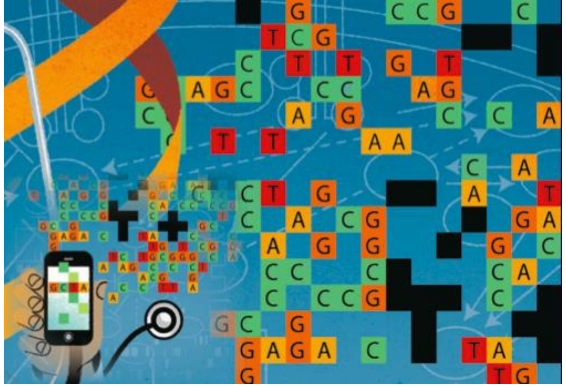

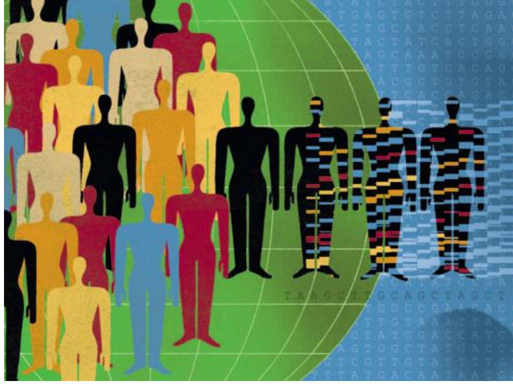

# Opportunities to Enhance Translation from Discovery to Health

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**Geoffrey S Ginsburg MD PhD**
Professor of Medicine and Biomedical Engineering

The Duke Center for Applied Genomics
& Precision Medicine
**Precisionmedicine.duke.edu**

Duke MEDx
**Medx.duke.edu**

Global Genomic
Medicine Collaborative

International Cohorts Summit

# Large Cohort Studies:
# The Goals Are the Same; The Tools Have Evolved

- Discovery: to explain the etiology of diseases, to understand health and health-to-disease transitions, to better define gene-environment interactions
- Translation: to provide the basis for
  - Novel risk models of disease
  - Clinical prevention and control measures for populations at risk
    - Biomarkers
    - Diagnostics
    - Therapeutics
  - Public health measures and practices
- Delivery – implementation and use of findings
  - Clinicians, public health practitioners
  - Public and policy makers awareness
  - Industry applications

Adapted from Colditz & Winn JNCI 2008

# “Factors of Risk”

**Annals of Internal Medicine**

*Established in 1927 by the American College of Physicians*

Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up Experience

Kannel WB et al.

