National Human Genome Research Institute

National Institutes of Health

U.S. Department of Health and Human Services

Genomic Medicine Working Group Update

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

Teri Manolio and Melpi Kasapi
National Advisory Council on Human Genome Research
September 11, 2017

NACHGR Genomic Medicine Working Group Members

Carol Bult	Jackson Lab
Rex Chisholm	Northwestern
Pat Deverka	Am Inst Research
Geoff Ginsburg	Duke
Howard Jacob	HudsonAlpha
Howard McLeod	Moffitt Cancer Ctr
Mary Relling	St. Jude
Dan Roden	Vanderbilt
Marc Williams	Geisinger
Eric Green	NHGRI
Melpi Kasapi	NHGRI
Teri Manolio	NHGRI
Laura Rodriguez	NHGRI

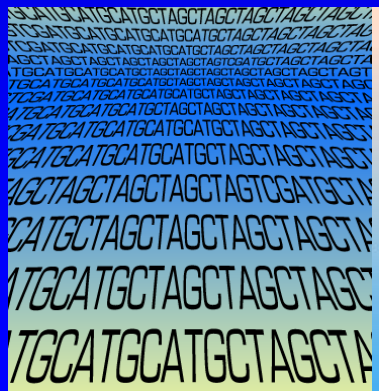
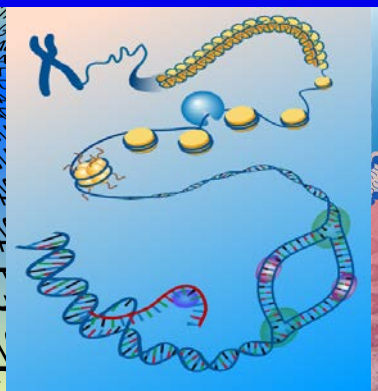
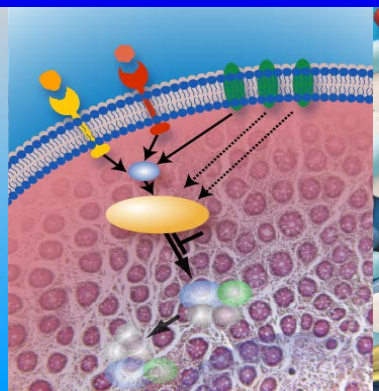
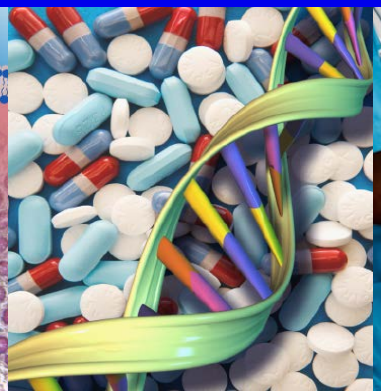
Spectrum of Disease-Related Genomics Research

Genomic Medicine

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


Notable Accomplishments in Genomic Medicine

National Human Genome

Search Genome.gov

Notable Accomplishments in Genomic Medicine

Perspective

Pharmacogenomics

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 20, 2017 VOL. 377 NO. 3

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

F.E. Dewey, V. Gusarova, R.L. Dunbar, C. O'Dushlaine, C. Schurmann, O. Gottesman, S. McCarthy, C.V. Van Hout, S. Bruse, H.M. Dansky, J.B. Leader, M.F. Murray, M.D. Ritchie, H.L. Kirchner, L. Habegger, A. Lopez, J. Penn, A. Zhao, W. Shao, N. Stahl, A.J. Murphy, S. Hamon, A. Bouzelmat, R. Zhang, B. Shumel, R. Pordy, D. Gipe, G.A. Herman, W.H.H. Sheu, I-T. Lee, K.-W. Liang, X. Guo, J.I. Rotter, Y.-D.I. Chen,* W.E. Kraus, S.H. Shah, S. Damrauer, A. Small, D.J. Rader, A.B. Wulff, B.G. Nordestgaard, A. Tybjærg-Hansen, A.M. van den Hoek, H.M.G. Princen, D.H. Ledbetter, D.J. Carey,* J.D. Overton, J.G. Reid, W.J. Sasiela, P. Banerjee, A.R. Shuldiner, I.B. Borecki, T.M. Teslovich, G.D. Yancopoulos, S.J. Mellis, J. Gromada, and A. Baras

