PANEL 4: METRICS OF PROGRESS AND MEASURES OF IMPACT INCLUDING COST-EFFECTIVENESS, OUTCOMES TO VALUE TO PAYERS, INFLUENCING QUALITY OF CARE THROUGH LEARNING HEALTHCARE SYSTEMS

Genomic Medicine VIII

This meeting will help NHGRI and its Genomic Medicine Working Group (GMWG) examine our genomic medicine portfolio in light of evolving scientific knowledge and opportunities.

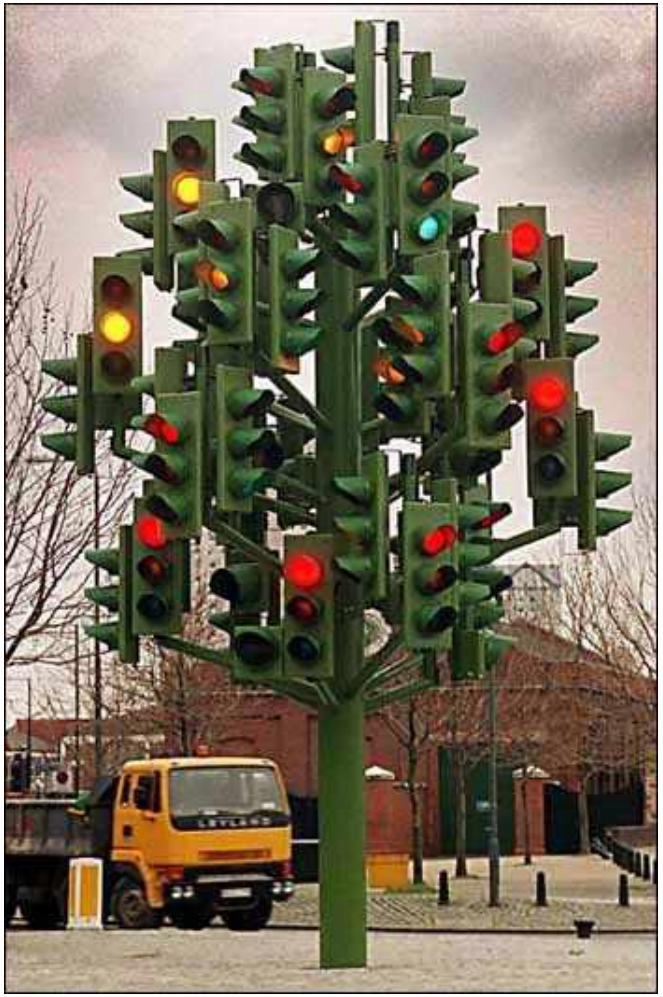
June 8-9, 2015
Rockville, Maryland

Panel Members

- Marc S. Williams, MD
  - Director, Genomic Medicine Institute, Geisinger Health System
  - eMERGE, NHGRI GMWG, G2MC, IOM EHR DIGITIZE, IGNITE (project scientific advisor)
- Erwin P. Bottinger, MD
  - Director Charles R. Bronfman Institute For Personalized Medicine
  - eMERGE, IGNITE
- Ruth Brenner, MD
  - Major USAF Medical Support Agency Medical Research & Innovations
  - IGNITE
- Warwick Anderson, B.Med.Sc., PhD
  - Secretary-General for Human Frontier Science Program in Strasbourg, France (almost)
  - G2MC

Charge?

- Metrics of Progress
- Measures of Impact
- Cost-effectiveness
- Outcomes of Value to Payers
- Quality of Care
- Learning Health Care Systems



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	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 sequence data into patient care			X	X	X								X				
Incorporate actionable variants into EMR, develop CDS			X	X	X								X				
Educate clinicians and patients on genomics in clinical care			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					
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 action ability 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

