Precision Medicine:
Opportunities for Impact Nationally and Globally

The Duke Center for Applied Genomics & Precision Medicine

Geoffrey S Ginsburg MD PhD
Professor of Medicine, Pathology
Biostatistics & Bioinformatics,
and Biomedical Engineering

@PersonalizedMed

DUKE CENTER for APPLIED GENOMICS & PRECISION MEDICINE

Disclosures

- Founder

MeTree&You

Global Genomic Medicine Collaborative

predigen

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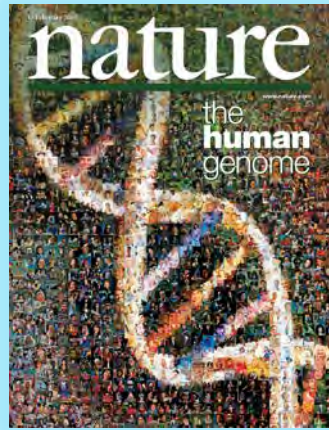 - Fabric Genomics
  - Origin Commercial Advisors

- Funding : NIH, DOD, NASA, Abbott, 23andMe

Implementation and Impact of Genomic and Precision Medicine ....

- Duke

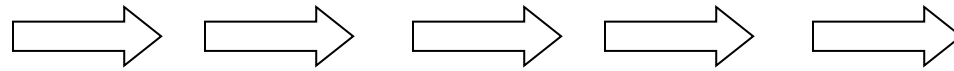- North Carolina

- Nationally

- Globally

2003: Genomic and Personalized Medicine
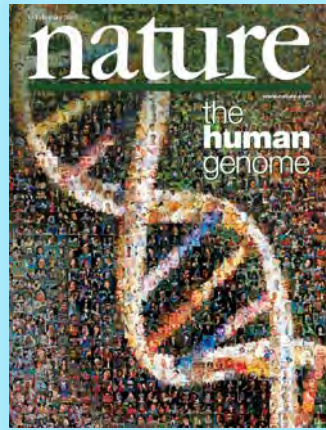

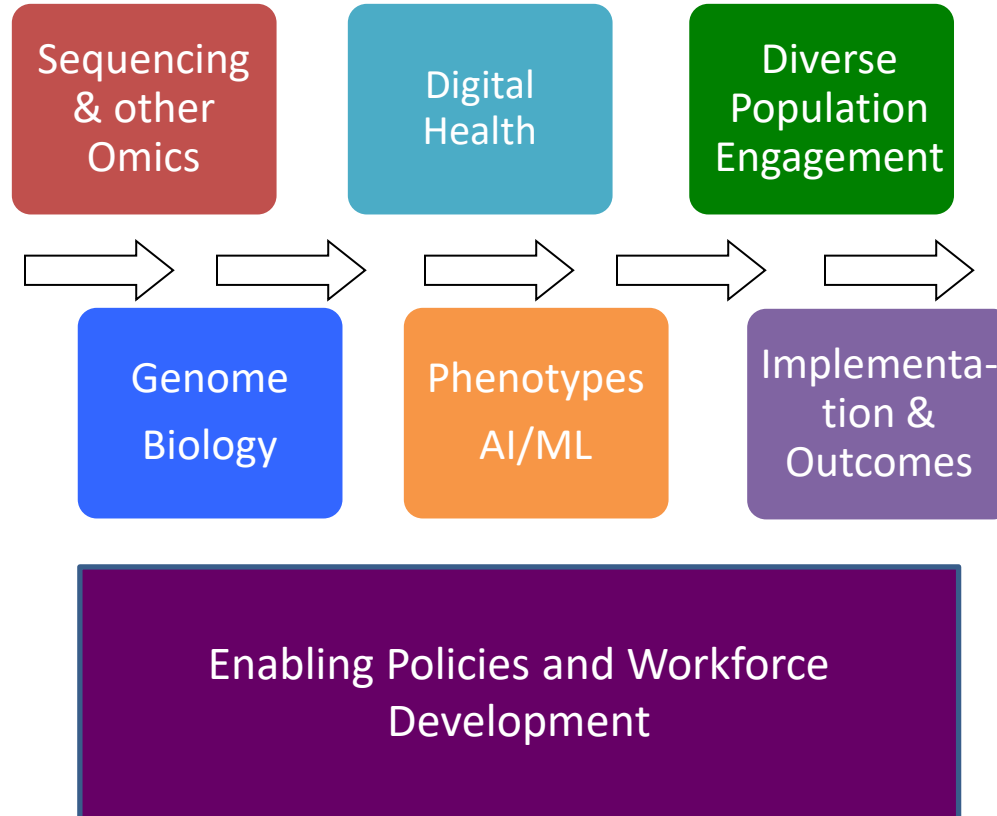Human Genome Project

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

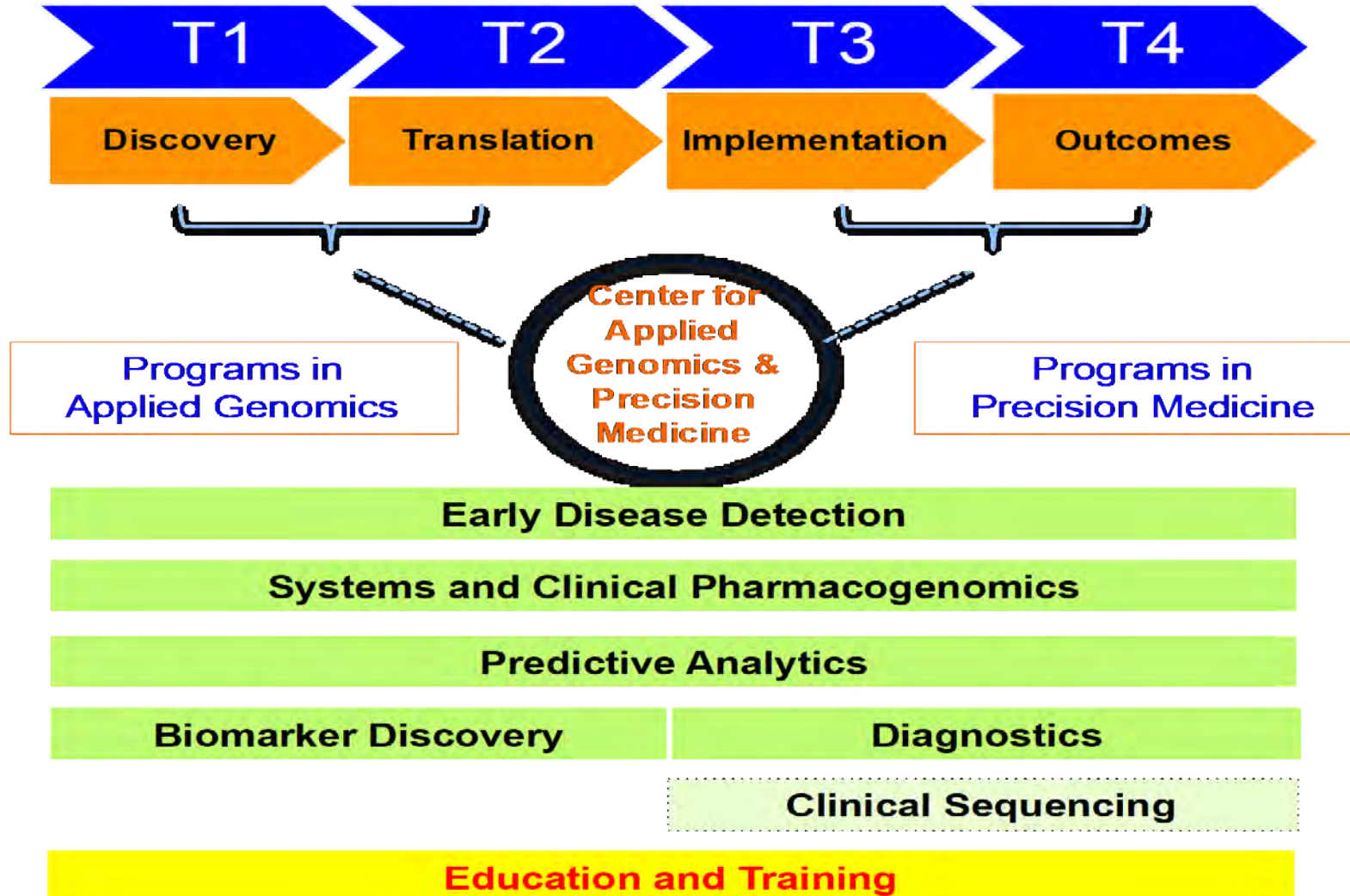Phenotypes AI/ML

Implementa-tion & Outcomes

Enabling Policies and Workforce Development