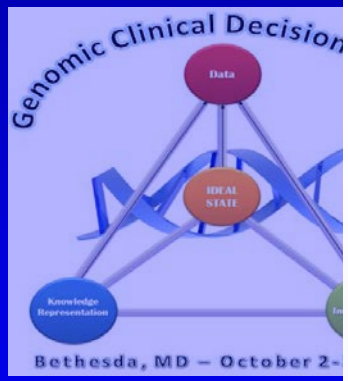
Research directions in the clinical implementation of pharmacogenomics

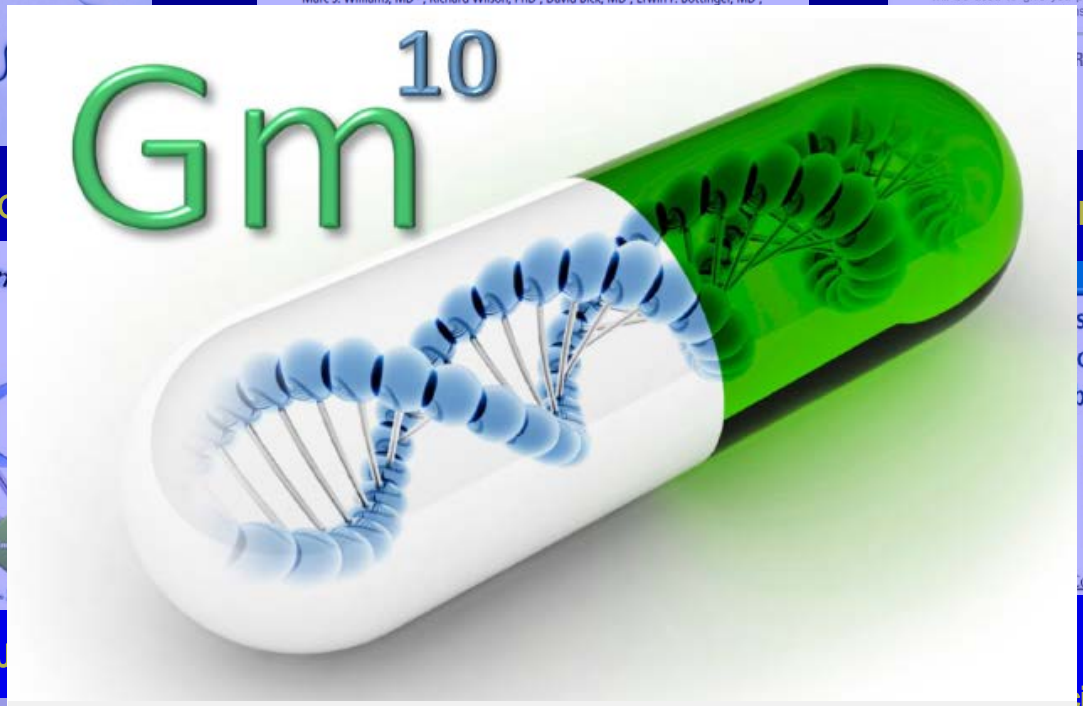
GM VIII: NHGRI's Genomic Medicine Programs, June 2015

