National Human Genome Research Institute

National Institutes of Health

U.S. Department of Health and Human Services

Genomic Medicine Programs of the National Human Genome Research Institute

U.S. Department of Health and Human Services
National Institutes of Health
National Human Genome Research Institute

Teri Manolio, M.D., Ph.D.
Genomic Medicine VIII Meeting
June 8, 2015

NHGRI's Genomic Medicine Portfolio

How did we get here?

Where are we now?

Where are we going?

Genomic Medicine: On the Threshold?

PERSPECTIVE

doi:10.1038/nature09764

- Identify risk
- Prevent disease
- Improve diagnostics
- Improve treatments
- Increase access

Chart … nomic medicine from … de

Eric D. Green[1], M… te*

There has been … sequence of the human genome was published. Opportunities … ented, as advances in genomics are harnessed to obtain robust … on of the human genome and about the genetic contributions … vision for the future of genomics research and describe the p…

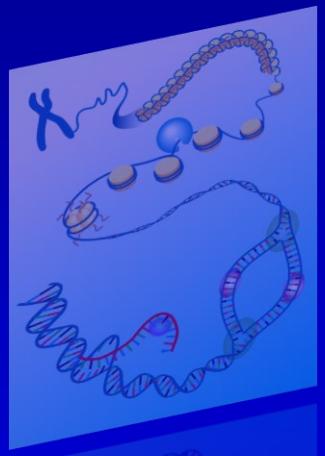
Since the end of the Human Genome Project (HGP) in 2003 and the publication of a reference human genome sequence[1,2], genomics has become a mainstay of biomedical research. The scientific community's foresight in launching this ambitious project[3] is evident in the broad range of scientific advances that the HGP has enabled, as shown in Fig. 1 (see rollfold). Optimism about the potential contributions of genomics for improving human health has been fuelled by new insights about cancer[4–7], quickly. Although genomics has already begun to improve diagnostics and treatments in a few circumstances, profound improvements in the effectiveness of healthcare cannot realistically be expected for many years (Fig. 2). Achieving such progress will depend not only on research, but also on new policies, practices and other developments. We have illustrated the kinds of achievements that can be anticipated with a few examples (Box 2) where a confluence of need and opportunities should

Green ED, Guyer MS. *Nature* 2011; 470:204-13.

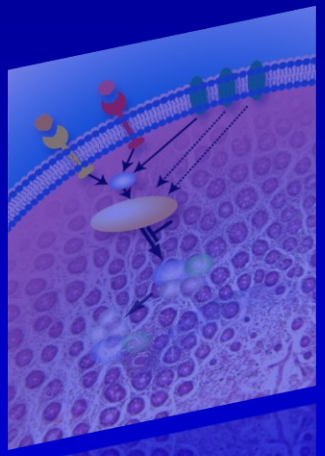
Five Domains of Genomics Research

Understanding the Structure of Genomes

Understanding the Biology of Genomes

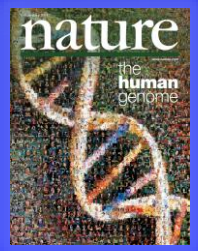


Understanding the Biology of Disease



Advancing the Science of Medicine

Improving the Effectiveness of Healthcare

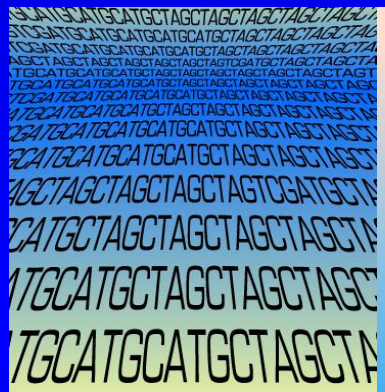
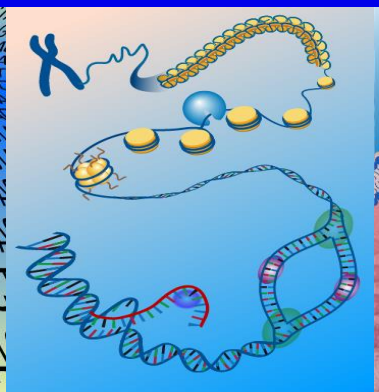
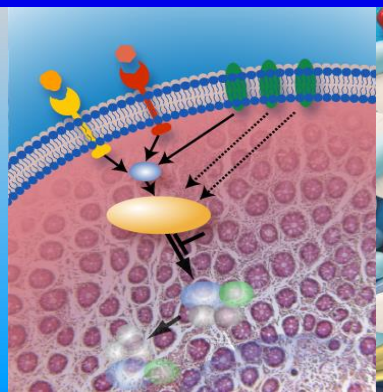


