Genomic Medicine Working Group
Update

Teri Manolio, M.D., Ph.D.
February 10, 2020
NACHGR Genomic Medicine Working Group Members

Carol Bult  Jackson Labs
Rex Chisholm  Northwestern
Pat Deverka  Innovation and Value Initiative
Geoff Ginsburg  Duke
Gail Jarvik  U Washington
George Mensah  NHLBI
Mary Relling  St. Jude
Dan Roden  Vanderbilt
Marc Williams  Geisinger

NHGRI
Eric Green  Robb Rowley
Teri Manolio  Cecelia Tamburro
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 for genomic medicine implementation
Rarul Sudden Death

Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults

Implications for Primary Prevention

Pharmacogenomics 2019
Clinical Implementation 2019
Sequencing 2019
Oncology 2019
Professional Guidelines and Policy 2019

November: Diagnostic gene sequencing panels: from design to implementation
Criteria for inclusion of papers

- Involve use of patients' individual genetic variant information in clinical decision-making
- Demonstrate impact of direct clinical implementation
- Are likely to be generalizable beyond original setting
- Are likely to have implications for healthcare systems or practice guidelines
- Are of sufficient size to be robust to sampling error
- Are broadly representative of the field beyond NHGRI-sponsored or US-funded programs

Send a nomination to GMWG@nih.gov

Lancet Genomic Medicine Series

Genomic Medicine 1

Genomic Medicine 2

Pharmacogenomics in practice: from discovery to implementation

Genomic Medicine 3

Genomics and personalisation of cancer therapy

Genomic Medicine 4

Family history and genetic risk assessment in the 21st century

Genomic Medicine 5

Building evidence and measuring clinical outcomes for genomic medicine

Josh F Peterson, Dan M Roden, Lori A Orlando, Andrea H Ramirez, George A Mensah, Marc S Williams
Research Directions in the Clinical Implementation of Pharmacogenomics: An Overview of US Programs and Projects

Simona Volpi¹, Carol J. Bulb², Rex L. Chisholm³, Patricia A. Deverka⁴, Geoffrey S. Ginsburg⁵, Howard J. Jacob⁶, Melpomeni Kasapi⁷, Howard L. McLeod⁷, Dan M. Roden⁸, Marc S. Williams⁹, Eric D. Green¹, Laura Lyman Rodriguez¹, Samuel Aronson¹⁰, Larisa H. Cavallari¹¹, Joshua C. Denny¹², Lynn G. Dressler¹³, Julie A. Johnson¹¹, Teri E. Klein¹⁴, J. Steven Leeder¹⁵, Micheline Piquette-Miller¹⁶, Minoli Perera¹⁷, Laura J. Rasmussen-Torvik¹⁸, Heidi L. Rehm¹⁹, Marylyn D. Ritchie²⁰, Todd C. Skaar²¹, Nikhil Wagle²², Richard Weinshilboum²³, Kristin W. Witzel²⁴, Robert Wildin²⁵, John Wilson²⁶, Teri A. Manolio¹ and Mary V. Relling²⁷

Response to a drug often differs widely among individual patients. This variability is frequently observed not only with respect to effective responses but also with adverse drug reactions. Matching patients to the drugs that are most likely to be effective and least likely to cause harm is the goal of effective therapeutics. Pharmacogenomics (PGx) holds the promise of precision medicine through elucidating the genetic determinants responsible for pharmacological outcomes and using them to guide drug selection and dosing. Here we survey the US landscape of research programs in PGx implementation, review current advances and clinical applications of PGx, summarize the obstacles that have hindered PGx implementation, and identify the critical knowledge gaps and possible studies needed to help to address them.
Genomic Medicine Meetings

Genomic Medicine XII: Genomics and Risk Prediction

Agenda

8:30 a.m. Welcome and Introductions
Teri Manolio, Dan Roden

Executive Summary
Meeting Summary

Video (Roden) - Video (Manolio) - Slides
GM XII: Research Directions in Genomic Medicine Implementation, May 6-7, 2019

Objectives:

- Review the state of science of polygenic risk scores and how it can be improved
- Examine other information sources that should be integrated with genetic variant information in predicting risk
- Identify research directions in development and implementation of genomic risk prediction
GM XII Meeting Recommendations

- Investigate how to accelerate adoption of evidence-based risk prediction from early adopting centers to diverse systems
- Research best ways to communicate risk to patients and whether and how patients will want to receive risk results
- Research best ways to deliver risk information to clinicians
- Prioritize validating existing PRS in diverse populations to determine how causal variants and effect sizes vary, and in conditions amenable to real-world implementation
- Find ways to incorporate PRS into existing risk estimation tools to improve and speed acceptance into professional societies’ guidelines
- Measure process outcomes and intermediate phenotypes related to clinical outcomes to increase PRS predictability

eMERGE RFAs (RFA-HG-19-013, -014, -015) will use EMRs to develop, evaluate, and disseminate genomic risk assessment and management tools for clinical use, and will validate existing PRS in diverse populations
GM XII Meeting Recommendations

- Investigate methods for integrating other ‘omic data into risk prediction, potentially using ‘omic data as a way to weight SNP-based risk scores
- Prioritize investigation of diseases with existing data, longitudinal cohorts, and availability of hard clinical endpoints
- Investigate how PRS can further stratify risk of developing disease in patients with monogenic disease or high-risk genetic variants
- Develop PRS for specific disease subtypes; a “one size fits all” approach does not always work when predicting disease risk, especially in non-EA populations

Panel on Multi-Condition PRS Studies: Capture Breadth of Conditions

- Disease incidence, risk variants, risk magnitudes across different ancestries
- Age of onset, optimal age of intervention
- Strength of environmental component and other non-genetic risk contributors
- Genetic architecture
- Burden/invasiveness of intervention
- Implementation model
- Availability of hard endpoints
• Review and highlight landscape of genomic medicine being applied to population and public health in U.S. and public health models that may be informative
• Explore significant barriers in reaching underserved communities and put them on equal footing with those who have access to academic health centers
• Define a research agenda building upon these efforts that will enable implementation of genomic medicine into settings not previously addressed by NHGRI
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<th>Program</th>
<th>Goal</th>
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<td>UDN¹</td>
<td>Diagnose rare and new diseases by expanding NIH’s Undiagnosed Diseases Program</td>
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<td>NSIGHT²</td>
<td>Explore possible uses of genomic sequence information in the newborn period</td>
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<td>CSER³</td>
<td>Generate evidence of clinical utility of sequencing in diverse clinical settings</td>
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<td>eMERGE⁴</td>
<td>Use biorepositories with EMRs for genomics; assess generalizability and clinical impact of genomic risk prediction</td>
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<td>IGNITE³</td>
<td>Conduct pragmatic clinical trials of genomic interventions (APOL1 testing and PGx for pain and depression treatment)</td>
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<td>ClinGen⁴</td>
<td>Develop and disseminate consensus information on genes and variants relevant to clinical care</td>
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<td>Investigator-Initiated</td>
<td>Clinical sequencing research, HIV/AIDS drug response and co-morbidities, serious ADRs, pharmacogenomics, etc.</td>
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<td>Training</td>
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¹NIH Common Fund; ²Co-Funded by NICHD; ³Co-Funded by NCI; ⁴Co-Funded by OD.