Genomic Medicine Colloquium, June 2011

GM II: Forming Collaborations, Dec 2011

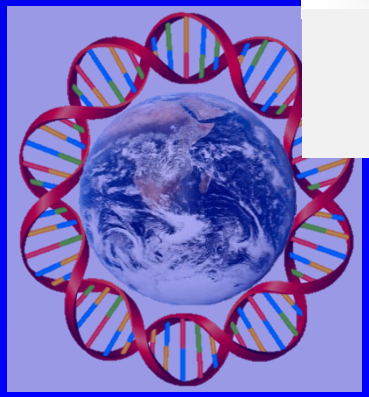
GM VII: Genomic CDS, C





keholders, May 2012

GM VI: Global Leaders, J



Research Directions in the Clinical Implementation of Pharmacogenomics

A Genomic Medicine Policy Framework

The College of American Pathologists

Debra G.B. Leonard, MD, PhD, FCAP

ian Education, Jan 2013

Genomic Medicine Meetings

National Human Genome Research Institute

Search Genome.gov

Genomic Medicine Meetings

On May 2-3, 2017, the National Human Genome Research Institute (NHGRI) sponsored its 10th Genomic Medicine meeting - ***Genomic Medicine X: Research Directions in Pharmacogenomics Implementation*** - at the Sheraton Silver Spring Hotel in Silver Spring, Maryland.

The objectives of the meeting were to:

- Survey national landscape of research programs in pharmacogenomics implementation
- Review current advances and clinical applications of pharmacogenomics
- Discuss limitations and obstacles in pharmacogenomics clinical implementation
- Identify evidence gaps and studies that are needed to address them
- Design strategies for large-scale evaluation and implementation of pharmacogenomics in clinical care in the United States.

Video Playlist: Genomic Medicine X: *Pharmacogenomics*

Meeting Summary

Executive Summary

Tweets from the meeting: #GenomicMed10

GOLDILOKs Study: Patient Booklet

Tuesday, May 2, 2017

Time	Topic	Speaker

GMWG Publications

Genetics

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 166C:93–104 (2014)

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COMMENTARY | Genetics inMedicine

PERSPECTIVE

Sci Transl Med 2015; 7:290ps13.

Cell

Leading Edge

Commentary

Cell 2017; 169:6-12.

Bedside Back to Bench: Building Bridges between Basic and Clinical Genomic Research

Teri A. Manolio,[1,*] Douglas M. Fowler,[2] Lea M. Starita,[2] Melissa A. Haendel,[3] Daniel G. MacArthur,[4,5] Leslie G. Biesecker,[1] Elizabeth Worthey,[6] Rex L. Chisholm,[7] Eric D. Green,[1] Howard J. Jacob,[6] Howard L. McLeod,[8] Dan Roden,[9] Laura Lyman Rodriguez,[1] Marc S. Williams,[10] Gregory M. Cooper,[6] Nancy J. Cox,[11] Gail E. Herman,[12] Stephen Kingsmore,[13] Cecilia Lo,[14] Cathleen Lutz,[15] Calum A. MacRae,[16] Robert L. Nussbaum,[17] Jose M. Ordovas,[18] Erin M. Ramos,[1] Peter N. Robinson,[19] Wendy S. Rubinstein,[20] Christine Seidman,[21,22,23] Barbara E. Stranger,[24] Haoyi Wang,[25] Monte Westerfield,[26] and Carol Bult[25]

*Correspondence: manolio@nih.gov

http://dx.doi.org/10.1016/j.cell.2017.03.005

SUMMARY

Genome sequencing has revolutionized the diagnosis of genetic diseases. Close collaborations between basic scientists and clinical genomicists are now needed to link genetic variants with disease causation. To facilitate such collaborations, we recommend prioritizing clinically relevant genes for

precisionFDA

ClinGen
Clinical Genome Resource

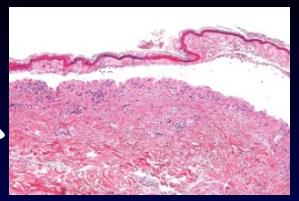
OPTUM

United Healthcare

Payers

Clin Action

G2MC



SJS/TEN

PAR-16-275

Serious ADRs

Cohort Summit

1 2 3 4 5 6 7 8 9

ISCC

NHS England

Annual Report of the Chief Medical Officer 2016

Generation Genome

eMERGE PGx

IGNITE
Implementing GeNomics In pracTicE

NATIONAL ACADEMY OF MEDICINE

DIGITizE

Health Education England

NHS

GM IX Recommendations: Bedside Back to Bench

COMMENTARY

Variant Interpretation: Functional Assays to the Rescue

Lea M. Starita,[1,*] Nadav Ahituv,[2,3] Maitreya J. Dunham,[1] Jacob O. Kitzman,[4,5] Frederick P. Roth,[6,7,8,9] Georg Seelig,[10,11] Jay Shendure,[1,12] and Douglas M. Fowler[1,13,*]

AJHG 2017; 101:315–25.