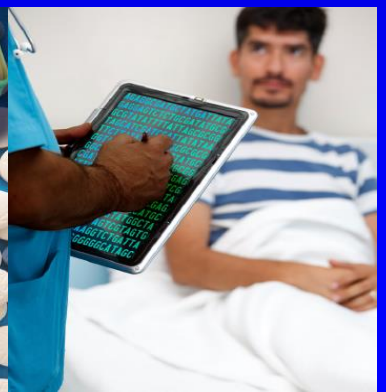
Green et al. 2011

NHGRI Strategic Planning Process
Airlie 'Finale Meeting': July 6-8, 2010

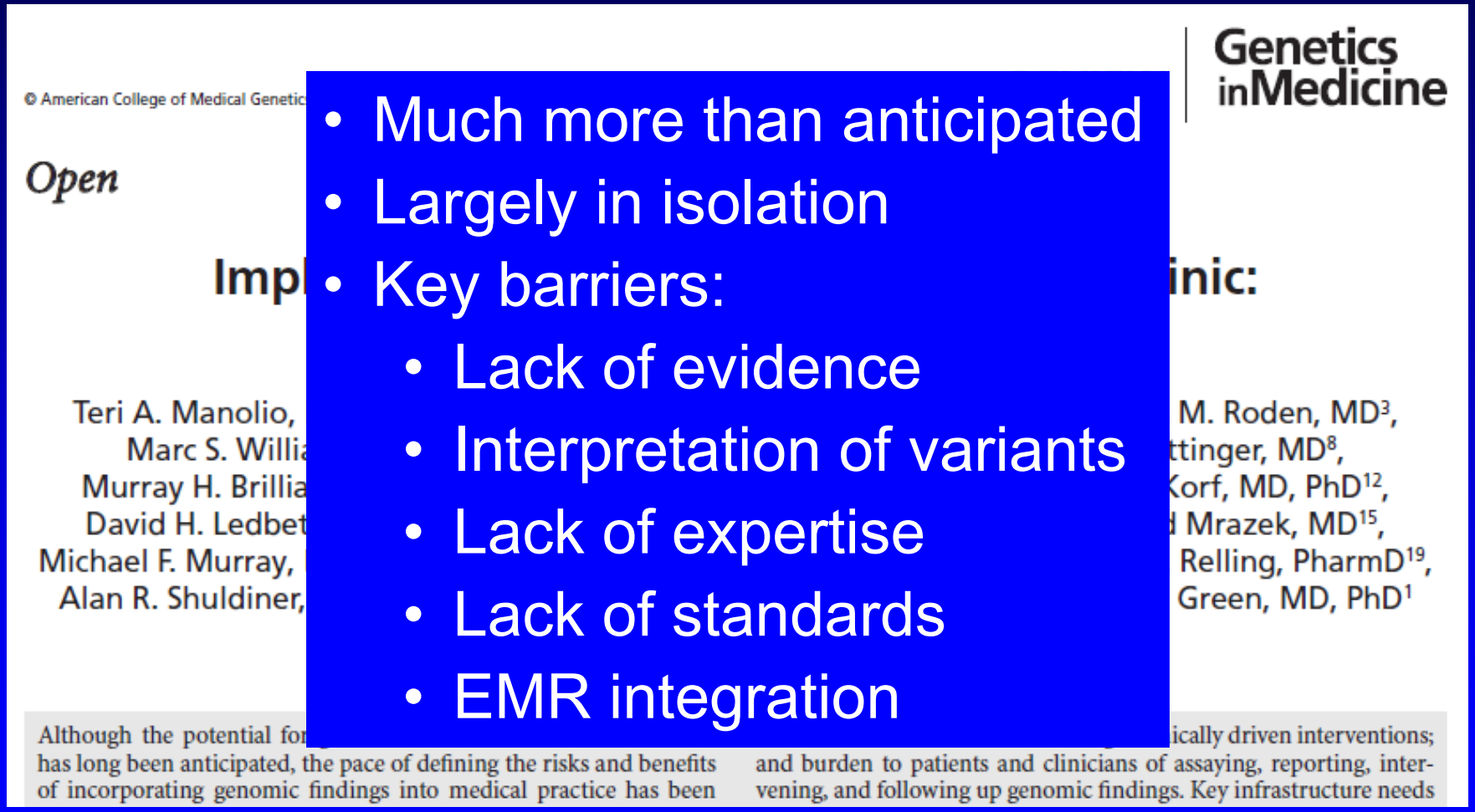
NHGRI Genomic Medicine Meetings, 2011

- GM Colloquium, June 2011, Chicago IL
  - Define landscape, identify commonalities
  - Develop implementation roadmap to share experiences and facilitate adoption
  - Identify common infrastructure and research needs



Genomic Medicine Colloquium Report
June 2011, Chicago, IL



- Much more than anticipated
- Largely in isolation
- Key barriers:
  - Lack of evidence
  - Interpretation of variants
  - Lack of expertise
  - Lack of standards
  - EMR integration

Genet Med 2012; 15:258-67.

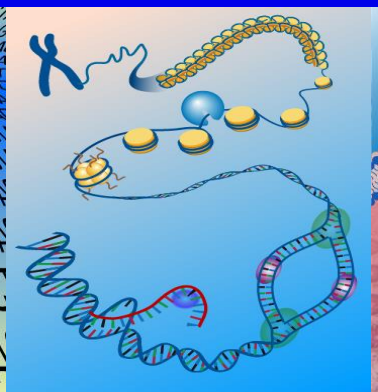
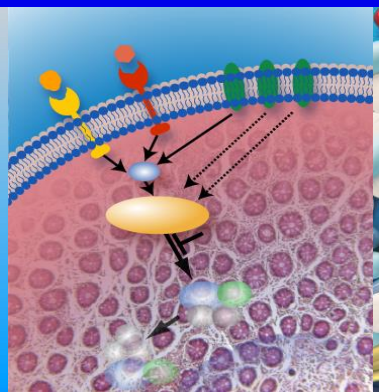
NACHGR Genomic Medicine Working Group Members

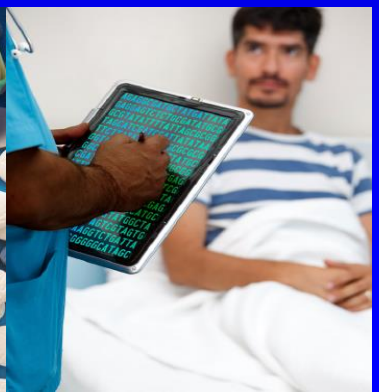
Carol Bult	Jackson Lab
Rex Chisholm	Northwestern
Geoff Ginsburg	Duke
Howard Jacob	Med Coll Wisconsin
Howard McLeod	Moffitt Cancer Ctr
Mary Relling	St. Jude
Dan Roden	Vanderbilt
Marc Williams	Geisinger
Eric Green	
Teri Manolio	
Laura Rodriguez	

Genomic Medicine Working Group - Charge

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

- Review current progress, identify research gaps and approaches for filling them
- Identify and publicize key advances
- Plan genomic medicine meetings on timely themes
- Facilitate collaborations, coordination
- Explore models for long-term infrastructure and sustainability of resulting efforts



National Human Genome Research Institute
Advancing human health through genomics research

SEARCH GENOME.GOV

Notable Accomplishments in Genomic Medicine

The NHGRI Genomic Medicine Working Group has compiled a list of interesting advances in the realm of gen

Genomic Medicine

Within NHGRI's Division of Policy, Communications, and Education, the Policy and Program Analysis and the Genomic Healthcare Branch (GHB) are both involved in helping pave the way for the widesp genomic medicine.