Precision Health& Medicine
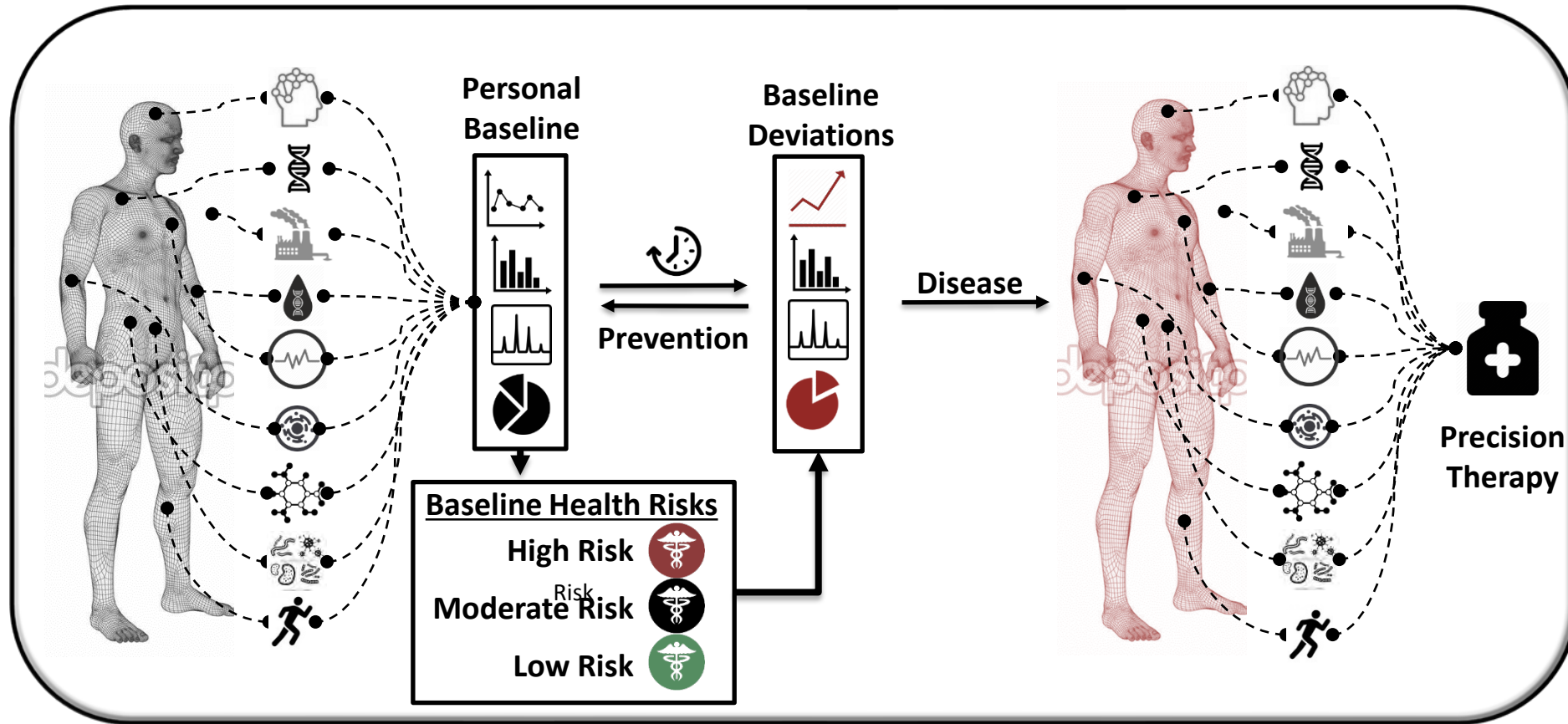
Our vision is to accelerate translation of discoveries in the genome and data sciences to improve health
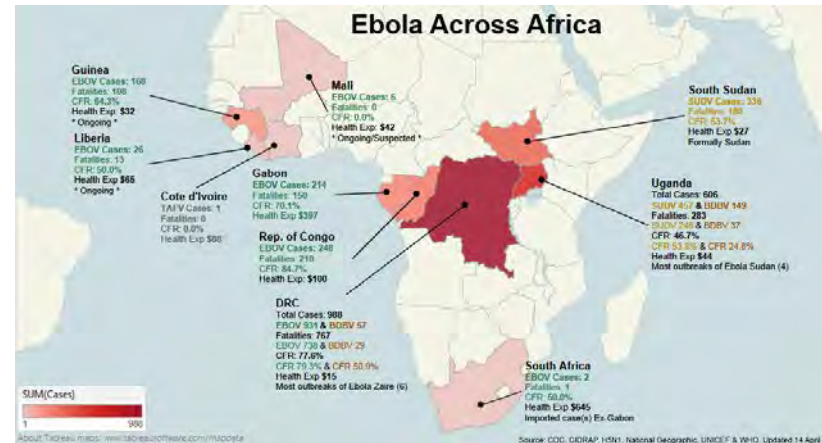
The (Decentralized) "Clinic" of the Future

Precision Health

Precision Medicine

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

COVID-19

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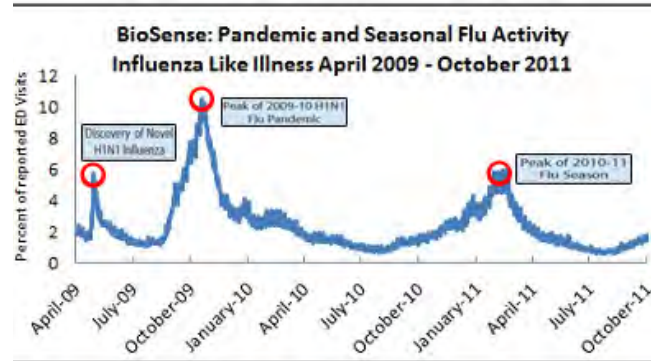
Woods, McClain, Tsalik, Ko, Petzold

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

VOLUNTEERS NEEDED
for paid clinical research

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A Host Viral Classifier Can Identify Those Who Will Become Sick....Days Before Symptoms

a

Mean and standard deviation for the discriminative factor

H1N1

b

Mean and standard deviation for the discriminative factor

H3N2

PCR

Clinical Sx

Hours

Detection 2-3 days before peak symptoms
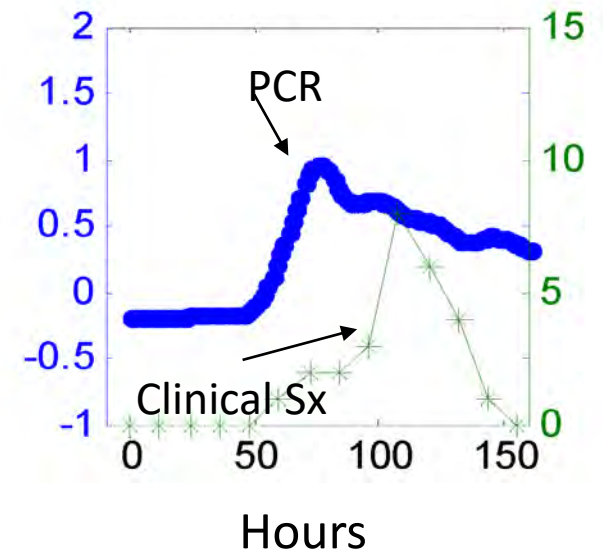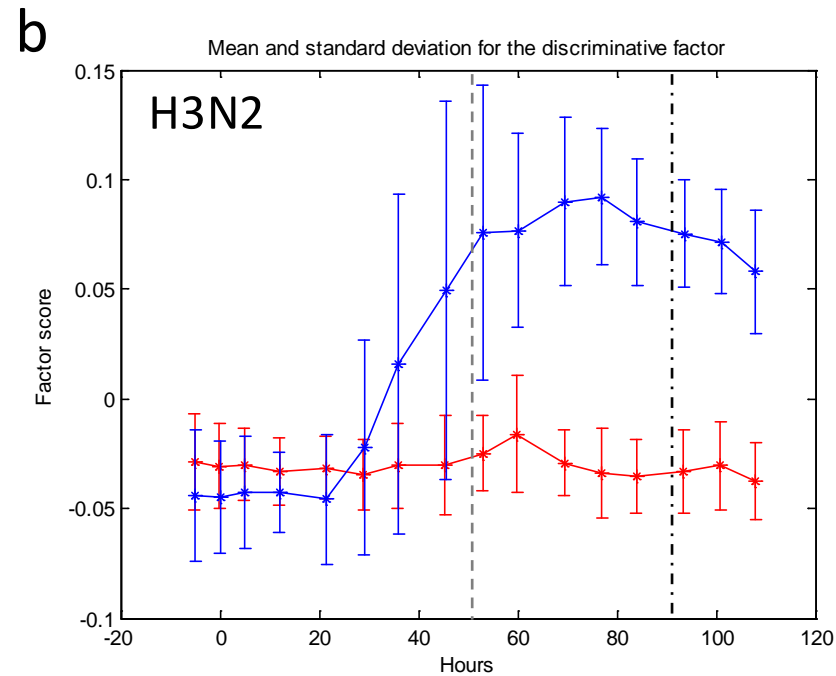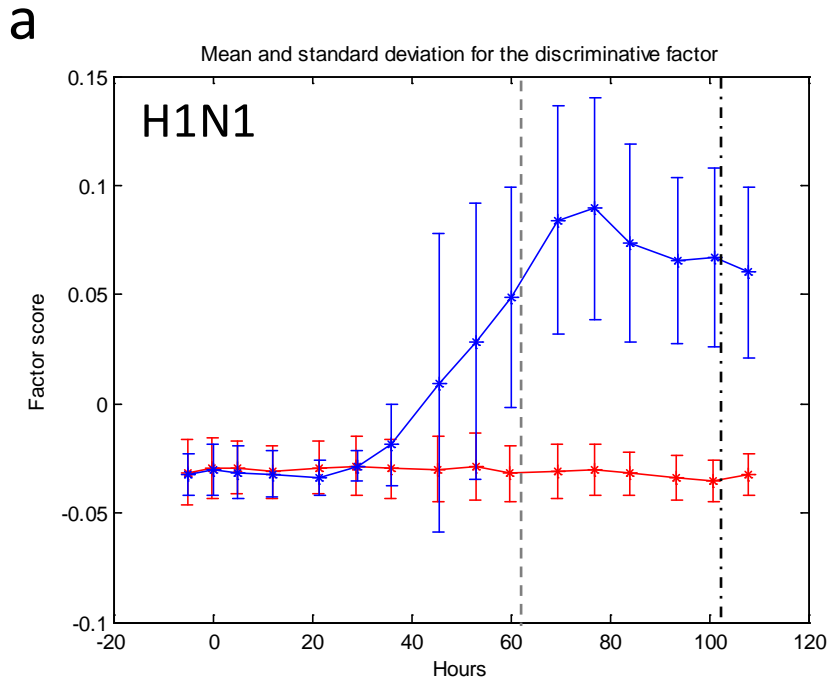
Blue = Symptomatic Patients