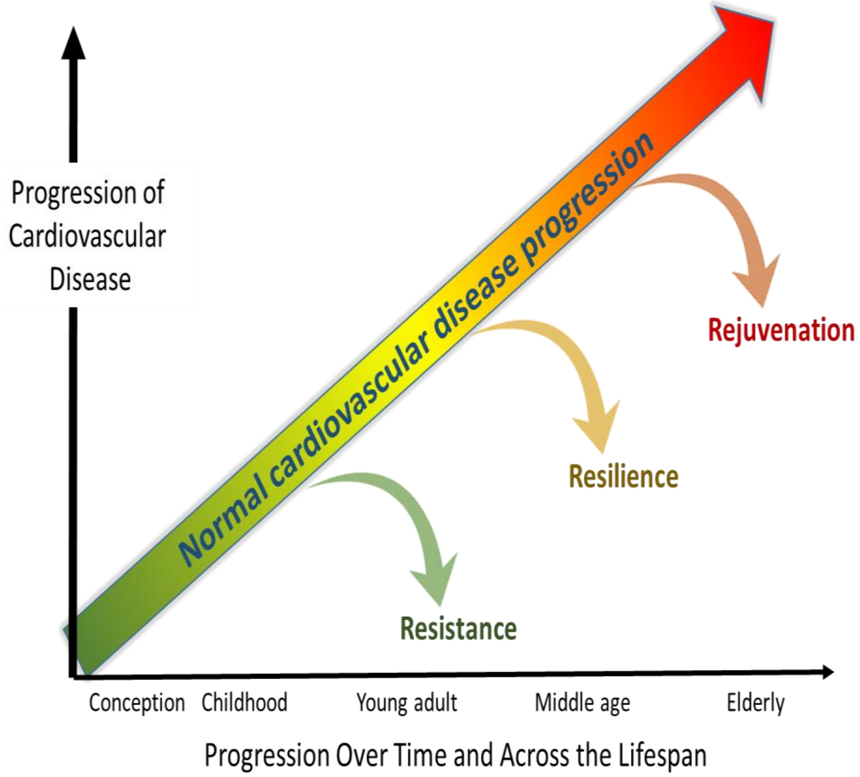
November 1961

- High blood pressure
- Increased cholesterol
- Smoking
- Diabetes
- Family history
- Male

Source: Kannel WB et al. *Ann Intern Med* 19961;55:33−50.

# "Factors of Resilience"

**Can we identify 'health protection' factors (vs risk factors) that preserve or restore health at multiple levels and their mechanisms of benefit**



- **Resistance:** Protection from adverse stressors, including risk factors and environment
- *Examples of scientific inquiry: novel risk models, "disease resistance factors"*
- **Resilience:** Subclinical evidence of disease but without progression to overt disease over time.
- *Examples of scientific inquiry: regression of disease*
- **Rejuvenation:** Expeditiously restoring health in those with established, symptomatic disease, including regeneration and recovery.
- *Examples of scientific inquiry: medication reduction, rapid uneventful recovery from surgery*

Courtesy Pam Douglas MD

# Genetic Resilience

ARTICLES

nature biotechnology

## Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases

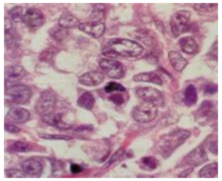
Rong Chen[1,2,12], Lisong Shi[1,2,12], Jörg Hakenberg[1,2], Brian Naughton[3,11], Pamela Sklar[1,2,4], Jianguo Zhang[5], Hanlin Zhou[5], Lifeng Tian[6], Om Prakash[7], Mathieu Lemire[8], Patrick Sleiman[6], Wei-yi Cheng[1,2], Wanting Chen[5], Hardik Shah[1,2], Yulan Shen[5], Menachem Fromer[1,2,4], Larsson Omberg[9], Matthew A Deardorff[6], Elaine Zackai[6], Jason R Bobe[1,2], Elissa Levin[1,2], Thomas J Hudson[8], Leif Groop[7], Jun Wang[10], Hakon Hakonarson[6], Anne Wojcicki[3], George A Diaz[1,2], Lisa Edelmann[1,2], Eric E Schadt[1,2] & Stephen H Friend[1,2,9]