NHGRI's Division of Policy, Communications, and Education, the Policy and Program Analysis Branch and the Genomic Healthcare Branch are both involved in helping pave the way

- GHB has been involved in promoting genetic literacy among healthcare workers through elect such as the Genetics and Genomics Competency Center [g-2-c-2.org] and the Global Genetics Community [g-3-c.org].

- My Family Health Portrait is the Web-based tool from NHGRI and the U.S. Surgeon General's F Initiative that helps you document your own family health history. Using any computer, an Int and an up-to-date Web browser, you provide your health information to build a drawing of you a chart of your family health history. Both the chart and the drawing can be printed and share family members and your doctor. Risk assessment tools for diabetes and colon cancer are als

Genomic Medicine Colloquium, June 2011

GM VII: Genomic CDS, Oct 2014

TOUCH HERE TO START

GM IV: Physician Education, Jan 2013

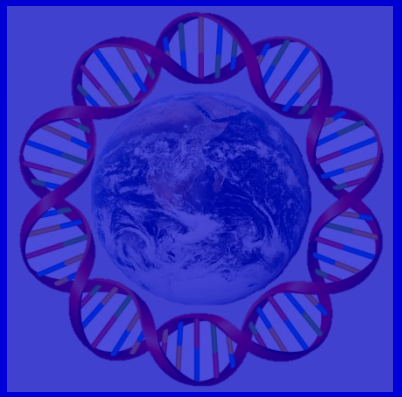
GM VIII: NHGRI's Genomic Medicine Programs, June 2015