Red = Asymptomatic Patients

Woods et al, PLoS ONE 2013

Pre-Symptomatic Detection in Naturally-Acquired Infection: An Index Case-Close Contact Study
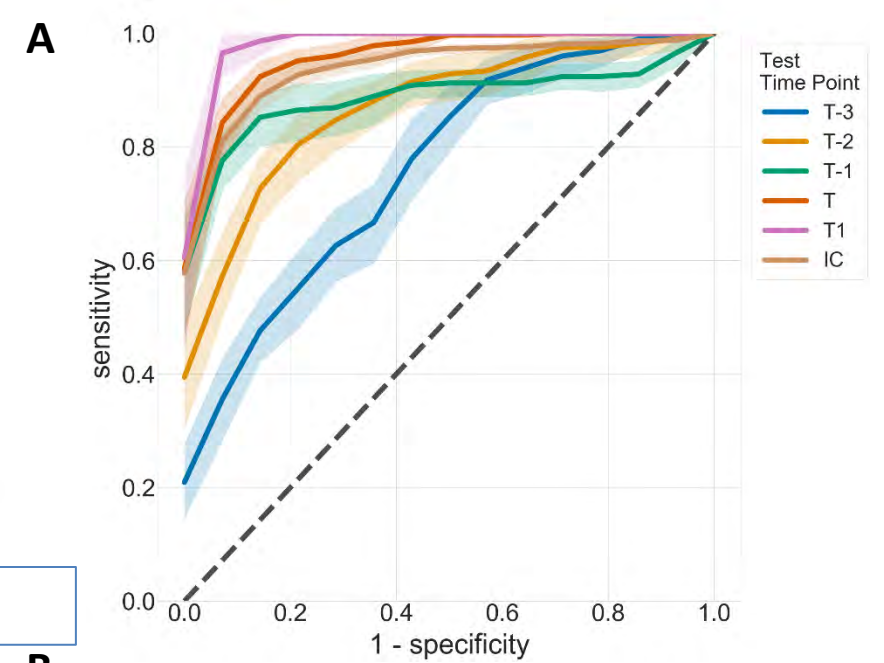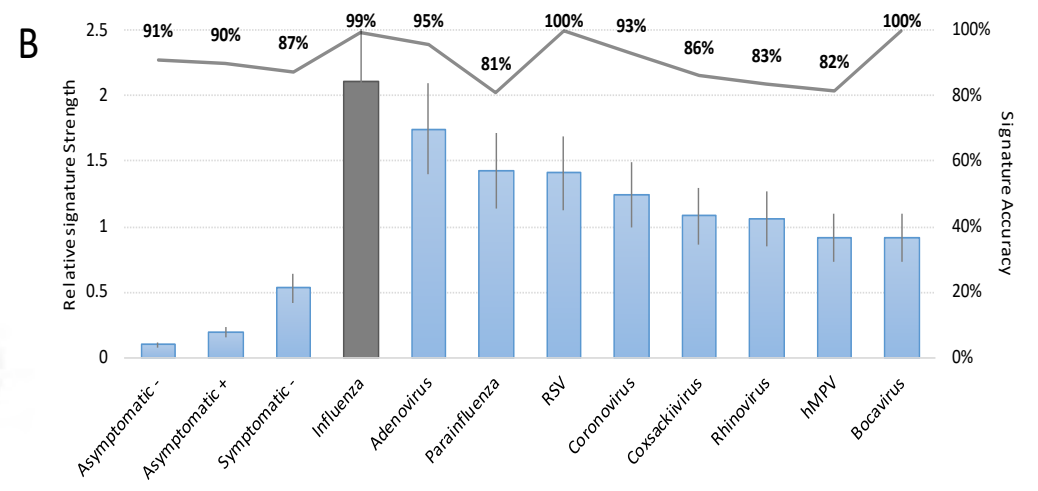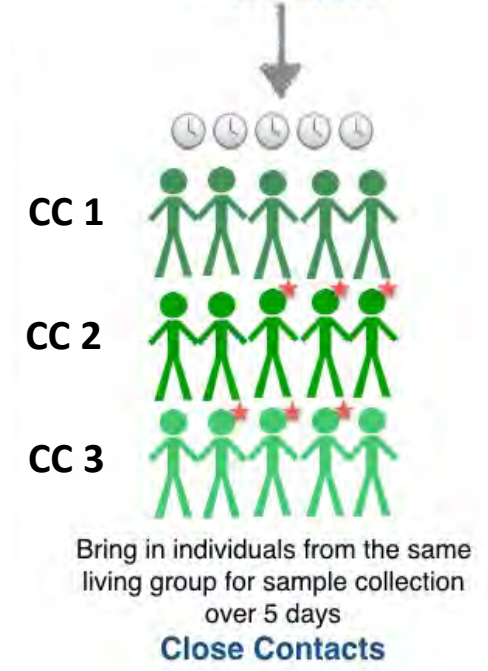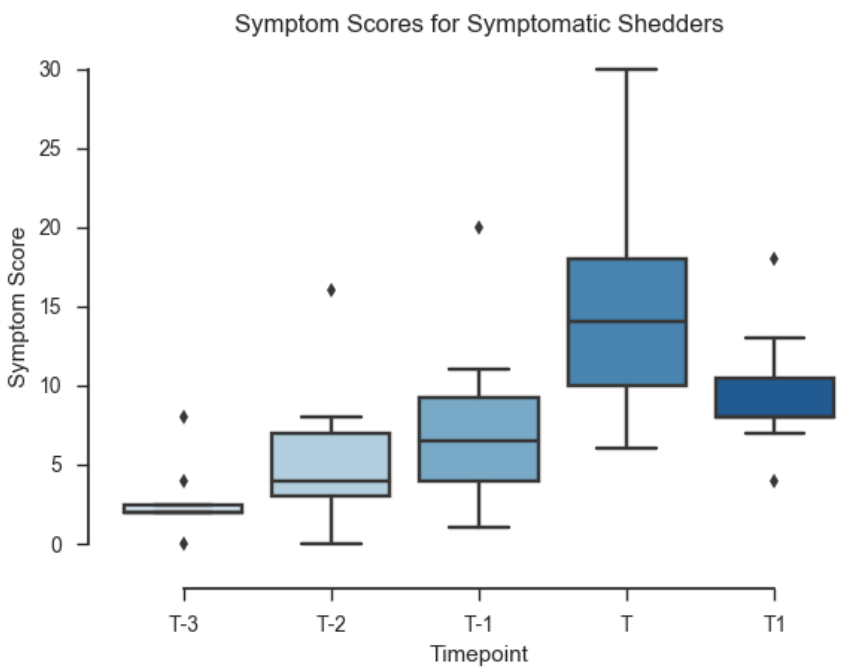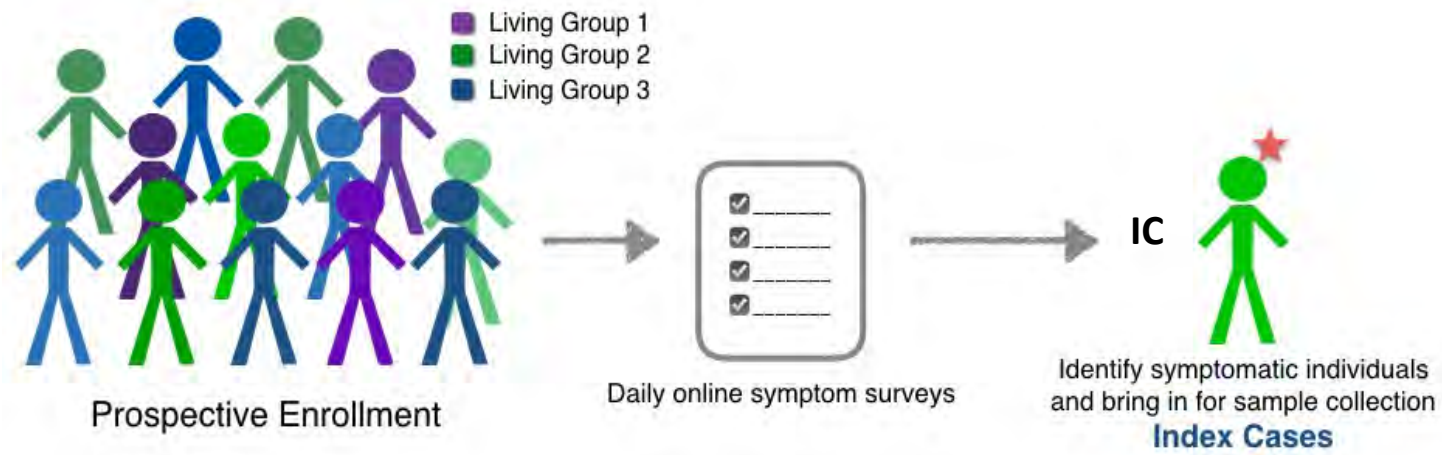
McClain et al, Lancet ID, 2020

