Precision Medicine: Opportunities for Impact Nationally and Globally

The Duke Center for Applied Genomics & Precision Medicine

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@PersonalizedMed
Disclosures

• Founder

  MeTree&You

• Consultant
  – Konica Minolta
  – Pappas Ventures
  – Peer Medical
  – Fabric Genomics
  – Origin Commercial Advisors

• Funding: NIH, DOD, NASA, Abbott, 23andMe
Implementation and Impact of Genomic and Precision Medicine ....

- Duke
- North Carolina
- Nationally
- Globally
2003: Genomic and Personalized Medicine

Human Genome Project → Sequencing & other Omics → Precision Health & Medicine
2021: Precision Health and Medicine

An interdisciplinary approach using individual information and population data to optimize health and clinical care

- Human Genome Project
- Sequencing & other Omics
- Digital Health
- Diverse Population Engagement
- Genome Biology
- Phenotypes AI/ML
- Implementation & Outcomes
- Enabling Policies and Workforce Development

Precision Health & Medicine
Our vision is to **accelerate translation** of discoveries in the genome and data sciences to improve health.

**T1**
- Discovery

**T2**
- Translation

**T3**
- Implementation

**T4**
- Outcomes

**Center for Applied Genomics & Precision Medicine**

- Programs in Applied Genomics
- Programs in Precision Medicine

- Early Disease Detection
- Systems and Clinical Pharmacogenomics
- Predictive Analytics
- Biomarker Discovery
- Diagnostics
- Clinical Sequencing

**Education and Training**
The (Decentralized) “Clinic” of the Future

Precision Health

Precision Medicine
Innovation in Early Disease Detection and Diagnosis: Emerging Infections Require Novel Methods

COVID-19

Woods, McClain, Tsalik, Ko, Petzold
DARPA: Predicting Health and Disease

Goal: To develop a predictor of incipient respiratory viral infection following exposure ... using the host response

Healthy Volunteers → Standard Viral Challenge → 5 Day Observation → Dense Time Series → Samples

- Transcriptome
- Proteome
- Clinical Predictors
- Metabolome
- Candidate Biomarkers

14 Human Viral Challenges Completed: RSV, HRV, INF
A Host Viral Classifier Can Identify Those Who Will Become Sick... Days Before Symptoms

![Graphs showing factor scores for H1N1 and H3N2 over time.](image)

**Mean and standard deviation for the discriminative factor**

- **H1N1**
  - Blue = Symptomatic Patients
  - Red = Asymptomatic Patients

- **H3N2**
  - Blue = Symptomatic Patients
  - Red = Asymptomatic Patients

Detection 2-3 days before peak symptoms

**Woods et al, PLoS ONE 2013**
Pre-Symptomatic Detection in Naturally-Acquired Infection: An Index Case-Close Contact Study

McClain et al, Lancet ID, 2020
Host Response to SARs-CoV2 Infection

- RNAseq from blood from 46 consecutive patients w COVID19
- 77 Time points
- Model comparisons:
  - Seasonal coronavirus
  - Influenza
  - Bacterial pneumonia
  - (Healthy controls)
- COVID19 AUC = 0.90

McClain et al, Nat Comm 2021
North Carolina Precision Health Collaborative (NCPHC)

**Vision:**
To advance transformative precision health through innovation and partnerships
• Expand and link existing genomic medicine efforts
• Develop implementation methods, in diverse settings and populations
• Contribute to evidence base regarding outcomes of incorporating genomic information into clinical care
• Disseminate best practices for genomic medicine implementation, diffusion, and sustainability

https://gmkb.org/
Duke University – Geoffrey Ginsburg, M.D., Ph.D.
   Lori Orlando, M.D. (Family History and Coordinating Center)

Mount Sinai School of Medicine – Carol Horowitz, M.D.
   (Hypertension and CKD)

University of Florida – Julie Johnson, Ph.D.
   (Pharmacogenomics)