Assessing Outcomes

- eMERGE
  - Outcomes assessed in eMERGE-PGx project
  - Mostly focused on process outcomes for alerts and reminders
  - Clinical Outcomes
    - Small pilot project looking at impact of suspected pathogenic variants in 2 actionable genes on PGRNSeq chip (*SCN5A* and *KCNH2*)
      - Conclusion: Rare protein-altering variants were often identified in SCN5A and KCNH2, but arrhythmia or ECG phenotypes are infrequent. Approaches to pathogenicity assessment must consider the a priori probability of disease, and these approaches should be shared across laboratories
      - Manuscript under review NEJM
    - Study looking at clinical diagnosis of hemochromatosis in *HFE* C282Y homozygotes and C181Y/H63D compound heterozygotes
      - Conclusion: Based on the higher rate of HH diagnosis compared to prior studies, the high penetrance of iron overload, and the frequency of at risk genotypes, in addition to other suggested actionable adult onset genetic conditions, opportunistic screening for HFE C282Y homozygotes in patients with existing genomic data should be considered.
      - Manuscript in revision
    - No study of clinical outcomes related to a genomic medicine intervention

Assessing Outcomes

- IGNITE
- Measurement of implementation characteristics to be adapted to standardized topics / subtopics of the Consolidated Framework for Implementation Research (CFIR) where feasible and practical
- Develop and apply common measures across diverse projects to assess
  - Implementation climate and readiness for implementation (Institutional characteristics)
  - Knowledge and beliefs about intervention and self-efficiency (Individual's characteristics)
  - Relative advantage and cost of intervention (Intervention characteristics)
  - Planning, execution and evaluation of the project (Process characteristics)
- Evidence expected for outcomes in clinical implementation of
  - pharmacogenetics (3 sites),
  - monogenic forms of common disease (1 site),
  - extended family history tool (1 site),
  - genetic risk for common disease in primary care (1 site)

Assessing Outcomes

- GAPH (Genomics and Personalized Health)
- ***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.

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Interpret sequence data in variety of clinical contexts			X	X													
Integrate sequence data into patient care			X	X	X								X				
Incorporate actionable variants into EMR, develop CDS			X	X	X								X				
Educate clinicians and patients on genomics in clinical care			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					
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 action ability 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				
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	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen	GM Mtgs	G2MC	CMG	CPIC	GA4GH	GAPH	IOM	ISCC	LSAC	PAGE	PhenX


MISSION
ACCOMPLISHED
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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						X							
Common data elements	X				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			
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					X											
Integration of genomic data in learning healthcare system			X	X	X	X				X				X							
Turnaround in clinically emergent settings			X		X																
Use cases for genomic CDS development					X					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																
Returning incidental findings												X									
REGULATORY NEEDS																					
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																			
Need for cloud computing																X					
Reimbursement policies and regulations					X		X														

Integration of Data

- Significant issue for CSER, eMERGE and IGNITE
- eMERGE and CSER EHR groups studied this issue and has done joint presentation and publication
- Subject of significant body of literature

ClinGen

- Multiple working groups working on different aspects of this problem
  - Informatics
  - Data Modeling
  - Pharmacogenomics

IGNITE

- Limited institutional support to operationalize integration of genomic data in EHR
- Difficult to engage clinical informatics teams
- Slow turn-around times for genetic test results
- Most providers are not familiar with ordering and/or interpreting genetic testing
- Fear of discrimination by insurers
- Different IT systems for inpatient and outpatient settings
- Concerns over privacy protection and genetic information in EHR
- Lack of understanding of regulatory bodies, i.e. IRB, Pharmacy&Therapeutics Board, etc.

CPIC

- Informatics Working Group is working on data issues specific to pharmacogenomics

IOM

BOX 6-1
Possible Next Steps Proposed by Individual Workshop Participants

Interoperability of EHRs

- Ensure that the quality of genomic data is clinical grade and that it is in an accessible format so that it can be used it for future research and to inform clinical care. (Risch)
- Support regulations that will make EHRs fully interoperable for genomic information. (Leffler)
- Establish data standards for genomics to allow for EHRs to communicate and for genomic data to flow more easily across labs and systems to providers. (Aronson, Fowler, Nolen)
- To demonstrate how the interoperability of systems can be increased, start with specific health problems whose outcomes are likely to be changed with genomic and other clinical data. (Hill)