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
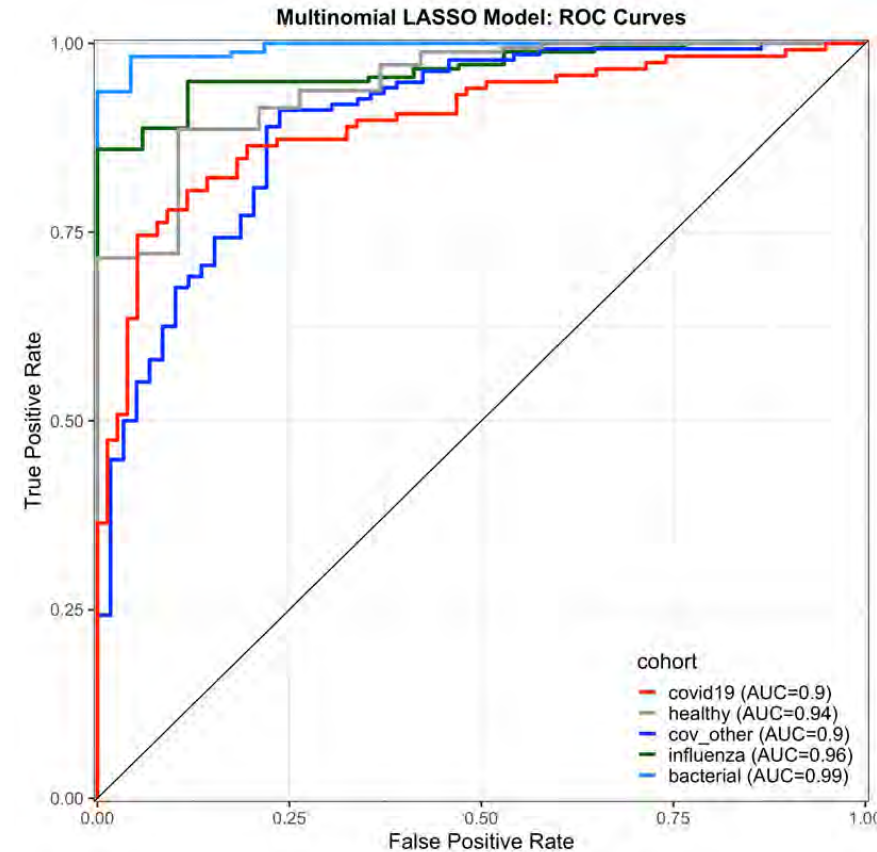
McClain et al, Nat Comm 2021

Multinomial LASSO Model: ROC Curves

cohort
- covid19 (AUC=0.9)
- healthy (AUC=0.94)
- cov_other (AUC=0.9)
- influenza (AUC=0.96)
- bacterial (AUC=0.99)

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North Carolina Precision Health Collaborative (NCPHC)

Vision:

To advance transformative precision health through innovation and partnerships

Imhof, Thomas
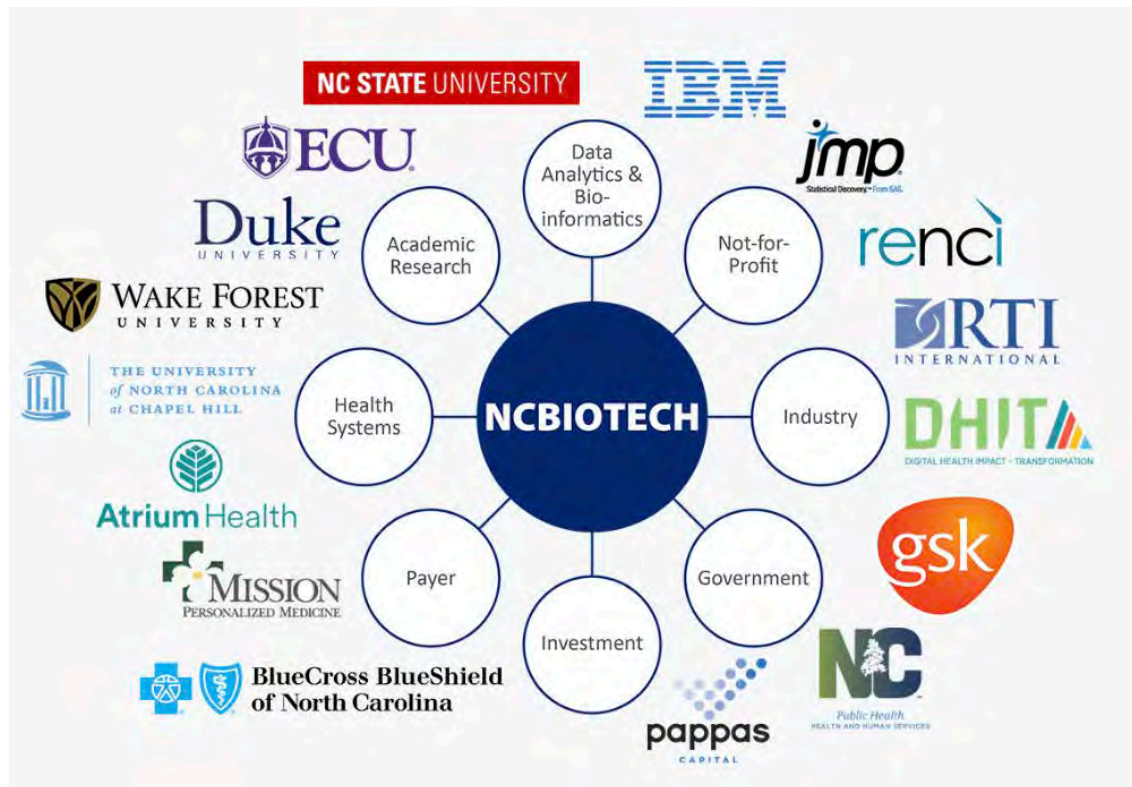
RESEARCH ARTICLE

Open Access

CrossMark

The IGNITE network: a model for genomic medicine implementation and research

Kristin Wiisanen Weitzel[1], Madeline Alexander[2], Barbara A. Bernhardt[3], Neil Calman[4], David J. Carey[5], Larisa H. Cavallari[1], Julie R. Field[6], Diane Hauser[4], Heather A. Junkins[7], Phillip A. Levin[8], Kenneth Levy[9], Ebony B. Madden[7], Teri A. Manolio[7], Jacqueline Odgis[7], Lori A. Orlando[10,19], Reed Pyeritz[3], R. Ryanne Wu[10,19], Alan R. Shuldiner[11,12], Erwin P. Bottinger[13], Joshua C. Denny[14,15], Paul R. Dexter[9], David A. Flockhart[9*], Carol R. Horowitz[16], Julie A. Johnson[1], Stephen E. Kimmel[2,17], Mia A. Levy[18], Toni I. Pollin[11], Geoffrey S. Ginsburg[19*] and on behalf of the IGNITE Network