National Human Genome Research Institute

Vanderbilt University – Joshua Denny, M.D.,
   Josh Peterson M.D. (Pharmacogenomics)

Indiana University – Todd Skaar, Ph.D., Paul
   Dexter, M.D. (Pharmacogenomics)
IGNITE I: The Realities of Genomic Medicine Research

- Implementation is a science -- and it is hard
  - Complex workflows must be understood
  - Process measures can optimize integration into patient/provider workflows
- EMRs are not ready to incorporate genomic data
- Local provider champions are key
- Network wide studies are enormously powerful
- Genomic medicine research may also help reduce disparities

Ginsburg Pers Med 2019
Implementing Genomics in Practice
Pragmatic Clinical Trials Network

Analytic Validity
- Accuracy, precision, and reproducibility

Clinical Validity
- Association of the test result with clinical outcomes of interest

Clinical Utility
- Evidence that test use influences physician decision-making and/or improves patient outcomes

Pharmacogenetics
Genetic Risk

Primary Care or Specialty Care Patient

Pragmatic Clinical Trials

Standard of Care → Outcome
Genomics-Guided → Outcome

Patient, Provider, System and Economic Outcomes

Ginsburg Genet in Med 2021
A Depression and Opioid Pragmatic Trial in Pharmacogenetics (ADOPT PGx)

Determine whether genotype-guided therapy of opioids and SSRIs leads to improved pain control and depressive symptoms.
Genetic testing to Understand Renal Disease Disparities across the U.S. (GUARDD-US)

To determine the effect of participant and provider knowledge of a positive $APOL1$ status on blood pressure management on change in systolic blood pressure (SBP) from baseline to 3 months after randomization among the $APOL1+$ participants.
• > 50 nations
• Explore synergies, redundancies, collaborative opportunities for implementation of genomics into medicine
• Opportunities to advance the genome sciences as an agenda to impact global health
Toward Eradicating SJS/TEN: Thailand and Singapore

SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation

HHS Public Access
Author manuscript
J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2019 January 01.
Published as final edited form as:

Name, family name, sex, and age
Result of laboratory screening
Interpretation: High risk of developing SJS/TEN when exposed to carbamazepine.

Suggestion: This patient is carrying the HLA-B*15:02 risk allele, which strongly associates with the development of SJS/TEN. Please avoid using carbamazepine or any drug that has a similar molecular structure.

For more information, please contact the following hotlines:

Signed by: molecular clinical pharmacist

Pharmacogenomics and Personalized Medicine
Faculty of Medicine, Ramathibodi Hospital

Interpreted by: ผลิตภัณฑ์ genotyping and genaMatch ผลิตภัณฑ์ genotyping and genaMatch
A Global Collaborative to Advance Genomic Medicine

Geoffrey S. Ginsburg 1,*

Working Groups

- Education
- Policy
- Evidence
- Flagship Projects
  - Family History
  - Rare Disease
  - Pharmacogenomics
  - Genetic Risk Testing
- Advocacy

https://g2mc.org

Belcher, Ginsburg, Ward 2020
https://www.genomicspolicy.org
Global Large Scale National Genomics Initiatives

- Genomics England
  - 100,000 genomes (Linked to NHS EMR data)
  - 5M over the next 5 years
- Genome Qatar
  - 300,000 Qatari genomes (Linked to CERNER EMR data)
- Estonian Genome Project
  - 100,000 genomes (Linked to health care data)
- Genomics Israel
  - 100,000 genomes (Clalit HMO)
- Genome Saudi Arabia
  - 150,000 genomes, focused on cardiovascular disease
- Singapore Genome Project
  - 10,000 expanding 100,000 WGS
- All of US (USA)
  - 1,000,000 Genomes (Linked to EMR and mHealth data)
- Million Veterans Program (Linked to VA EMR)
  - 1M Genomes/genotypes
- Initiating efforts in Korea, Malaysia, Scotland, France, Africa, South America
International HundredK+ Cohorts Consortium