Policy Framework

The College of American Pathologists
Debra G.B. Leonard, MD, PhD, FCAP

GM III: Stakeholders, May 2012

GM VI: Global Leaders, Jan 2014



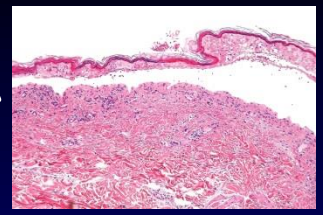
Outgrowths of GM Meetings

ClinGen
Clinical Genome Resource

FDA

UNITED STATES AIR FORCE

G2MC



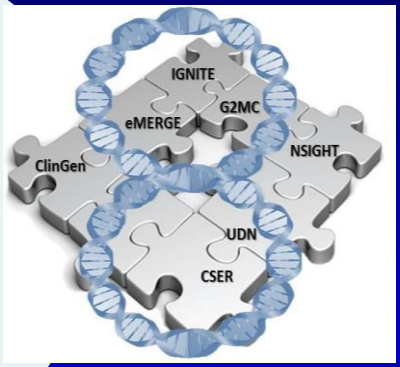
SJS/TEN

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Payers

Clin Action

1 2 3 4 5 6 7



GM VIII

ISCC

NIH

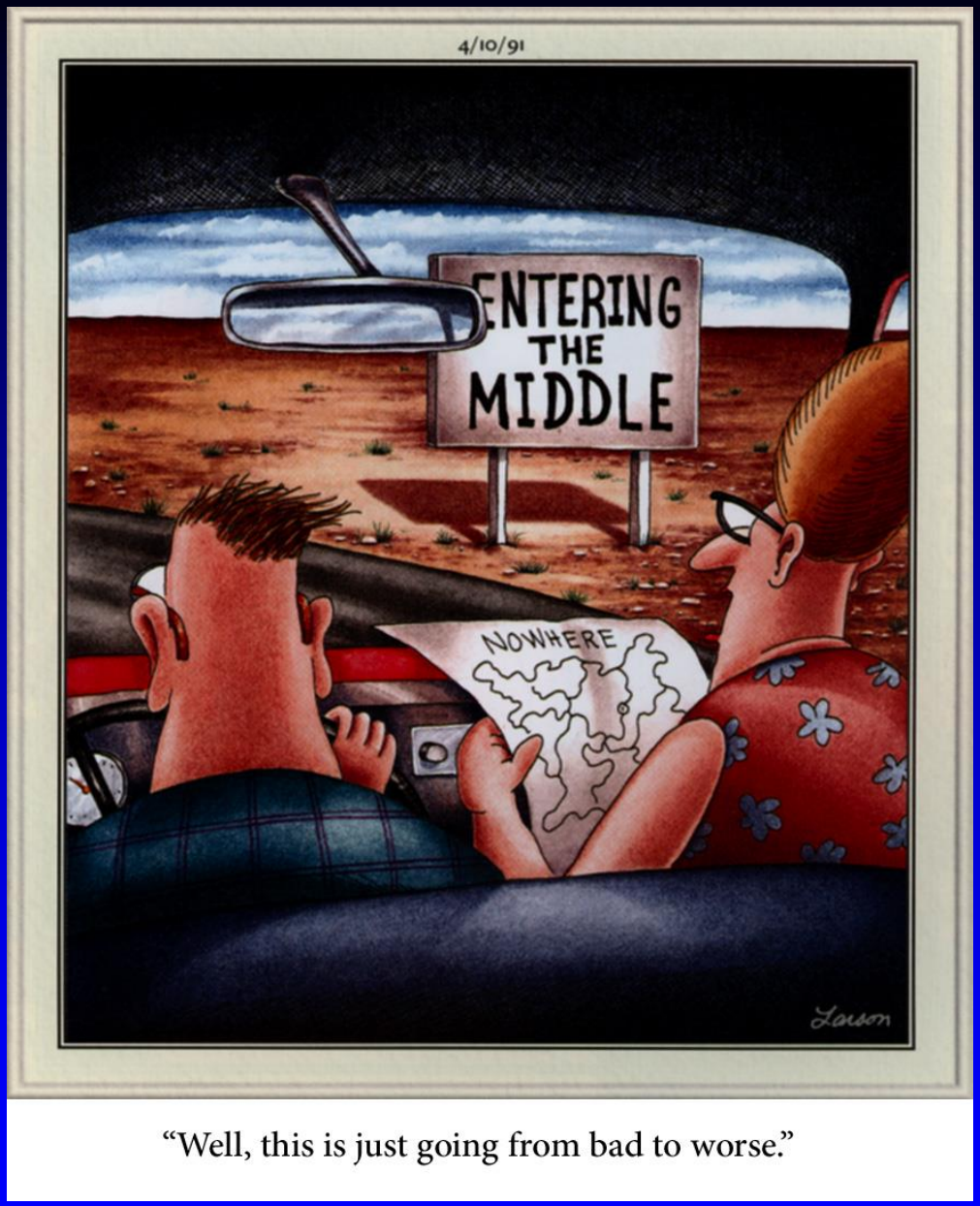
Trans-NIH WG

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Genomics Roundtable

eMERGE
PGx

IGNITE
Implementing GeNomics In pracTicE



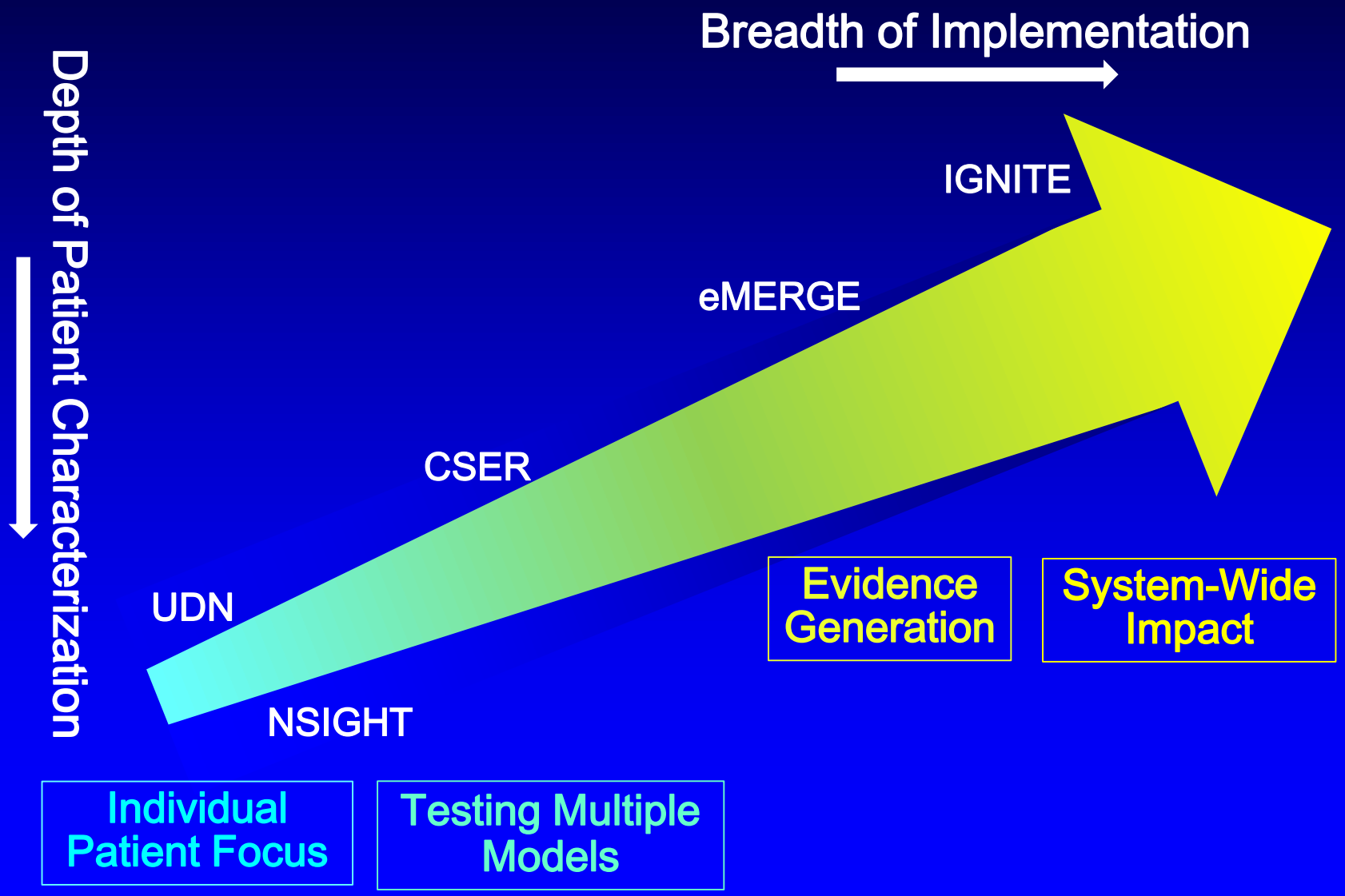
"Well, this is just going from bad to worse."

Larson, G. *The Complete Far Side*. 2003.

NHGRI's Genomic Medicine Research Programs

Program	Goal	Σ $M	Years
UDN	Diagnose rare and new diseases by expanding NIH's Undiagnosed Diseases Program	67.9	FY13-17
NSIGHT	Explore possible uses of genomic sequence information in the newborn period	10.0	FY13-16
CSER	Explore infrastructure, methods, and issues for integrating genomic sequence into clinical care	66.5	FY12-16
eMERGE II	Use biorepositories with EMRs and GWA data to incorporate genomics into clinical research and care	31.1	FY11-14
eMERGE-PGx	Apply PGRN's validated VIP array for discovery and clinical care in ~9,000 patients	9.0	FY12-14
eMERGE III	Identify rare variants in 25,000 patients and determine their penetrance and actionability	54.0	FY15-18
IGNITE	Develop and disseminate methods for incorporating patients' genomic findings into their clinical care	32.3	FY13-16
ClinGen	Develop and disseminate consensus information on variants relevant for clinical care	25.0	FY13-16

Spectrum of Genomic Medicine Implementation: Intensity vs. Breadth



Share Print

NIH Undiagnosed Diseases Program

- Overview
- Program Background
- Program Information
- Program News
- Program Contact

See Also:

Undiagnosed Diseases Network

On Other Sites:

Undiagnosed Diseases Network

Overview

The NIH Undiagnosed Diseases

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NIH National Cen for Advancin Translational