- **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/

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NIH NHGRI

IGNITE Implementing GeNomics In pracTicE

IGNITE — Implementing GeNomics In pracTicE

* IGNITE Principal Site
☆ New sites

Medical College of Wisconsin
Marshfield Clinic
Aurora Health Care
Regenstrief Institute / Eskenazi Health Center / Indiana University *
Duke University *
Duke University — Coordinating Center
Essentia Health
Icahn School of Medicine at Mount Sinai * / The Institute for Family Health
University of Maryland / Geisinger * / VA — Baltimore Veterans Affairs Medical Center / Bay West Endocrinology Associates
U.S. Air Force
National Human Genome Research Institute
Middle Tennessee Research Institute (MTRI) at Nashville Veterans Affairs Medical Center / Vanderbilt University * / Nashville General Hospital at Meharry — Metropolitan Nashville Hospital Authority
University of Florida * / The Florida State University College of Medicine / Tallahassee Memorial HealthCare / UF & Shands The University of Florida Academic Health Center

● 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 Peterseon M.D.   (Pharmacogenomics)

★ Indiana University – Todd Skaar, Ph.D., Paul
   Dexter, M.D.   (Pharmacogenomics)

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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

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IGNITE
Implementing GeNomics In pracTicE

Implementing Genomics in Practice Pragmatic Clinical Trials Network
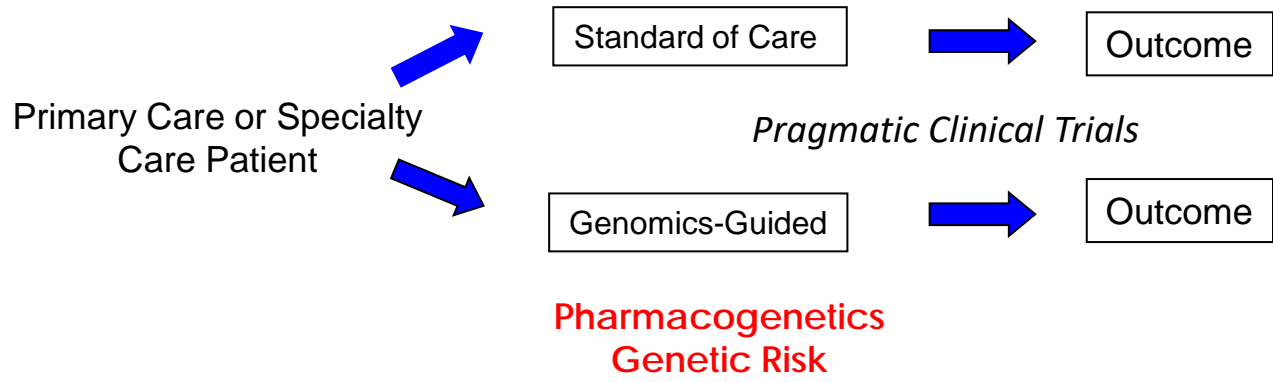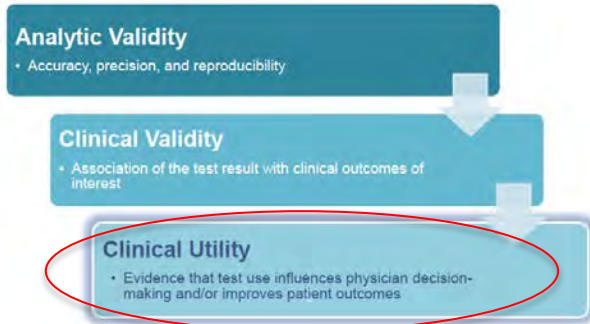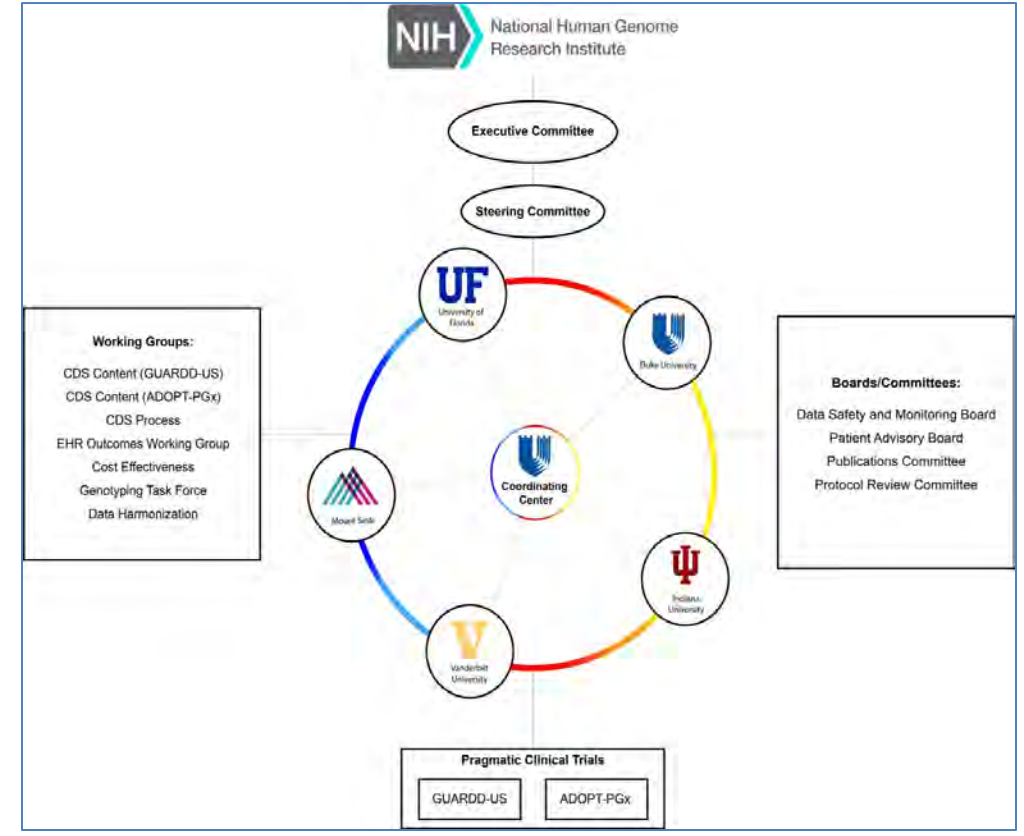
Ginsburg Genet in Med 2021

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

Orlando, Voora, Myers
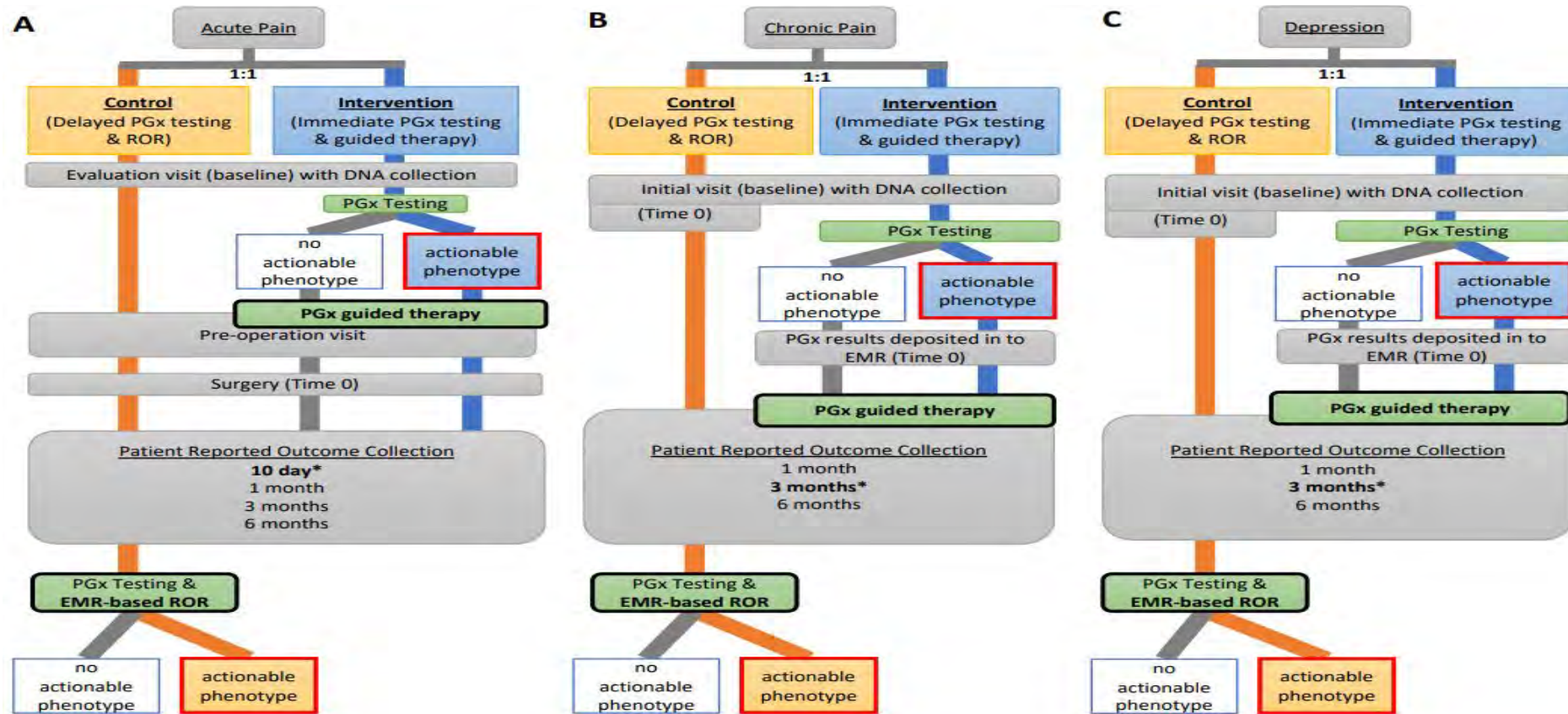
Genetic testing to Understand Renal Disease Disparities across the U.S. (GUARDD-US)