Geoff Ginsburg, M.D., Ph.D.
Teri Manolio M.D., Ph.D.
Peter Goodhand

IHCCGLOBAL.ORG
International 100K+ Cohorts Consortium (IHCC): Premise

- Large cohort studies have been established world-wide (some for decades)
- Each constrained by size, ancestral origins, and geographic boundaries
- Constraints limit analyses – e.g., subgroup, exposures, and interactions
- *Combining data from these cohorts enables addressing pressing global health questions none can answer alone*
  - Enhance value of each
  - Leverage enormous investments in them
IHCC: Vision

Vision:
A global community of cohorts working together to advance science and improve health for all.

Mission:
Enabling cohorts to revolutionize population health science by providing sustainable data infrastructure, a collaborative research environment, and policies and best practices that foster connectivity, interoperability, and reciprocity.
Relevant History

- 2015: NIH compiled information on large cohort programs (≥100K participants)
- 2017: HIROs agreed to bring cohorts together, to encourage data sharing, improve efficiencies, & maximize investments
- March 2018: First Cohorts Summit at Duke University
- April 2019: Second Cohorts Summit in Iceland
- May 2020: Third (Virtual) Summit
Goals:

- Explore prospects for collaboration and compatibility of cohorts
- Discuss a searchable global cohort registry
- Understand barriers to data and specimen sharing

Criteria for cohort participation:

- ≥100,000 participants
- Not selected for disease
- Available biospecimens
- Potential for longitudinal follow-up
First Summit (2018): 100 Attendees, 24 Countries

~60 cohorts, ~30M participants
Challenges to Combining Cohorts

- Complexity and limited documentation of available data
- Lack of standardization and harmonization of questionnaires
- Inability to move, send, receive, or utilize data/samples due to regulatory restrictions and national laws
- Lack of standards for phenotyping and health outcomes
- Cross-cultural and differences in risk tolerance and privacy
Potential Solutions

- Articulate data standards to encourage and facilitate sharing
- Standardize data collection prospectively using tools such as PROMIS and PhenX
- Move analysis to data sets rather than vice versa
- Develop automated approaches to phenotyping based on EHRs
- Use digital health devices or apps for phenotypes
- Use existing frameworks to help address privacy, security, consent, such as *All of Us* and GA4GH
Compelling Scientific Questions that can be Addressed with Millions of Individuals

• Risks associated with rare exposures and outcomes
• Generalizability of risk factors and associations
• Population-specific determinants of health
• Molecular and social etiology of rare and common disease
• Human knock-out identification and phenotyping
Overarching Goals

• Develop the **information technology** to promote ‘discoverability’ of the cohorts and sharing of data
• Develop a robust **scientific plan** that leverages cross cohort collaboration and maximizes input from the global scientific community
• Develop the **policy agenda** to advance data sharing, engagement with industry
Second Summit (2019):
Reykjavik April 23-24

• 117 representatives of 67 cohorts from 29 countries
• 10 HIRO groups: AMED, A-STAR, BMGF, CIHR, EC, MRC, NIH, ICMR, MRC, WT
• Actions:
  – Finalize information technology and policies to support the science
  – Pilot science and demonstrate it can be done
  – Develop a formal collaborative structure and charter
  – Rules of engagement for biopharma and tech firms
Proof of Concept Study: Polygenic Risk Scores
(Patrick Sleiman, CHOP, USA, lead)

- Pilot demonstration of cross-cohort data to develop polygenic risk scores for asthma, blood pressure, BMI, T2D, height
- Unique weight files for causal variants created by CHOP and sent to cohorts
- 8 cohorts’ data from 5 countries with a federated analyses completed
- Trans-Ethnic scores outperform all population specific scores in non-European cohorts with similar predictive values.
- The ‘federated’ approach of generating scores at each site had challenges, but the process worked well for efficient analysis
IHCC Cohort Atlas Project