Diseases

ORDR Home > Undiagnosed Di

UNDIAGNOSED

ORDR Programs

Research Funding Resources

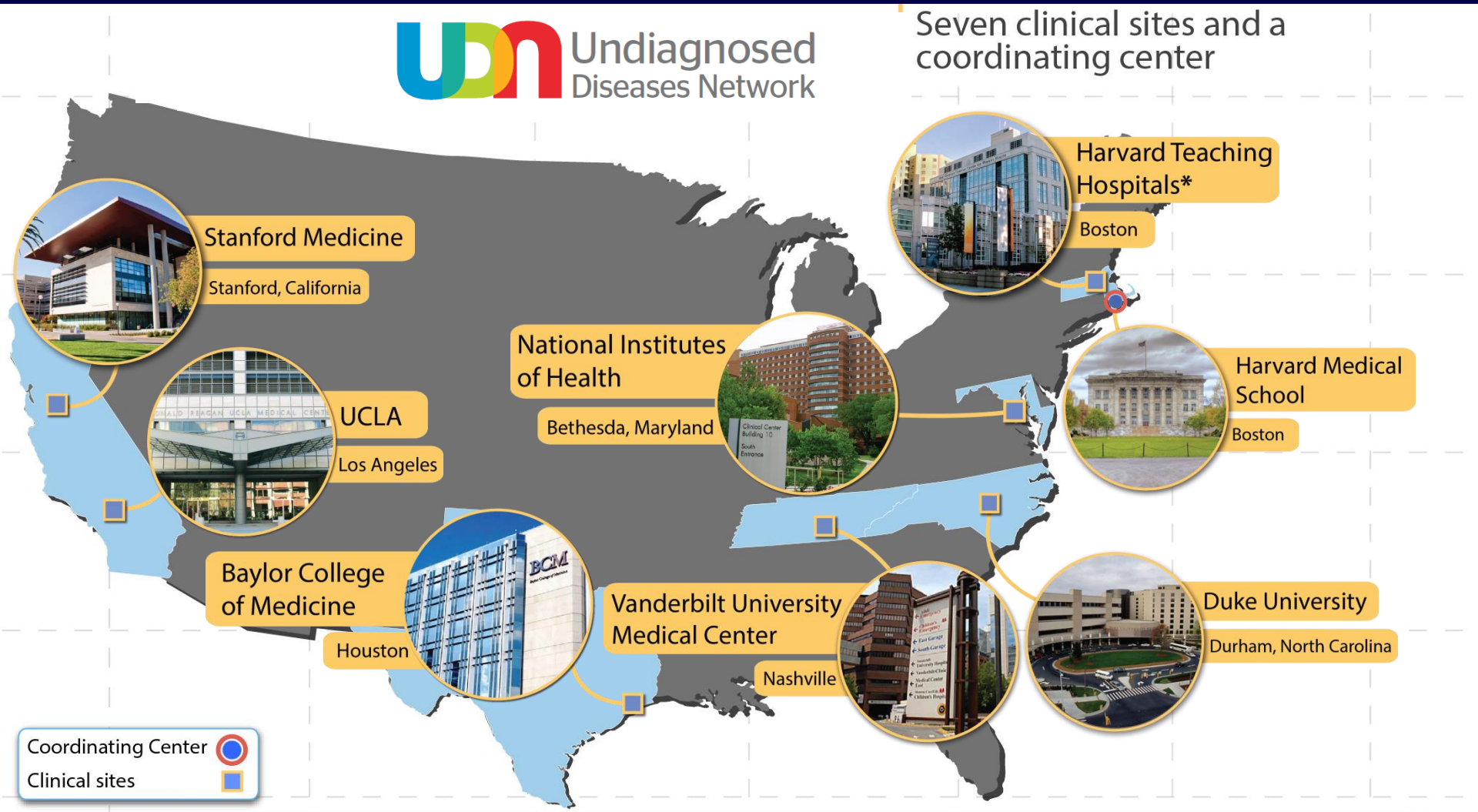
Tools for Researchers

Get Involved in Research

Undiagnosed Diseases Network (UDN)

- Build upon successful NIH experience in the Undiagnosed Diseases Program to improve diagnosis and care for patients with undiagnosed diseases
- Facilitate research into etiology of undiagnosed diseases
- Create integrated and collaborative research community across multiple clinical sites and among laboratory and clinical investigators to identify improved options for optimal patient management

Undiagnosed Diseases Network (UDN)

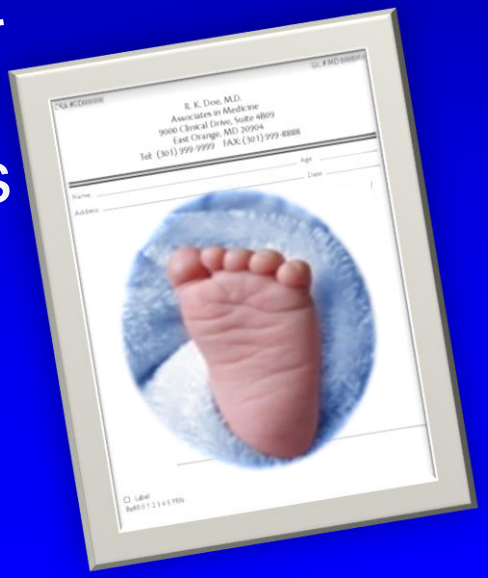


The NIH site will continue to enroll about 150 patients per year; each of the clinical sites will ultimately enroll about 50 patients per year. A DNA sequencing core facility to be announced in the coming weeks.

*Boston Children's Hospital, Brigham and Women's Hospital and Massachusetts General Hospital participate jointly in the Harvard Center for Integrated Approaches to Undiagnosed Diseases

Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) Program

- Explore implications, opportunities, and challenges of using genomic sequence information in the newborn period; what it adds to current screening
- Specifically,
  - Acquire, analyze, and make available genomic datasets relevant to the newborn period
  - Advance understanding of disorders identifiable via sequenced-based newborn screening
  - Investigate ELSI implications of implementation of genomic sequencing of newborns



NSIGHT Projects

- Robert Green, Alan Beggs, Brigham
  NICU and healthy newborns, 240 exomes, data sharing, return of results (RoR)
- Stephen Kingsmore, Children's Mercy Hospital,
  NICU, 1000 genomes, data sharing optional, RoR
- Robert Nussbaum, UCSF
  NBS, 1620 exomes,
  limited data sharing, RoR
- Cynthia Powell, Jonathan Berg, UNC Chapel Hill
  NBS, 400 exomes, data sharing optional, RoR options

Clinical Sequencing Exploratory Research (CSER)

Investigate challenges in applying sequence data to clinical care, including:

- Implementing clinical workflow
- Interpreting and translating data for clinicians
- Communicating findings to patients