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.
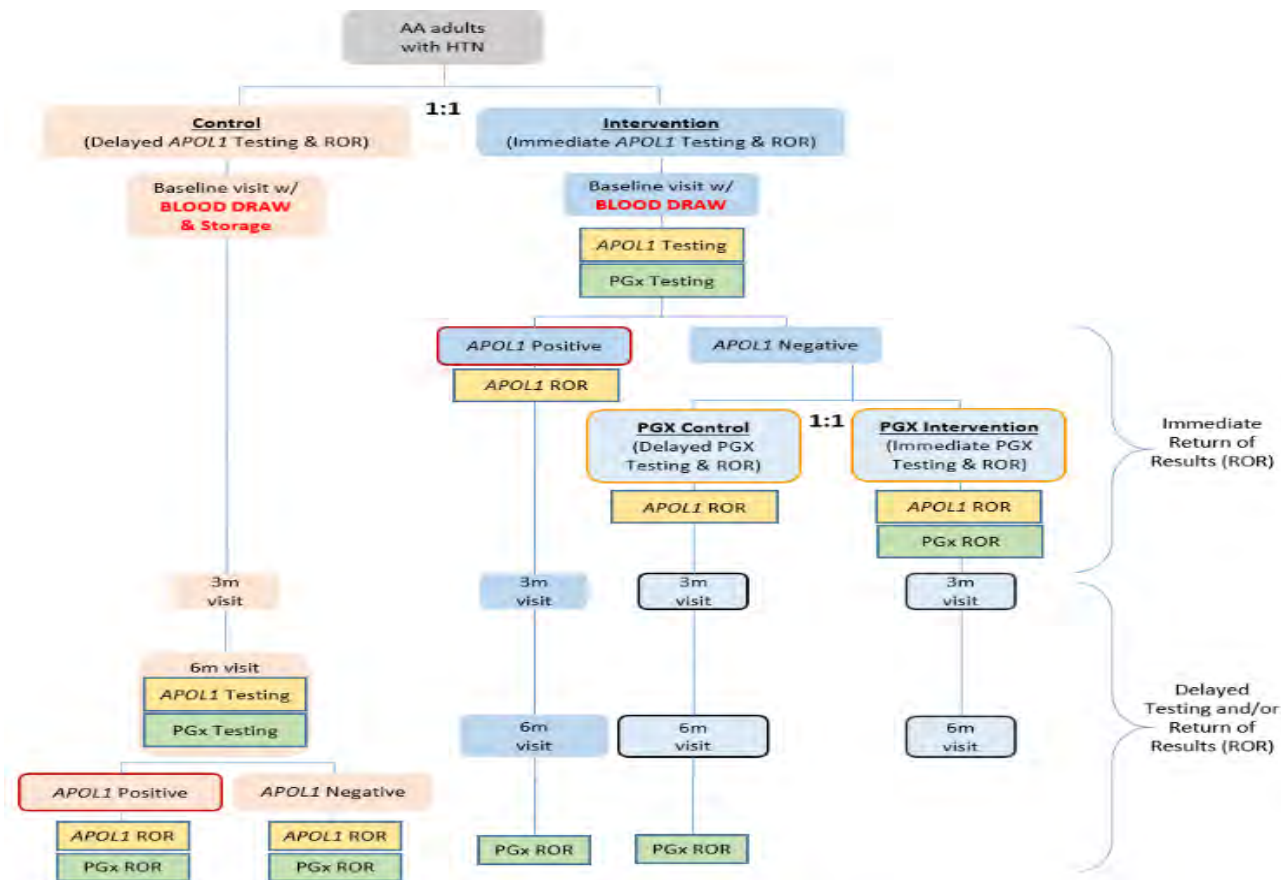
Global Genomic Medicine Collaborative (G2MC)

PERSPECTIVE

POLICY

Global implementation of genomic medicine: We are not alone

Teri A. Manolio,[1*] Marc Abramowicz,[2] Fahd Al-Mulla,[3] Warwick Anderson,[4] Rudi Balling,[5] Adam C. Berger,[6] Steven Bleyl,[7] Aravinda Chakravarti,[8] Wasun Chantratita,[9] Rex L. Chisholm,[10] Vajira H. W. Dissanayake,[11] Michael Dunn,[12] Victor J. Dzau,[13] Bok-Ghee Han,[14] Tim Hubbard,[15] Anne Kolbe,[16] Bruce Korf,[17] Michiaki Kubo,[18] Paul Lasko,[19] Erkki Leego,[20] Surakameth Mahasirimongkol,[21] Partha P. Majumdar,[22] Gert Matthijs,[23] Howard L. McLeod,[24] Andres Metspalu,[20] Pierre Meulien,[25] Satoru Miyano,[26] Yaakov Naparstek,[27] P. Pearl O'Rourke,[28] George P. Patrinos,[29] Heidi L. Rehm,[30] Mary V. Relling,[31] Gad Rennert,[32] Laura Lyman Rodriguez,[1] Dan M. Roden,[33] Alan R. Shuldiner,[34] Sukdeb Sinha,[35] Patrick Tan,[36] Mats Ulfendahl,[37] Robyn Ward,[38] Marc S. Williams,[39] John E. L. Wong,[40] Eric D. Green,[1] Geoffrey S. Ginsburg,[41*]
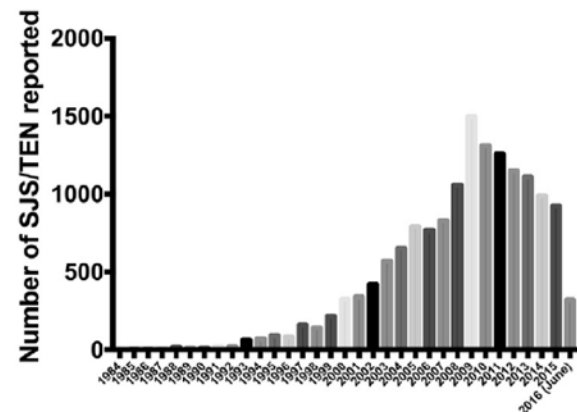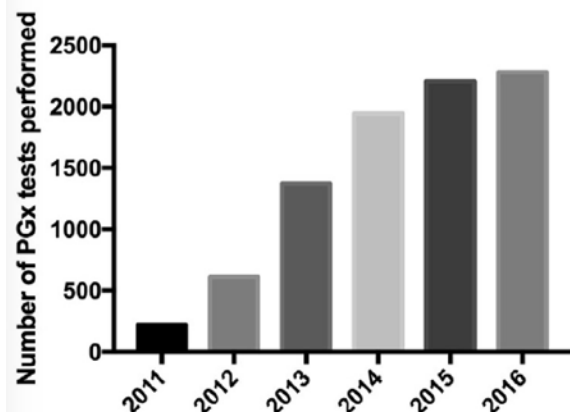
Sci Trans Med 2015

- > 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

FORUM

A Global Collaborative to Advance Genomic Medicine

Geoffrey S. Ginsburg[1],*

SCIENCE TRANSLATIONAL MEDICINE | EDITORIAL

GENOMICS

Global approaches to genomic medicine implementation

Since the sequencing of the human genome, the potential of genomic medicine has stimulated global investment not only in research but also in initiatives to drive genomic medicine implementation in health care. In 2014, European chief medical officers discussed the policy implications of genomic research advances for health systems and called for coordinated engagement to develop and harmonize policies within the European Union (EU) (1). In the same year, leaders in genomic medicine from more than 25 countries discussed the range of approaches for genomic medicine implementation and identified areas that would benefit from multinational collaboration (2). This group became the Global Genomic Medicine Collaborative (G2MC; https://g2mc.org/) in 2016 and recommended that implementation projects around the world should be identified and an inventory created of the policy issues being considered. To this end, the G2MC policy working group has used several strategies to elucidate the approaches that different countries are taking to move genomics from research into routine clinical care.

workforce skills (35 initiatives); ethical, legal, and social implications of genomics (33 initiatives); and public education and awareness (30 initiatives). The policy themes that are least often considered are governance and leadership (18 initiatives) and regulation (17 initiatives). A small number of initiatives also include themes that have been collectively categorized as "other"—such as plans to promote private investment in genomics and the role of biorepositories (13 initiatives). The relative frequency of each theme is likely to reflect the perceived importance of that issue in each local context and the available expertise and sphere of influence of those involved.