Classical genetic approaches for interpreting variants, such as case-control or co-segregation studies, require finding many individuals with each variant. Because the overwhelming majority of variants are present in only a few living humans, this strategy has clear limits. Fully any com nic vari pro- vide ere, we d s in disea ith machine learning and clinical knowledge for the development of "lookup tables" of accurate pathogenicity predictions. A coordinated effort to produce, analyze, and disseminate large-scale functional data generated by multiplex assays could be essential to addressing the variant-interpretation crisis.

Multiplex assays of variant effect (MAVE)

Goal: A MAVE-data-driven prediction for every variant.

Introduction

Technological advances are making the routine sequencing of human genomes increasingly practical, including in clinical settings. However, our inability to interpret the clinical consequences of genetic variants discovered by

nately, over half of the interpreted variants are considered variants of uncertain significance (VUSs) (Figure 1A, right), which are "trapped in the interpretive void" between benign and pathogenic.[3] Each of the variants that have been previously detected, as well

terpretations for the individual rare variants.

Historically, when a rare or de novo genetic variant was observed in a gene that was already implicated in an individual's phenotype, the variant was deemed causal. As increasing numbers

GM IX Recommendations: Bedside Back to Bench

- Identify clinically relevant genes as priorities for functional studies
- Encourage development of high-throughput assays and animal models for these genes
- Develop larger reference variant databases linking to phenotypes
- Develop and adopt standards for phenotype description and data sharing
- Promote cross-disciplinary understanding and opportunities for interaction

Genomic Medicine X: Research Directions in PGx Implementation May 2-3, 2017, Silver Spring MD

Genomic Medicine X: *Research Directions in Pharmacogenomics Implementation*

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- Review current advances and clinical applications of pharmacogenomics
- Discuss limitations and obstacles in pharmacogenomics clinical implementation
- Identify evidence gaps and studies that are needed to address them
- Design strategies for large-scale evaluation and implementation of pharmacogenomics in clinical care in the United States.

YouTube Video Playlist: Genomic Medicine X: *Pharmacogenomics*

Meeting Summary

Executive Summary

Tweets from the meeting: #GenomicMed10

GOLDILOKs Study: Patient Booklet

Prominent GM X Recommendations

- Identify minimum quality standards (coverage, variants) for PGx testing in clinical use

- Develop improved coding system for genetic testing to augment or replace CPT codes, based on NCBI's GTR

- Encourage development of "plug in" EMR modules for PGx drug-gene interactions built on CPIC guidelines

CPIC®
Clinical Pharmacogenetics Implementation Consortium

Prominent GM X Recommendations

- Leverage opportunities for data re-use by re-analyzing existing genotype data in prior trials
- Create registries for patients who've undergone PGx testing that allow follow-up for outcomes
- Convene PGx skeptics to examine large-scale trials that include randomization to no PGx testing
- Consider research approaches such as staggered roll-out with later groups serving as controls for early implementing groups





GMWG irons in the fire….

Collaborating with Payers

- Develop collaborative evidence generation project
- Facilitate development of revised genetic testing coding system
- Promote genomic medicine through common policy and public engagement opportunities
- Access Optum data for assessing outcomes of genetic testing
- Obtain advice on compelling outcomes and other aspects of design of implementation studies

Defining Quality Measures with National Quality Forum (NQF)

- Tumor-based screening for Lynch syndrome followed by cascade screening in relatives
- *BRCA 1/2* testing in all ovarian cancer patients and breast cancer pts meeting criteria, followed by cascade screening in relatives
- Genetic testing in patients with sustained elevated cholesterol levels, followed by cascade screening in relatives
- PGx testing (abacavir, clopidogrel)

Potential Evidence Generation Projects in NHS England Implementation

Build evidence-generating research on top of NHS's implementation of the CMO repo

- Clinical
- Public e
  educatio
- Provide
  feedbac
- Policy and regulatory strategies

