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

The NEW ENGLAND JOURNAL of MEDICINE

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

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
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.

**Tuesday, May 2, 2017**

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**YouTube Video Playlist: Genomic Medicine X: Pharmacogenomics**

**Meeting Summary**

**Executive Summary**

**Tweets from the meeting: #GenomicMed10**

**GOLDILOKs Study: Patient Booklet**
Bedside Back to Bench: Building Bridges between Basic and Clinical Genomic Research

Teri A. Manolio,1,4 Douglas M. Fowler,2 Lea M. Starita,2 Melissa A. Haendel,3 Daniel G. MacArthur,4,5 Leslie G. Biesecker,1 Elizabeth Worthy,5 Rex L. Chisholm,7 Eric D. Green,3 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 Bult25

SUMMARY

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

Variant Interpretation: Functional Assays to the Rescue

Lea M. Starita,1,2,* 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. Fowler1,13,*

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 exploring the effects of any common variant is a daunting task. Therefore, we developed a data-driven approach that leverages 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.

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. Each of the variants that have been previously detected, as well interpretations 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

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.

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
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

• *BRCA1/2* 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 report

• Clinical
• Public engagement and education
• Provider education and feedback
• Policy and regulatory strategies

NHS rollout of genomic medicine services planned for early 2019

To be continued...
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
Timeline of NHGRI Genomic Medicine Programs

You are here: Sept 2017

<table>
<thead>
<tr>
<th>Program</th>
<th>Fiscal Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>eMERGE</td>
<td>11 12 13 14 15 16 17</td>
</tr>
<tr>
<td>CSER</td>
<td></td>
</tr>
<tr>
<td>IGNITE</td>
<td></td>
</tr>
<tr>
<td>ClinGen</td>
<td></td>
</tr>
<tr>
<td>UDN (CF)</td>
<td></td>
</tr>
<tr>
<td>NSIGHT (HD)</td>
<td></td>
</tr>
</tbody>
</table>

- **Renewal Phases**
- **Projected Phases**

?
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

<table>
<thead>
<tr>
<th>Program</th>
<th>Goal</th>
<th>Σ$M</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDN¹</td>
<td>Diagnose rare and new diseases by expanding NIH’s Undiagnosed Diseases Program</td>
<td>121</td>
<td>FY13-17</td>
</tr>
<tr>
<td>NSIGHT²</td>
<td>Explore possible uses of genomic sequence information in the newborn period</td>
<td>25</td>
<td>FY13-17</td>
</tr>
<tr>
<td>CSER³</td>
<td>Explore infrastructure, methods, and issues for integrating genomic sequence into clinical care</td>
<td>83</td>
<td>FY12-16</td>
</tr>
<tr>
<td>eMERGE⁴</td>
<td>Use biorepositories with EMRs for genomics; (III) assess penetrance of 106 clinically relevant genes in 25,000 individuals, develop e-phenotypes, CDS</td>
<td>135</td>
<td>FY07-18</td>
</tr>
<tr>
<td>IGNITE³</td>
<td>Develop and disseminate methods for incorporating patients’ genomic findings into their clinical care</td>
<td>28</td>
<td>FY13-17</td>
</tr>
<tr>
<td>ClinGen⁴</td>
<td>Develop and disseminate consensus information on genes and variants relevant to clinical care</td>
<td>28</td>
<td>FY13-16</td>
</tr>
</tbody>
</table>

¹NIH Common Fund; ²Co-Funded by NICHD; ³Co-Funded by NCI; ⁴Co-Funded by OD.
Emphasis Areas of Genomic Medicine Programs

<table>
<thead>
<tr>
<th></th>
<th>UDN</th>
<th>NSIGHT</th>
<th>CSER2</th>
<th>eMERGE</th>
<th>IGNITE</th>
<th>ClinGen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variant Curation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimating Penetrance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Establishing Clinical Utility</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissemination and Clinical Decision Support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Evaluation and Deep Phenotyping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prenatal, Newborn and Pediatric Care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- UDN
- NSIGHT
- CSER2
- eMERGE
- IGNITE
- ClinGen

Primary

Prenatal, Newborn and Pediatric Care
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