In terms of the geographic diversity of these initiatives, 37 different locations around the world are represented, including initiatives in each of the six regions defined by the World Health Organization (http://www.who.int/about/regions/en/). When resource availability is considered, 71% of the initiatives (46 of 65) are in high-income countries, as defined by the World Bank measure based on gross national income per capita (https://datahelpdesk.worldbank.org/knowledgebase/

Belcher, Ginsburg, Ward 2020
https://www.genomicspolicy.org

Working Groups

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

https://g2mc.org

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Global Genomic Medicine Collaborative

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

The Telegraph

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News

All children to receive whole genome sequencing at birth, under ambitions laid out by Matt Hancock

November 5, 2019

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Global Genomic Medicine Collaborative

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

G2MC   Global Genomic Medicine Collaborative   Global Alliance for Genomics & Health   GA4GH

Collaborate. Innovate. Accelerate.

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1st International Cohorts Summit
Duke University, USA (March 2018)

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

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First Summit (2018): 100 Attendees, 24 Countries
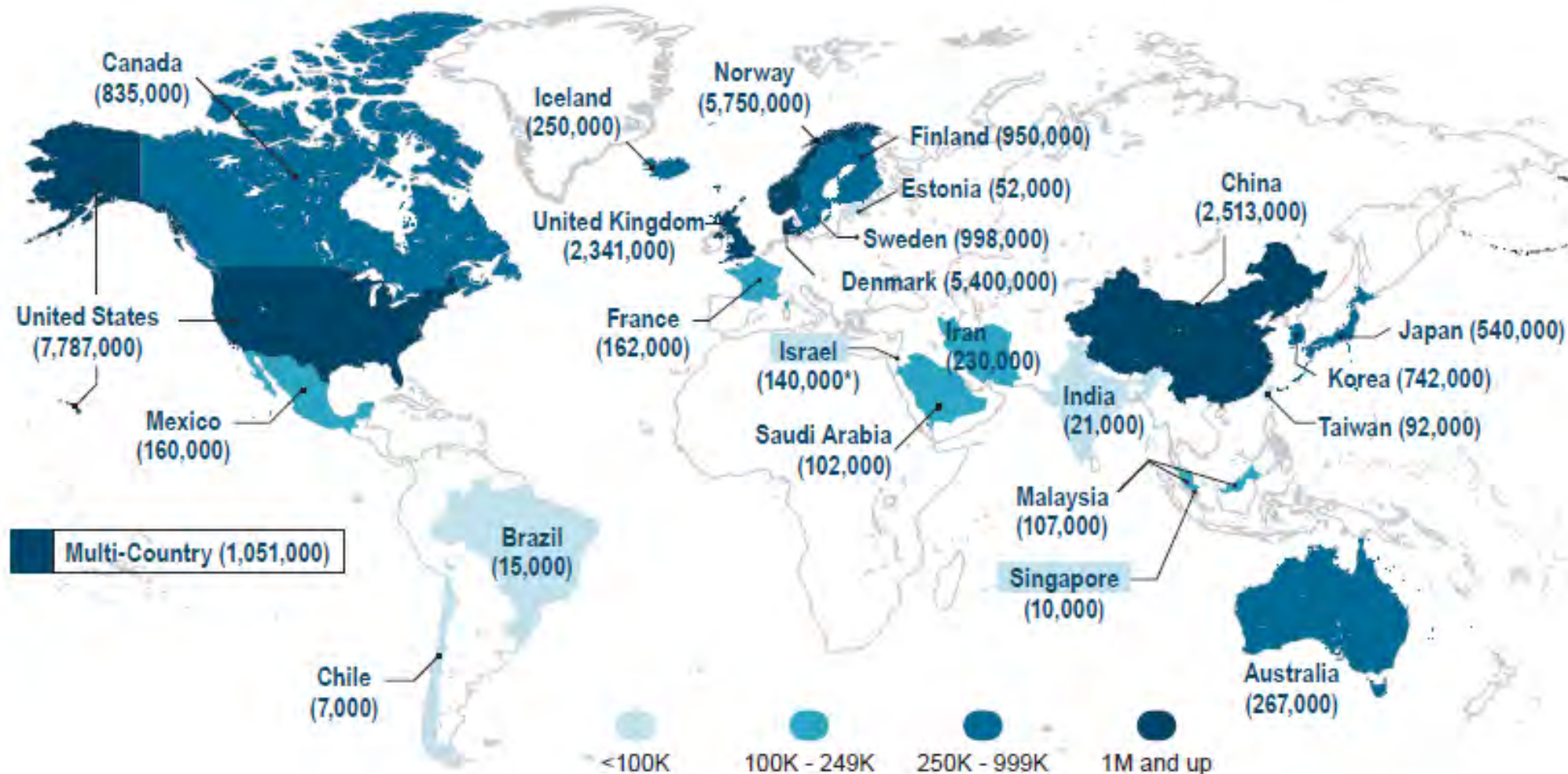
~60 cohorts, ~30M participants

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
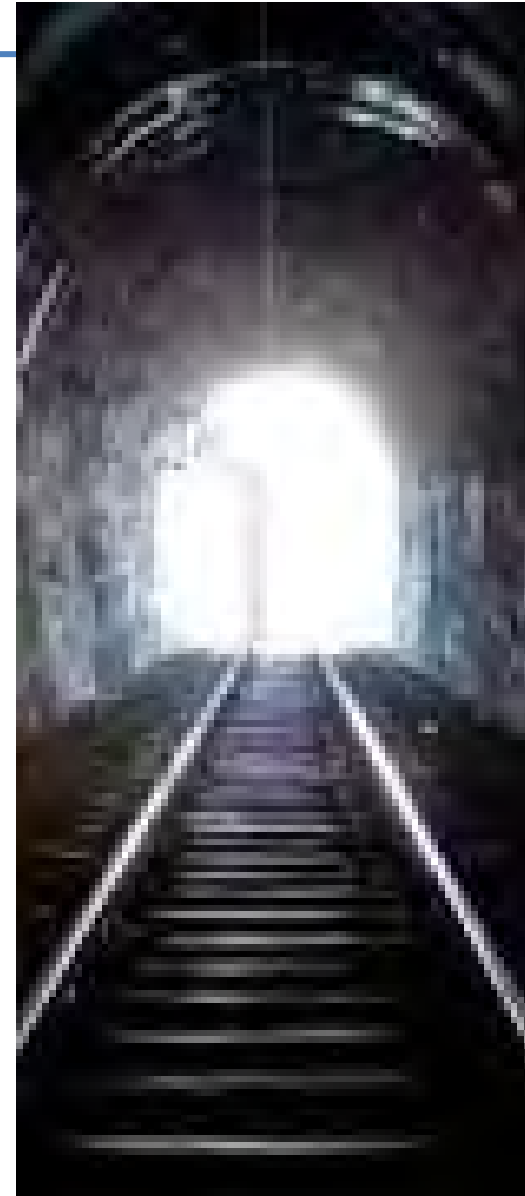
Compelling Scientific Questions that can be Addressed with Millions of Individuals

- 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
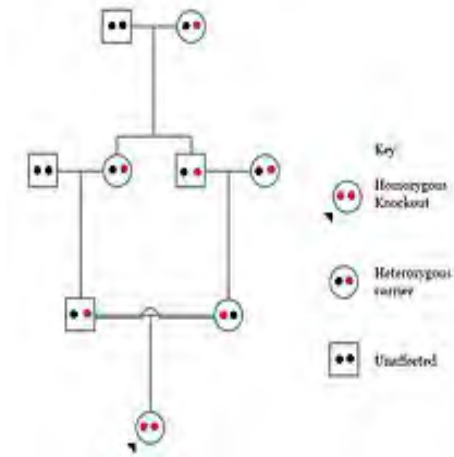
Overarching Goals