Nine Projects:

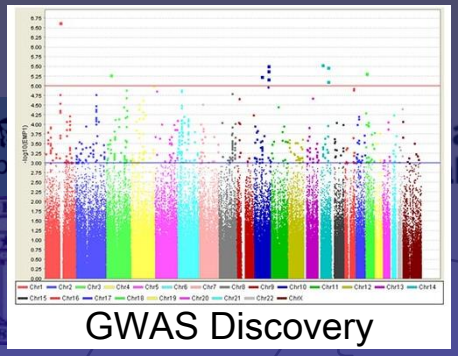
- Cancer care (3)
- Adult medicine (2)
- Pediatrics (2)
- Pediatric cancer care
- Pre-natal carrier testing

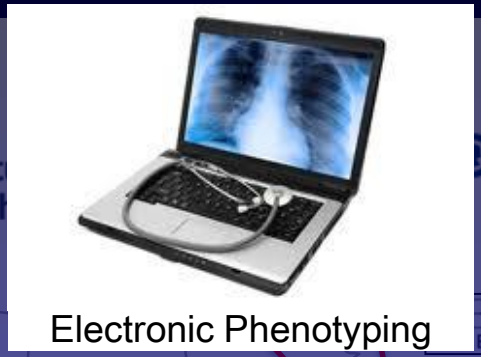
CSER Projects

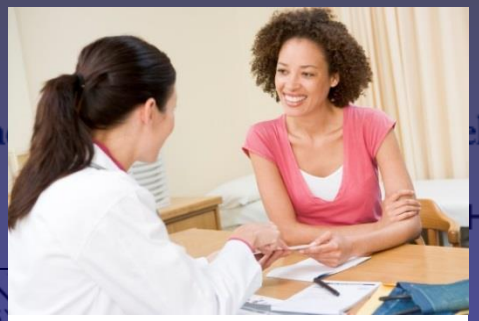
Site	Disease/Condition
Baylor*	Pediatric Cancer
Brigham	Healthy Pts, Hypertrophic Cardiomyopathy
CHOP	Pediatric Diseases (Intellectual Disability)
Dana-Farber	Solid Tumors
Hudson-Alpha	Children with Intellectual Dysfunction
Kaiser Portland	Preconception Carrier Screening
U Michigan*	Adults and Children with Advanced Cancer
UNC	Cardiomyopathy, Cancer
UW*	CRC and Polyposis

*Co-funded by NCI.

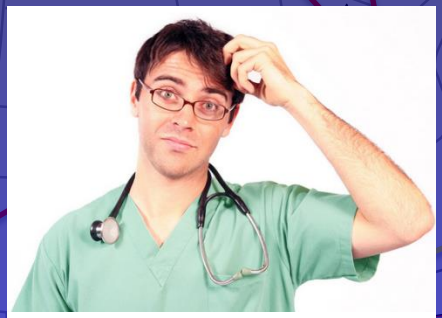
Electronic Medical Records and Genomics (eMERGE) Network


GWAS Discovery


Electronic Phenotyping


Consent Methodology


Clinician/Pt Education


Decision Support


Community Consultation


Pharmacogenomics


Pediatrics


Data Privacy

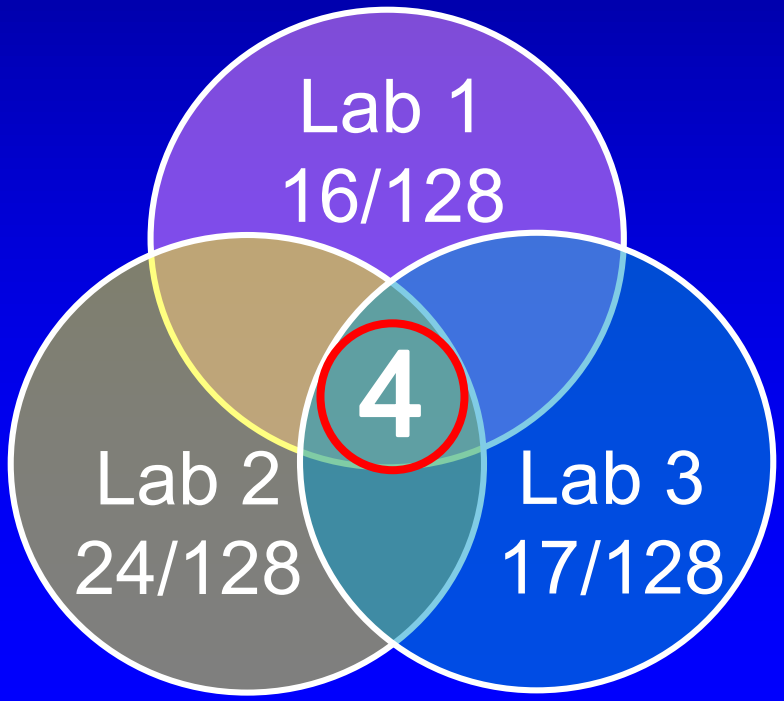
Phase I Sites ★ Coord. ase II Sites ★ Pediatric Sites

eMERGE Phase II Clinical Implementation

- Begin to incorporate genotyping data and state-of-the-art electronic phenotyping and privacy protections into EMRs for improving clinical care.
- Example projects:
  - *CFH* and risk of age-related macular degeneration
  - RCT of CHD genomic risk score vs. clinical risk factors for impact on patient attitudes, behaviors
  - RCT of *APOL1* genotype vs clinical risk factors for management of hypertensive nephropathy
  - Effect of return of *HFE* and *FVL* risk variants on physician and patient attitudes, behaviors

Preliminary PGRN-Seq Results *SCN5A* and *KCNH2* in 2,000 Patients

- 83 rare (MAF < 1%) in *SCN5A,* 45 in *KCNH2*
- 121/128 MAF < 0.5%, 92 singletons
- Three labs assessed known/likely pathogenicity



Of total 40 variants, only 4 called pathogenic by all 3 labs

Sequencing in Clinical Care Systems: eMERGE III Goal and Aims

Continue genomic medicine discovery and implementation research utilizing large biorepositories linked to EMRs

