
2. Community Engagement and Health Disparities
3. Participant Engagement
4. Electronic Health Records
5. Mobile Technologies

## Five Key Publications:

1. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med.* 2015 Feb 26;372(9):793-5.



# Genomic Medicine VIII: NHGRI's Genomic Medicine Portfolio



June 8-9, 2015

Hilton - Washington DC / Rockville

1750 Rockville Pike, Rockville, MD 20852

(301) 468-1100

## HOTEL and TRAVEL LOGISTICS INFORMATION

### MEETING LOCATION:

Hilton – Washington DC / Rockville Hotel & Executive Meeting Center

1750 Rockville Pike

Rockville, MD 20852

Tel# (301) 468-1100 / Fax# (301) 468-0308

[www.washingtondcrockville.hilton.com](http://www.washingtondcrockville.hilton.com)

### AIRPORTS:

IAD - Washington Dulles - <http://www.metwashairports.com/dulles/208.htm>

DCA - Reagan National Airport - <http://www.metwashairports.com/reagan/1261.htm>

BWI - Baltimore / Washington International Airport - <http://www.bwiairport.com/en>

### DIRECTIONS TO THE HILTON – WASHINGTON DC / ROCKVILLE HOTEL & EXECUTIVE MEETING CENTER

#### (DCA) WASHINGTON NATIONAL AIRPORT DIRECTIONS

Depart from Ronald Reagan Washington National Airport, VA (0.6 mi.)

Take ramp right and follow signs for George Washington Memorial Pky North (11.7 mi.)

Take ramp right and follow signs for I-495 North (4.3 mi.)

Keep left onto I-270 N Spur (2.0 mi.)

Keep straight onto I-270 N (0.9 mi.)

Keep right to stay on I-270 N / Dwight D Eisenhower Hwy / I-270 Local Lanes / Washington National Pike (0.3 mi.)

At exit 4A, take ramp right for Montrose Road toward Tower Oaks Blvd (1.1 mi.)

Keep left onto Montrose Pkwy (1.2 mi.)

Take ramp left for MD-355 N / Rockville Pike (0.7 mi.)

Arrive at MD-355 N / Rockville Pike on the right (0.0 mi.)

Distance From Hotel: 22.9 mi. / Travel Time: 34 min.

Subway/Rail \$8.00 USD / Taxi \$55.00 USD – One Way

#### (IAD) WASHINGTON DULLES INTERNATIONAL AIRPORT DIRECTIONS

Depart Saarinen Circle toward Dulles Airport Access Rd (0.3 mi.)

Keep right onto Dulles Airport Access Rd (12.1 mi.)  
Take ramp right for VA-267 E toward Exit 18-19 / Richmond / Baltimore (1.1 mi.)  
At exit 18B, take ramp right for I-495 North toward Baltimore (7.5 mi.)  
Keep left onto I-270 N Spur (2.0 mi.)  
Keep straight onto I-270 N (0.9 mi.)  
Keep right to stay on I-270 N / Dwight D Eisenhower Hwy / I-270 Local Lanes / Washington National Pike (0.3 mi.)  
At exit 4A, take ramp right for Montrose Road toward Tower Oaks Blvd (1.1 mi.)  
Keep left onto Montrose Pkwy (1.2 mi.)  
Take ramp left for MD-355 N / Rockville Pike (0.7 mi.)  
Arrive at MD-355 N / Rockville Pike on the right (0.0 mi.)  
Distance from Hotel: 27.2 mi. / Travel Time: 35 min.  
Taxi \$60.00 USD – One Way

### **(BWI) BALTIMORE/WASHINGTON INTERNATIONAL DIRECTIONS**

Depart from Baltimore-Washington Thurgood Marshall International Airport, MD (0.5 mi.)  
Keep left onto I-195 W (1.9 mi.)  
At exit 2B, take ramp right for MD-295 South toward Washington (3.0 mi.)  
Take ramp right for MD-100 West toward Ellicott City (2.6 mi.)  
At exit 5A-B, take ramp right for I-95 South toward Washington (15.8 mi.)  
At exit 27, take ramp right for I-495 West toward Silver Spring (9.7 mi.)  
At exit 34, take ramp right for MD-355 toward Rockville / Wisconsin Ave / Bethesda (3.4 mi.)  
Arrive at MD-355 N / Rockville Pike on the right (0.0 mi.)  
Distance from Hotel: 36.8 mi. / Travel Time: 45 min.  
Taxi \$75.00 USD

### **METRO RAIL SYSTEM**

From Ronald Reagan National Airport only  
Take the Yellow Line towards Georgia Avenue/Petworth.  
Get off at Gallery Place/Chinatown, transfer station to the Red and Green Lines.  
Take the Red Line towards Shady Grove.  
Exit train at the Twinbrook Stop.  
The Hilton is located across the street from the station.

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## June 8-9, 2015

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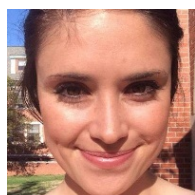


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