Clinical Decision Support

- Reach agreement on allele and test code nomenclature to facilitate the development of clinical decision support tools for genomics. (Chute)
- Create warehouses of clinical decision support tools that can be shared and used widely. (Ginsburg)
- Measure outcomes to determine the validity of algorithms used to guide practice. (Moss)
- Develop a core infrastructure to handle clinical decision support and the long-term storage of complex data. (Nolen)

Data Sharing

- Build platforms with reusable components that are scalable and can be implemented anywhere. (Friedman)
- Standardize data so that they can be re-used. (Chute)
- Foster interoperable health care systems to enable genomic data sharing. (Terry)
- Inform the public about data sharing to cultivate a "data donor" culture. (Chute)
- Network data from around the world to increase the size of databases and power of research studies. (Aronson)
- Integrate patient-provided data into health care information technology systems. (Baker)
- Examine whether personally controlled health databanks can make data accessible for sharing while protecting privacy. (Friedman)
- Support research to understand and generate personalized user interfaces and preferences. (Baker)

IOM

- DIGITizE: Displaying and Integrating Genetic Information Through the EHR
- Major ongoing effort to complete an end-to-end implementation for 2 pharmacogenomic use cases

Reimbursement Policies and Regulation

- Genomic Medicine Working Group
  - GM III devoted to this topic
    - One follow-up workshop focused on partnerships to develop evidence relevant to payers
  - GMWG is engaging with HMORN (soon to become HCSRN) Genomic Special Interest Group to explore possible collaborative opportunities
- IGNITE
  - Evolving evidence base and changes in clinical practice
  - Limited evidence for clinical validity and utility
  - Limited evidence for cost effectiveness
  - Preference to reimburse single tests rather than test panels

Evidence Base

- Identified as a barrier across most studies
- ClinGen project in part developed to have a central repository of annotated variants in clinically actionable genes associated with evidence synthesis
- CPIC developed to create evidence-based guidelines for use of pharmacogenomic information in clinical care
  - Guidelines are written for the scenario that PGx information is already obtained and available for use
- Inseparable from reimbursement issues
- Dependent on outcomes