Annual Report of the
Chief Medical Officer 2016

nomic
medicine services planned for early 2019

Many Thanks…

Joy Boyer
Lisa Brooks
Heather Colley
Erin Currey
Alvaro Encinas
Eric Green
Sarah Gould
Jyoti Gupta
Lucia Hindorff
Ellen Howerton
Jean Jenkins
Sheethal Jose
Melpi Kasapi
Dave Kaufman
Rongling Li
Nicole Lockhart
Ebony Madden
Jean McEwen
Donna Messersmith
Kiara Palmer
Erin Ramos
Laura Rodriguez
Simona Volpi
Ken Wiley
Anastasia Wise

Carol Bult, Rex Chisholm, Pat Deverka, Geoff Ginsburg, Howard Jacob, Howard McLeod, Mary Relling, Dan Roden, Marc Williams

eMERGE network
ELECTRONIC MEDICAL RECORDS AND GENOMICS

IGNITE
Implementing GeNomics In practicE

NSIGHT

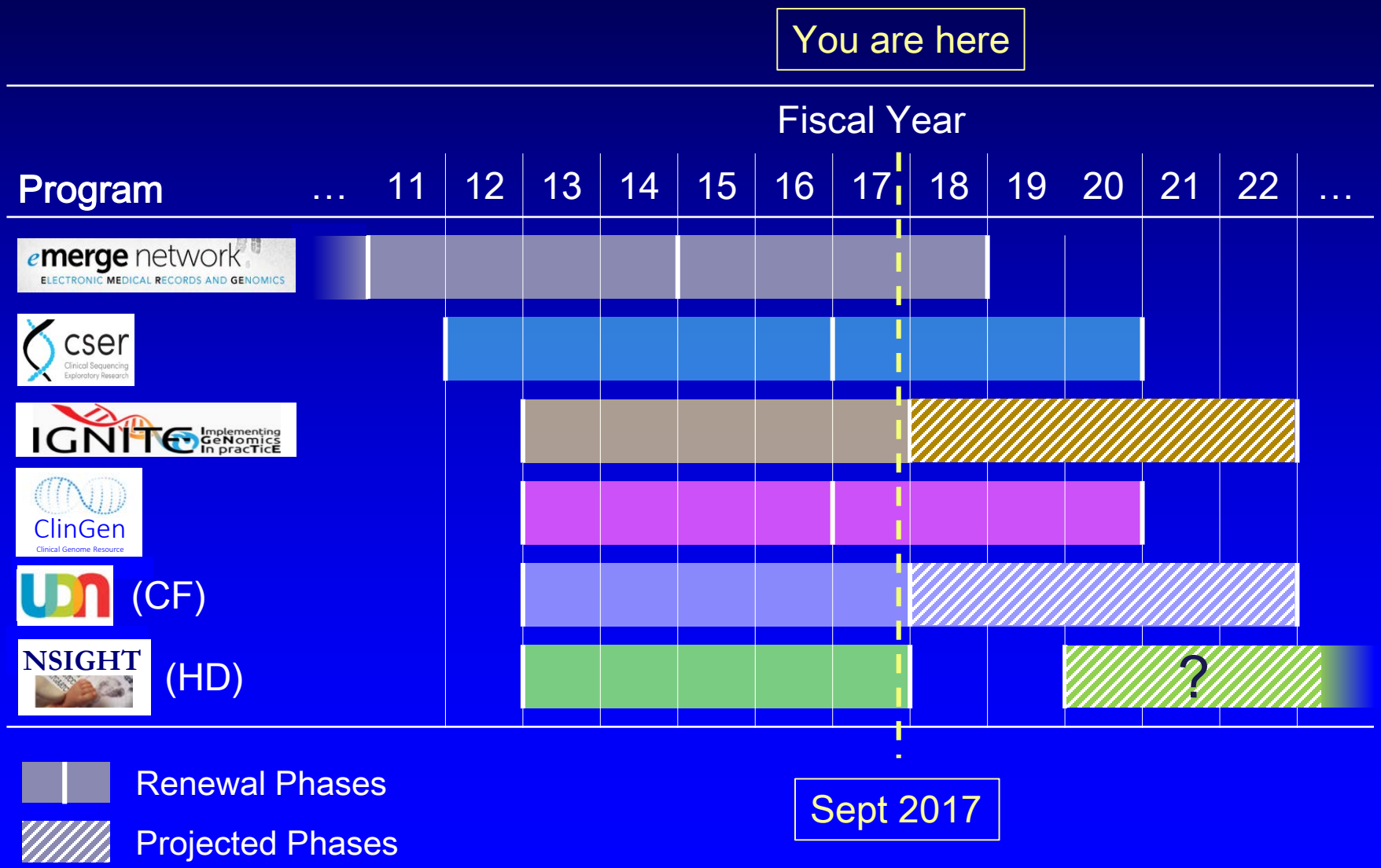
Newborn Sequencing

cser
Clinical Sequencing Exploratory Research

UDN
Undiagnosed Diseases Network