Bring together several axes of cohort data, e.g. disease status, data use, sample collection parameters, genotype, and phenotype

IHCC consists of a highly diverse set of over one hundred cohort data dictionaries

IHCC Cohort Atlas aims to:
- Survey and collate cohort data dictionaries for all IHCC cohorts
- Semantically harmonize the cohort metadata
- An online cohort atlas to enable discovery across IHCC cohorts
Current status

- ~100 IHCC cohort members
- 66 cohorts with public metadata
- 25 shared dictionaries
- 9 recontacted individually
- 7 respondents
- 6 loaded in the IHCC Atlas browser
- 5 mapped
Reykjavik Summit: Policy Platform

- Enabling the scientific agenda
  - Data Sharing
  - Governance
  - Consent harmonization
- General Data Protection Regulation (GDPR) considerations
- Incentives/value for participating consortia
- Rules of engagement for industry
3rd International Cohorts Summit: Virtual May 5-6, 2020

- 177 attendees, 27 countries, 87 cohorts
- Coalesce around visionary charter and path forward
- Introduce IHCC Cohorts Atlas
- Finalize the IHCC charter and governance
- Identify new scientifically meritorious cross-cohort research projects
- New: Develop IHCC scientific agenda for COVID 19
Francis Collins, MD, PhD

Director
National Institutes of Health
USA

Opening Keynote
## Multi Cohort Scientific Strategy – Fall 2020

<table>
<thead>
<tr>
<th>Proposal Title</th>
<th>Number of IHCC Cohorts</th>
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<tbody>
<tr>
<td>Global Mental Health Impact of the COVID-19 Pandemic</td>
<td>19</td>
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<tr>
<td>Strengthening biospecimen collection for Global Longitudinal Population Studies in the COVID-19 era</td>
<td>15</td>
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<tr>
<td>Novel coronavirus host susceptibility study in South Africa (COVIGen-SA)</td>
<td>5</td>
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<tr>
<td>High-Throughput Metabolomic Biomarker Measures in Diverse Ancestries</td>
<td>5</td>
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<tr>
<td>Opioid cohort consortium (OPICO) to investigate the effects of regular opioid use on mortality and on cancer development</td>
<td>8</td>
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<tr>
<td>Exploring the role of genetically determined BMI in early life on colorectal cancer in later life</td>
<td>9</td>
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Scientific Strategy – Alzheimer's Disease
(Hakon Hakonarson, Elias Zerhouni – leads)

Our Vision for 2025
A Cohort of Five Million People with or At Risk for Alzheimer’s

2025

Currently Recruited

Maximizing the Power of Cohorts
Initial Scientific Aims

1. Understand the Heterogeneity
   - Aim: To identify new targets for Alzheimer’s therapeutics using large global cohorts of genetically and phenotypically diverse populations, including

2. Deploy Novel Technologies
   - Aim: To explore the use of all emerging novel technologies, including minimally invasive approaches, including
The Current IHCC Horizon – elements in a 5-year plan (1)

- Continually building an inclusive cohorts’ community
- Expansion of the Cohorts Atlas and federated data model
- Cohort enhancements
- Evergreen Policy Agenda
- Educational and workforce
The “Ideal State” for large blood-based cohorts

*Size:* reliable assessment of associations with risk factors requires studies with thousands of cases of each condition

*Diversity:* include sufficiently large numbers of participants across the full range of internal (e.g. genetic and ethnic) and external exposures (e.g. lifestyle and environment)

*Depth:* detailed characterization may yield the greatest value

*Follow-up:* establish long-term follow-up of health outcomes can be achieved securely

*Sustainability:* develop infrastructure to maintain the study long-term (including local research capacity and training)
Visit https://ihccglobal.org/

~110 cohorts, ~60M participants
IHCC Sponsors

Contact: geoffrey.ginsburg@duke.edu