- 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

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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

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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
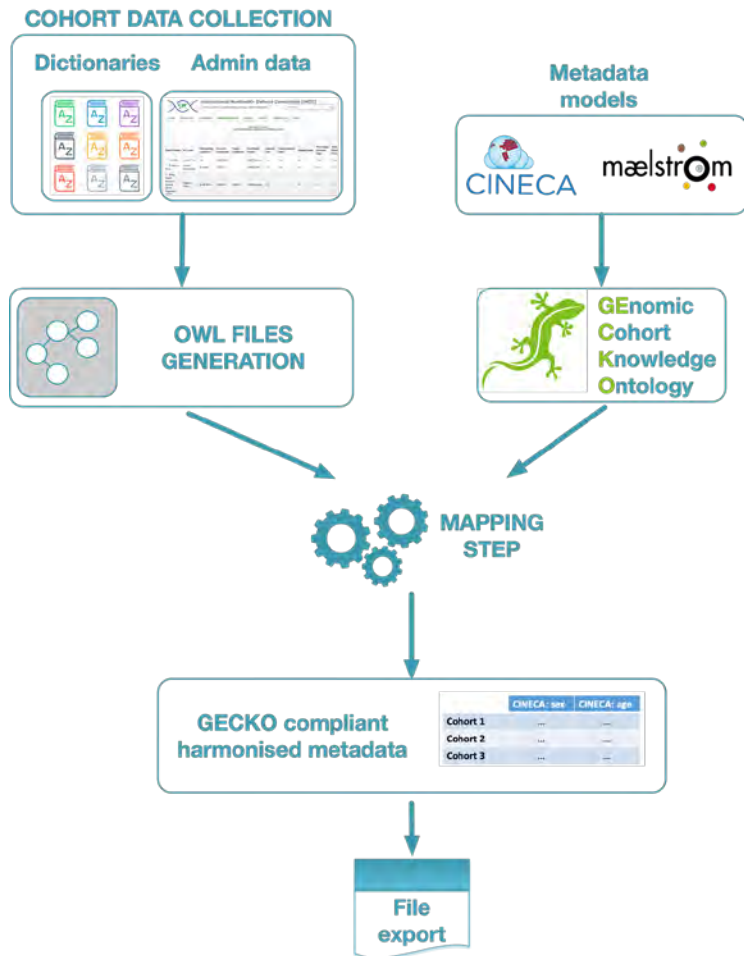
~ 100 IHCC cohort members

66 cohorts with public metadata

25 shared dictionaries

9 recontacted individually

7 respondents

6 loaded in the IHCC Atlas browser

5 mapped

The IHCC Cohort Atlas currently has a combination of real and mock data for demo purposes. The data is not appropriate for research.

Countries

Search · Less

Wales	3
Canada	2
Denmark	2
France	2
Iran	2
Malaysia	2
Netherlands	2
Northern Ireland	2
☑ South Africa	2
Austria	1
Bangladesh	1
Brazil: six cities	1
Cambodia	1
Canada (Province of Newfoundland and Labrador)	1
Channel Islands	1
Chile	1
Estonia	1
Europe	1
Europe (7)	1
Finland	1
Germany	1
Greece	1

CLEAR | COUNTRIES is | South Africa ✕

Cohorts by Country

2

South Africa

Biosample Types

stool
urine
saliva

Africa Health Research Institute (AHR

SAPRIN (South African Population Re

Showing 1 - 2 of 2 cohorts

Cohort Name	Countries	Current Enrollment	Genomic Data	Environmental Data	Biospecimen Data	Clinical Data	Data Sharing Potential	PI Lead	Website
Africa Health Resear...	South Africa	130000	✓	✗	✓	✓	✓	Deenan Pillay	🌐
SAPRIN (South Africa...	South Africa	350000	✗	✗	✓	✓	✓	Kobus Herbst	🌐

Show 20 ⬍ rows

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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

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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

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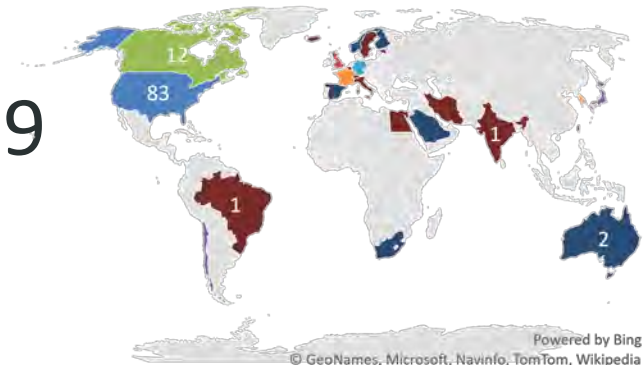
Director
National Institutes of Health USA

Opening Keynote

Francis Collins,
MD, PhD

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3rd International Cohorts
Summit

Multi Cohort Scientific Strategy – Fall 2020

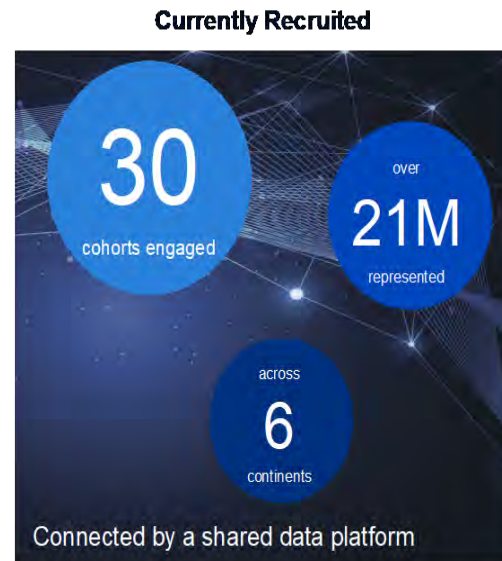| Proposal Title	Number of IHCC Cohorts
Global Mental Health Impact of the COVID-19 Pandemic	19
Strengthening biospecimen collection for Global Longitudinal Population Studies in the COVID-19 era	15
Novel coronavirus host susceptibility study in South Africa (COVIGen-SA)	5
High-Throughput Metabolomic Biomarker Measures in Diverse Ancestries	5
Opioid cohort consortium (OPICO) to investigate the effects of regular opioid use on mortality and on cancer development	8
Exploring the role of genetically determined BMI in early life on colorectal cancer in later life	9

Scientific Strategy – Alzheimer's Disease
(Hakon Hakonarson, Elias Zerhouni – leads)

Davos Alzheimer's Collaborative

GLOBAL CEOINITIATIVE · WORLD ECONOMIC FORUM

Our Vision for 2025

A Cohort of Five Million People with or At Risk for Alzheimer's

2025

Cohort 1   Cohort 2   Cohort 3   Cohort 4-X...

DAC/IHCC Global Collaborative

DAC Technology Backbone
- Integrated target discovery platform
- Brain tissue collection relevant across CNS diseases

Currently Recruited

30 cohorts engaged

over 21M represented

across 6 continents

Connected by a shared data platform
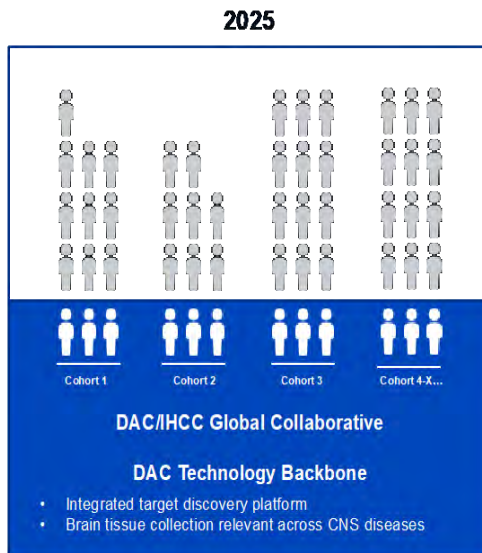
Maximizing the Power of Cohorts

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:

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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)

R Collins et al

Canada (835,000)

Norway (6,450,000)

Sweden (1.023,000)

Denmark (5,698,000)

Finland (950,000)

Estonia (160,000)

Iceland (250,000)

United Kingdom (2,380,000)

Netherlands (842,000)

Germany (190,000)

Switzerland (6,842,000)

China (3,045,000)

Japan (757,000)

Korea (1,097,000)

United States (11,811,000)

Mexico (160,000)

(150,000)

(220,000)

Saudi Arabia (102,000)

(381,000)

(39,000)

Malaysia (107,000)

Singapore (10,000)

Multi-Country (3,897,000)

Brazil (15,000)

Chile (9,000)

South Africa (480,000)

Australia (267,000)

Visit https://ihccglobal.org/

<100K   100K-249K   250K-999K   1M and up

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~110 cohorts, ~60M participants

IHCC Sponsors

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