ClinGen
Clinical Genome Resource

Timeline of NHGRI Genomic Medicine Programs



NHGRI Genomic Medicine Definition August 2012

Genomic Medicine: *An emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the other implications of that clinical use.*

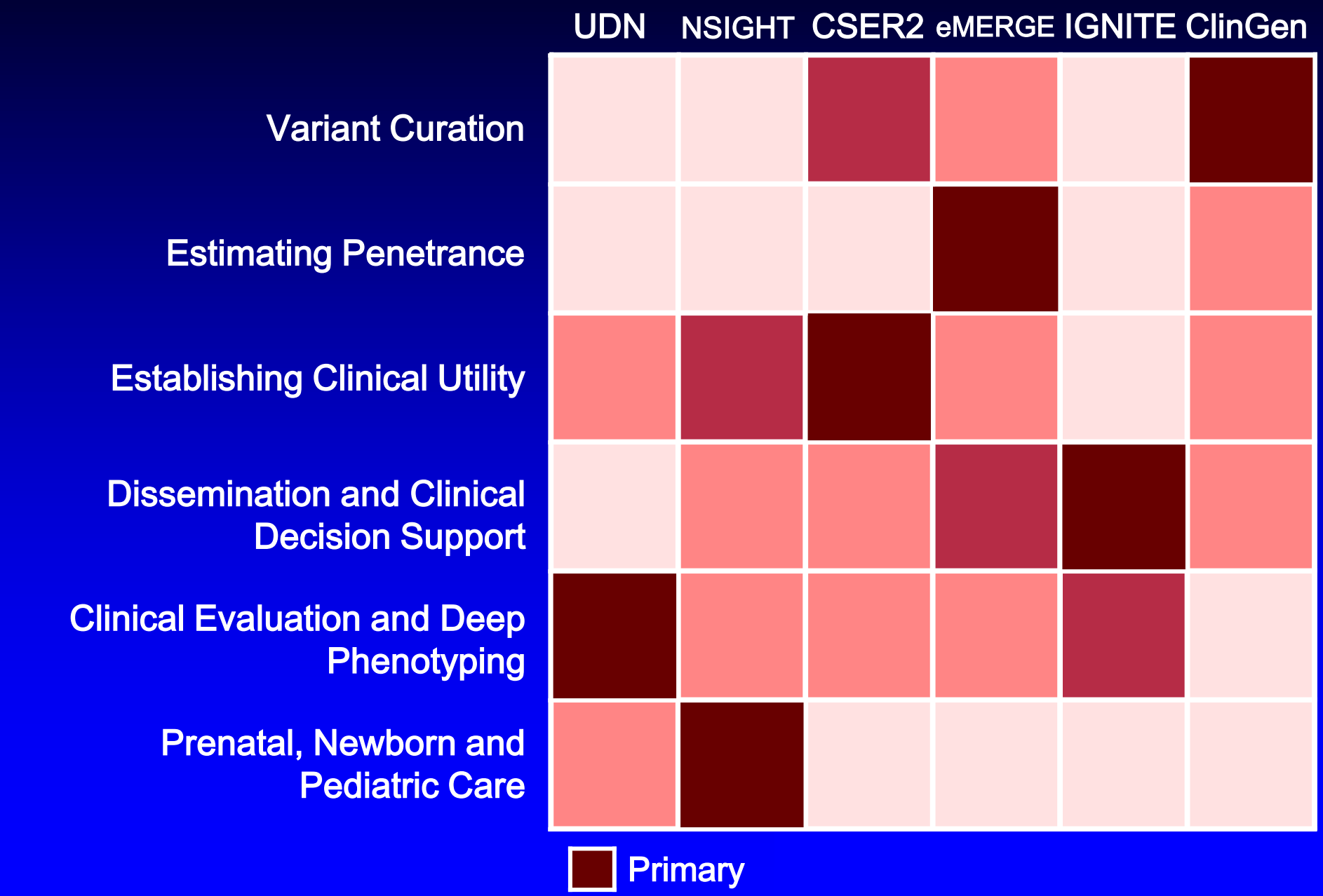
- Purposefully narrow
- By 'genomic,' NHGRI means direct information about DNA or RNA; downstream products outside immediate view
- NHGRI recognizes dominant portion of its current portfolio appropriately supports the foundational research that will ultimately produce the discipline of genomic medicine
- Fourth and fifth NHGRI strategic plan domains capture research activities under umbrella of genomic medicine
- Metaphorically viewed as key 'destination' for attaining mission of improving health through genomics research