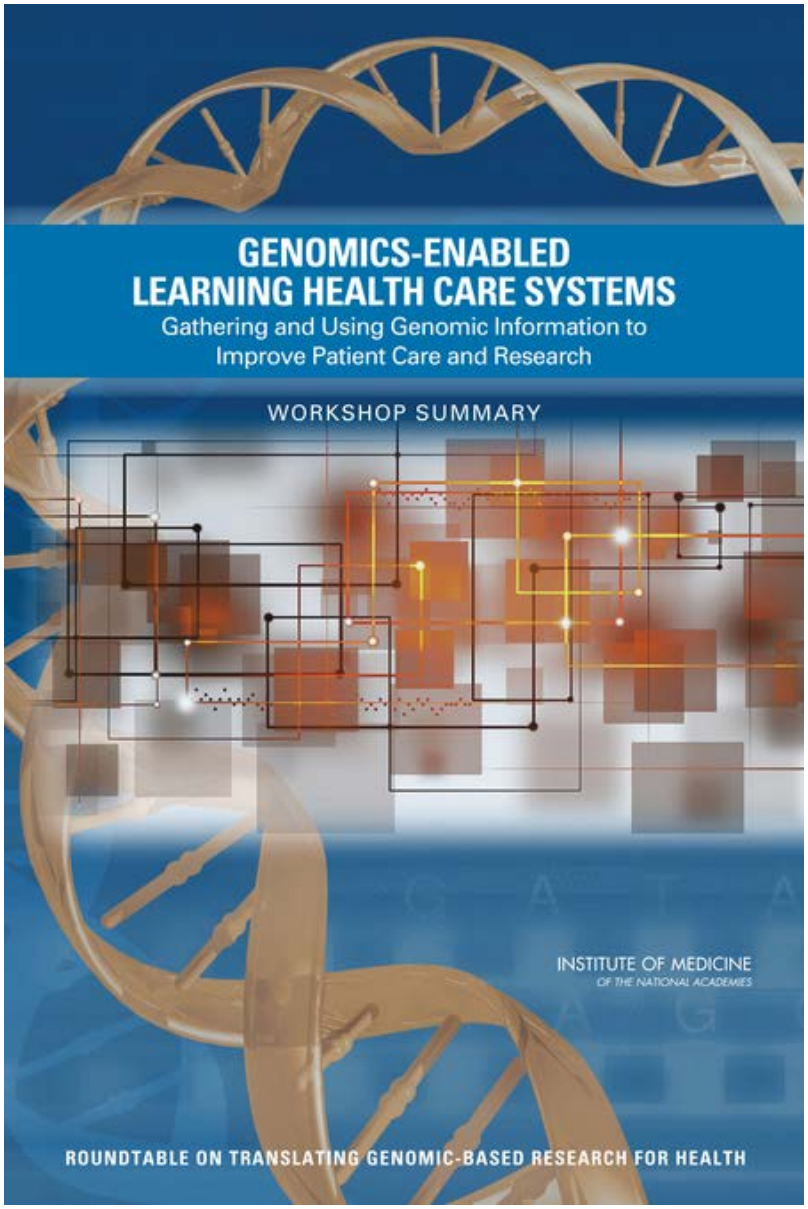
IGNITE

- Goal
  - Contribute to the evidence base regarding outcomes of incorporating genomic information into diverse clinical care environments
- Outcome barriers
  - Patient ascertainment, recruitment, retention
  - Engagement of providers and patients
  - Provider knowledge and education gap
  - Clinical validity and utility evidence gap
  - Reimbursement gap
  - Funding gap

Evidence Base per Reed Tuckson (GM III)

- We can't afford incremental benefit with extraordinary costs or another 'add-on' technology
- We are looking to you (genomics implementers) to transform the way we care for patients and "solve the problems of the healthcare system"

Central ‘Dogma’


GENOMICS-ENABLED
LEARNING HEALTH CARE SYSTEMS
Gathering and Using Genomic Information to
Improve Patient Care and Research
WORKSHOP SUMMARY
INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES
ROUNDTABLE ON TRANSLATING GENOMIC-BASED RESEARCH FOR HEALTH

Definition

Knowledge-generating health care system refers to an automated system that relies upon large databases of research and patient information. Information gleaned from patients and clinical research is used in learning networks to inform clinical decisions and create a more efficient way to improve health care for future patients. This concept is also referred to as a *learning health care system* (IOM, 2012) or a *rapid learning health care system* (Etheredge, 2014).

eMERGE

- eMERGE II
  - Developing a number of open source tools for phenotyping
  - Studying strategies to use infobuttons to provide just in time point of care education
  - Clinical Decision Support Rules Repository
- eMERGE III
  - More focus on return of results
  - Proposals needed to describe potential outcomes including cost-effectiveness

IGNITE activities to create a genomics-enabled learning health care system

- Develop, share, evaluate and disseminate genomic medicine implementation processes and tools in academic and non-academic clinical practice settings
  - Processes to enhance buy-in of Leadership, Providers, Clinical Informatics (EHR)
  - Processes and tools to overcome common barriers
  - Processes to advance reimbursement
  - Processes to assess clinical validity and utility
  - Processes and tools to overcome knowledge gap

GAPH

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

IOM

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Implementation

- Engage groups with a particular interest and who value genomics, such as people with undiagnosed or chronic diseases, to demonstrate the full potential of this information. (Terry)
- Measure and track health and health care disparities to determine the impact of genomics-based interventions. (Ommaya)
- Support social science and behavioral research to understand the priorities and values of patients and providers when genomics is introduced in the clinic. (Ginsburg)

Proposed Discussion Points

- Lots of groups working in data and informatics
  - Are all gaps/barriers being addressed?
  - Is coordination across projects adequate?
- Focus on measuring outcomes of interest to patients, delivery systems and payers
- Role of standardize approaches, such as IGNITE
- Develop and apply common measures across diverse projects to assess
  - Implementation climate and readiness for implementation (Institutional characteristics)
  - Knowledge and beliefs about intervention and self-efficiency (Individual's characteristics)
  - Relative advantage and cost of intervention (Intervention characteristics)
  - Planning, execution and evaluation of the project (Process characteristics)
- Could this be accomplished across projects?