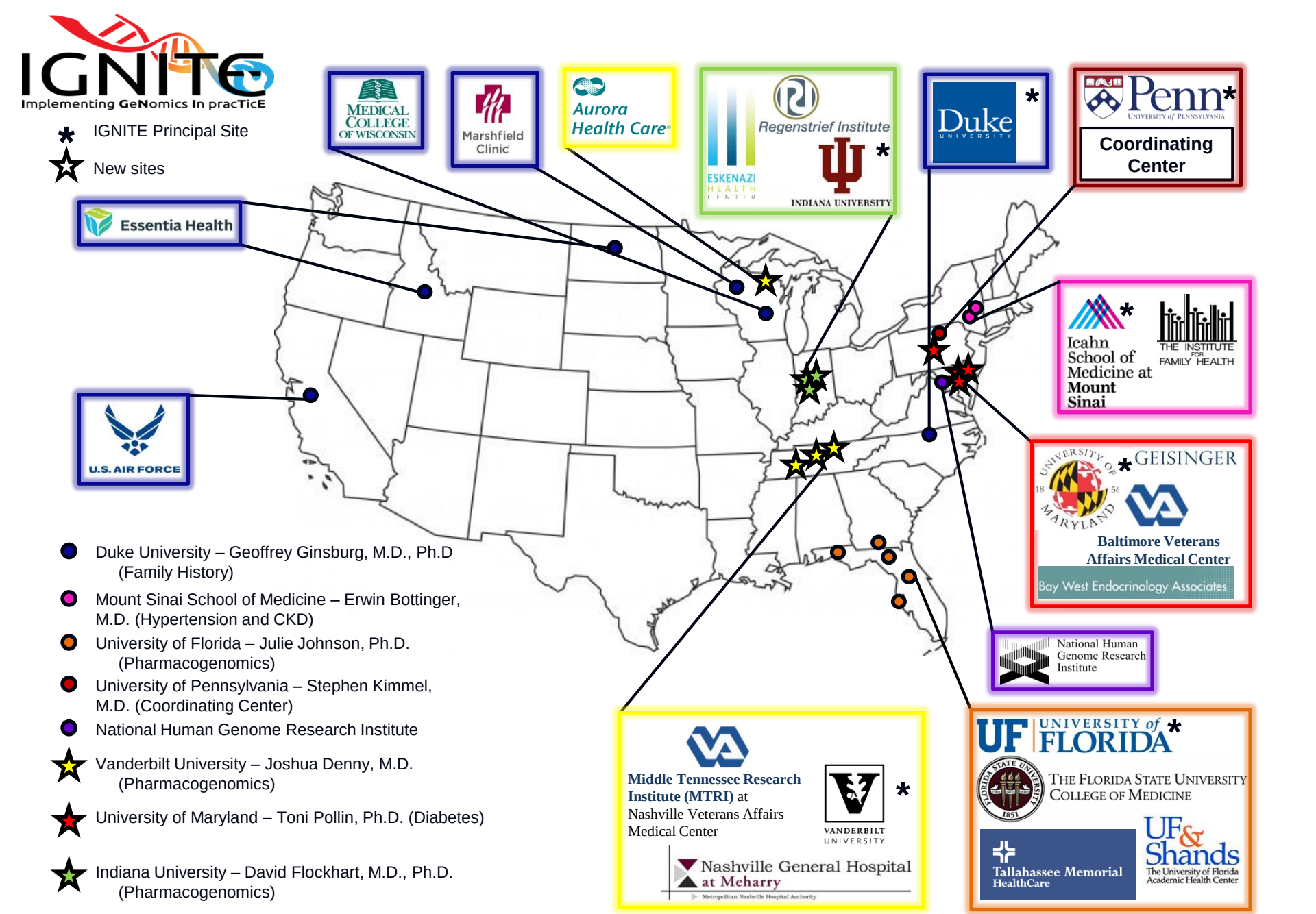
- Identify rare variants with presumed major impact on function of ~100 clinically relevant genes
- Assess phenotypic implications of variants by leveraging well-validated EMR data or re-contact
- With appropriate consent and education, report actionable variants to pts, (families), clinicians
- Assess impact to pts, clinicians, and institutions on pt outcomes and cost of care

Implementing Genomics Into Clinical Practice (IGNITE) Network

- Expand and link existing genomic medicine efforts
- Develop new collaborative projects and methods, in diverse settings and populations
- Contribute to evidence base regarding outcomes of incorporating genomic information into clinical care
- Define and share processes of genomic medicine implementation, diffusion, and sustainability

www.ignite-genomics.org

IGNITE
Implementing GeNomics In pracTicE



Courtesy Ebony Madden, NHGRI

IGNITE Projects

- Duke: Family hx clinical decision support (CDS) in CVD, thrombosis, lung cancer, diabetes
- Mount Sinai: *ApoL1* genotyping and HTN management
- U Florida: PGx genotyping for clopidogrel, *TPMT*, *IL28B*, *CYP2D6* and opioids
- Indiana: PGx genotyping for 24 widely used drugs for improved clinical outcomes and reduced costs
- Vanderbilt: PGx and cancer genomic testing and CDS in settings with diverse EHRs and informatics
- UMd: diabetes gene sequencing to identify Mendelian variant carriers

www.ignite-genomics.org

IGNITE
Implementing GeNomics In pracTicE

Clinical Genome Resource (ClinGen)

Improving our knowledge of genomic variation requires a massive effort in data sharing and collaborative curation