NHGRI's Genomic Medicine Research Program

Program	Goal	Σ$M	Years
UDN[1]	Diagnose rare and new diseases by expanding NIH's Undiagnosed Diseases Program	121	FY13-17
NSIGHT[2]	Explore possible uses of genomic sequence information in the newborn period	25	FY13-17
CSER[3]	Explore infrastructure, methods, and issues for integrating genomic sequence into clinical care	83	FY12-16
eMERGE[4]	Use biorepositories with EMRs for genomics; (III) assess penetrance of 106 clinically relevant genes in 25,000 individuals, develop e-phenotypes, CDS	135	FY07-18
IGNITE[3]	Develop and disseminate methods for incorporating patients' genomic findings into their clinical care	28	FY13-17
ClinGen[4]	Develop and disseminate consensus information on genes and variants relevant to clinical care	28	FY13-16

[1]NIH Common Fund; [2]Co-Funded by NICHD; [3]Co-Funded by NCI; [4]Co-Funded by OD.

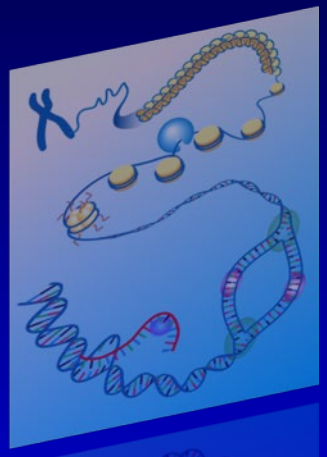
Emphasis Areas of Genomic Medicine Programs



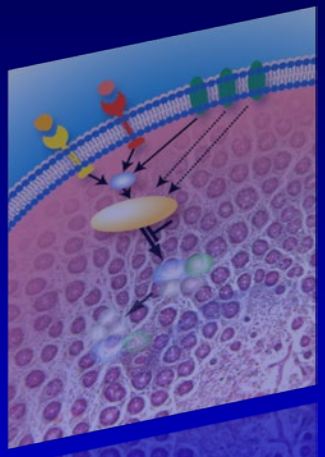
Five Domains of Genomics Research

Understanding the Structure of Genomes

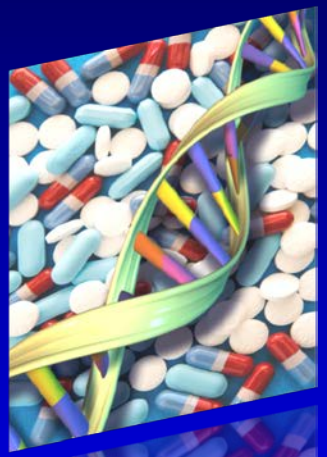
Understanding the Biology of Genomes



Understanding the Biology of Disease



Advancing the Science of Medicine



Improving the Effectiveness of Healthcare

Green et al. 2011