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?

There has been unprecedented optimism that genomics will bring about radical improvements in human health. 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).

Optimism about the potential contributions of genomics for improving human health has been fuelled by new insights about cancer, 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 believe that the kinds of achievements that can be anticipated with a few examples (Box 2) where a confluence of need and opportunities should

Identify risk
Prevent disease
Improve diagnostics
Improve treatments
Increase access
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

Planning the Future of Genomics:
Foundational Research and Applications in Genomic Medicine
Airlie Center, Warrenton, Virginia
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
Much more than anticipated
Largely in isolation
Key barriers:
  • Lack of evidence
  • Interpretation of variants
  • Lack of expertise
  • Lack of standards
  • EMR integration
NACHGR Genomic Medicine Working Group Members

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

Eric Green  
Teri Manolio  
Laura Rodriguez  

Jackson Lab  
Northwestern  
Duke  
Med Coll Wisconsin  
Moffitt Cancer Ctr  
St. Jude  
Vanderbilt  
Geisinger
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
NHGRI defines genomic medicine as "an emerging medical discipline that involves using genomic information about an individual as part of their clinical care and the health outcomes and policy implications of that clinical use."

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 for the widespread use of genomic medicine.

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- GHB has been involved in promoting genetic literacy among healthcare workers through electronic resources 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 a Web-based tool from NHGRI and the U.S. Surgeon General’s Family History Initiative that helps you document your own family health history. Using any computer, an Internet connection, and an up-to-date Web browser, you provide your health information to build a drawing of your family health history. Both the chart and the drawing can be printed and shared with family members and your doctor. Risk assessment tools for diabetes and colon cancer are also included.
Outgrowths of GM Meetings

1. Clin Gen
2. Action
3. Payers
4. Clin
5. Action
6. ISCC
7. GM

- FDA
- CMS
- G2MC
- SJS/TEN
- NIH WG
- Trans-NIH WG
- Genomics Roundtable
- Institute of Medicine
- eMERGE PGx
- IGNITE
“Well, this is just going from bad to worse.”

# NHGRI’s Genomic Medicine Research Programs

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

The NIH Undiagnosed Diseases Program is designed to help people with rare diseases that are not currently recognized by medical professionals. The program focuses on identifying and understanding these diseases through research, clinical trials, and collaboration with other organizations and institutions.

See Also:
- Undiagnosed Diseases Network

On Other Sites:
- Undiagnosed Diseases Network

Related Content:
- ORDR Home > Undiagnosed Diseases
- 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
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
<table>
<thead>
<tr>
<th>Site</th>
<th>Disease/Condition</th>
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<tbody>
<tr>
<td>Baylor*</td>
<td>Pediatric Cancer</td>
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<tr>
<td>Brigham</td>
<td>Healthy Pts, Hypertrophic Cardiomyopathy</td>
</tr>
<tr>
<td>CHOP</td>
<td>Pediatric Diseases (Intellectual Disability)</td>
</tr>
<tr>
<td>Dana-Farber</td>
<td>Solid Tumors</td>
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<tr>
<td>Hudson-Alpha</td>
<td>Children with Intellectual Dysfunction</td>
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<tr>
<td>Kaiser Portland</td>
<td>Preconception Carrier Screening</td>
</tr>
<tr>
<td>U Michigan*</td>
<td>Adults and Children with Advanced Cancer</td>
</tr>
<tr>
<td>UNC</td>
<td>Cardiomyopathy, Cancer</td>
</tr>
<tr>
<td>UW*</td>
<td>CRC and Polyposis</td>
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*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
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

<table>
<thead>
<tr>
<th>Lab</th>
<th>Variants</th>
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<tr>
<td>Lab 1</td>
<td>16/128</td>
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<tr>
<td>Lab 2</td>
<td>24/128</td>
</tr>
<tr>
<td>Lab 3</td>
<td>17/128</td>
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</tbody>
</table>

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
Duke University – Geoffrey Ginsburg, M.D., Ph.D. (Family History)
Mount Sinai School of Medicine – Erwin Bottinger, M.D. (Hypertension and CKD)
University of Florida – Julie Johnson, Ph.D. (Pharmacogenomics)
University of Pennsylvania – Stephen Kimmel, M.D. (Coordinating Center)
National Human Genome Research Institute
Vanderbilt University – Joshua Denny, M.D. (Pharmacogenomics)
University of Maryland – Toni Pollin, Ph.D. (Diabetes)
Indiana University – David Flockhart, M.D., Ph.D. (Pharmacogenomics)

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

Courtesy Erin Ramos, NHGRI
### Issues Addressed by Key NHGRI Genomic Medicine Programs

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<tr>
<th>Issue</th>
<th>UDN</th>
<th>NSIGHT</th>
<th>CSER</th>
<th>eMERGE</th>
<th>IGNITE</th>
<th>ClinGen</th>
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<td>ELSI of Seq</td>
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<td>Integrate Seq in Clinic, EMR</td>
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<td>Outcomes of Clinical Use</td>
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<td>Variant Discovery</td>
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<td>Penetrance</td>
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<tr>
<td>Translate Outside Specialized Ctrs</td>
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<td>Standardize Clin Annotation, Interp</td>
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<tr>
<td>Define/Share Impl Processes</td>
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NHGRI’s Genomic Medicine Portfolio

How we got here…

Where we are 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!

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Dan Roden
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