ClinGen
Clinical Genome Resource

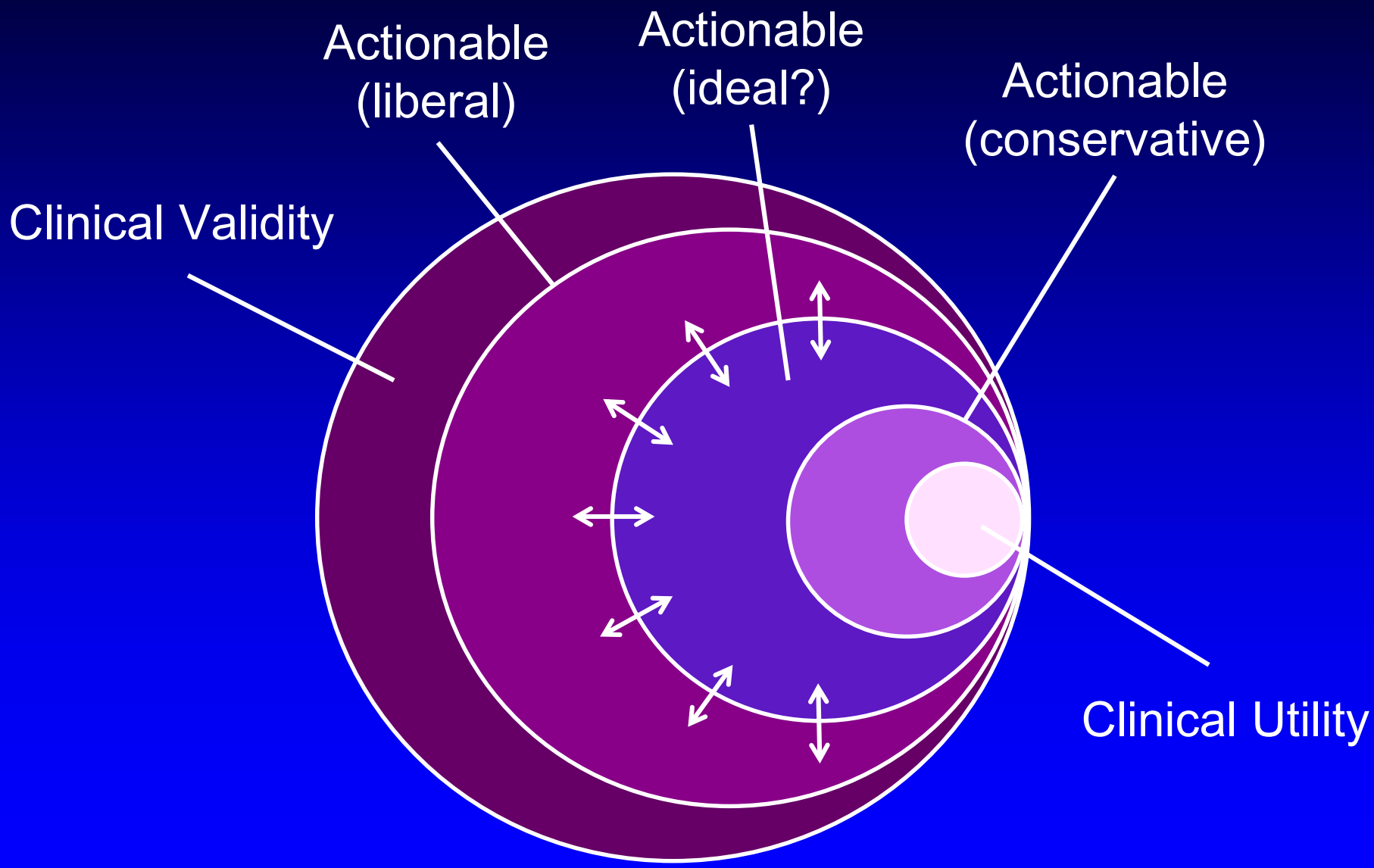
Courtesy Erin Ramos, NHGRI

Gene-Disease Validity

Definitive	Repeatedly demonstrated in research & clinical settings.
Strong	Excess of pathogenic variants in cases vs. controls & supporting experimental data.
Moderate	≥3 unrelated probands with pathogenic variants & supporting experimental data.
Limited	<3 probands w/ pathogenic variants.
No Evidence Reported	"Candidate" genes based on animal models or disease pathways, but no pathogenic variants reported.
Disputed	Significant evidence *refuting* a role for gene in this disease.
Evidence Against	Evidence refuting the role of the gene significantly outweighs any supporting evidence.

Courtesy Erin Ramos, NHGRI

Range of Clinical Actionability?



After Ramos E *et al.*, *AJMG Pt C* 2014; 166C:93–104.

Clinical Actionability

- Develop clear and robust criteria to guide decisions regarding actionable secondary findings
- Focus on findings associated with specific therapeutic or surveillance interventions in pre-symptomatic individuals
  1. Define elements of actionability
  2. Standardize evidence reviews
  3. Score gene-disease pairs with a semi-quantitative actionability metric

Clinical Actionability

- ✓ *Severity*
- ✓ *Likelihood of disease*
- ✓ *Efficacy of intervention*
- ✓ *Nature of intervention*
- ✓ *Level of evidence*

ClinGen
Clinical Genome Resource

Courtesy Erin Ramos, NHGRI

Putting the Pieces Together

Issues Addressed by Key NHGRI Genomic Medicine Programs

Issue	UDN	NSIGHT	CSER	eMERGE	IGNITE	ClinGen
Genomic Dx	+	+	+			
ELSI of Seq		+	+	+		
Integrate Seq in Clinic, EMR			+	+	+	
Clinician/Pt Educ			+	+	+	+
Outcomes of Clinical Use				+	+	
Variant Discovery	+	+	+	+		
Penetrance				+		
Translate Outside Specialized Ctrs					+	
Standardize Clin Annotation, Interp						+
Define/Share Impl Processes	+		+	+	+	+

NHGRI's Genomic Medicine Portfolio

How we got here…

Where we are we now…

Where are we going?

Topics to Address; Questions to Answer

1) Evidence gaps
2) Variant interpretation
3) Changing evidence
4) Program metrics
5) EHR functionality
6) Patient diversity
7) Clinical workflow
8) Education/training
9) Patient-facing tools

1) Importance and impact of topic
2) Current programs addressing it
3) Gap areas and/or opportunities
4) Synergies across programs
5) Training opportunities and/or needs

Many Thanks…

GenomMed Programs Investigators and Participants!

Alice Bailey

Ebony Bookman

Joy Boyer

Lisa Brooks

Deborah Colantuoni

Cati Crawford

Eric Green

Lucia Hindorff

Carolyn Hutter

Jean Jenkins

Heather Junkins

Rongling Li

Nicole Lockhart

Jean McEwen

Jacqueline Odgis

Erin Ramos

Laura Rodriguez

Simona Volpi

Robert Wildin

Ken Wiley

Anastasia Wise

Rex Chisholm

Geoff Ginsburg

Howard Jacob

Howard McLeod

Mary Relling

Dan Roden

Marc Williams

(Pearl O'Rourke)