2016

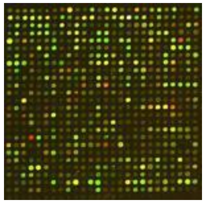
# Transitions over 50 Years

## Biology

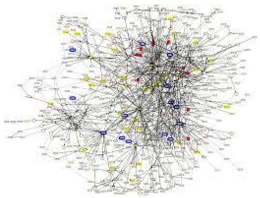
Observational Science



Genomic (Digital) Science



Systems Science

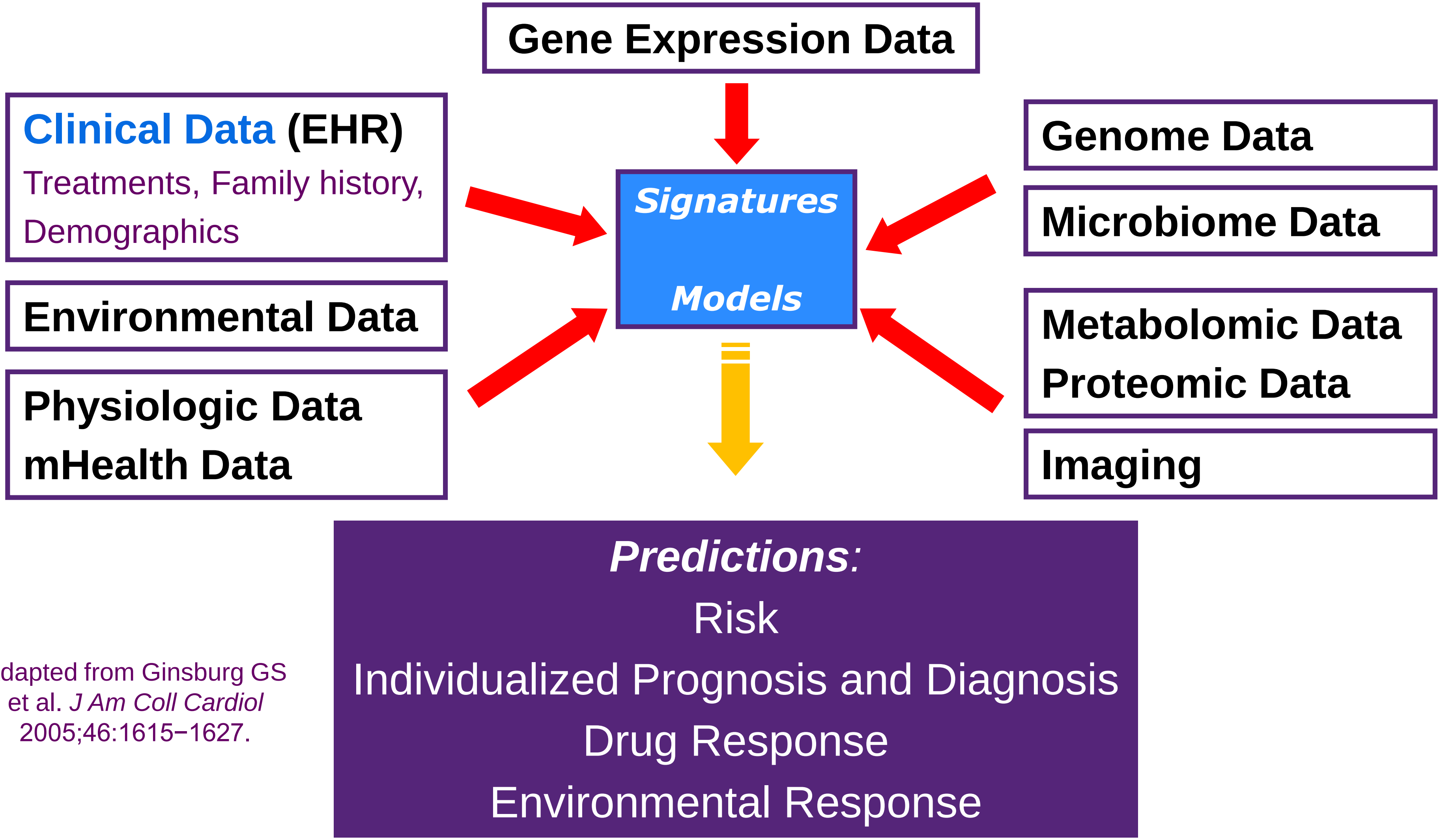


## Medicine

| Yesterday | Today | Tomorrow |
|---|---|---|
| Symptom Based | Population Pattern Based | Individual Algorithm Based |
| **Intuitive Medicine** | **Evidence-based Medicine** | **Precision Medicine** |

***"People with this history and lab values also had…***
***… and responded to this treatment"***

# Diverse Data Enables Novel Predictive Models of Health and Disease



**Gene Expression Data**

**Clinical Data (EHR)**
Treatments, Family history, Demographics

**Environmental Data**

**Physiologic Data**
**mHealth Data**

**Genome Data**

**Microbiome Data**

**Metabolomic Data**
**Proteomic Data**

**Imaging**

***Signatures***

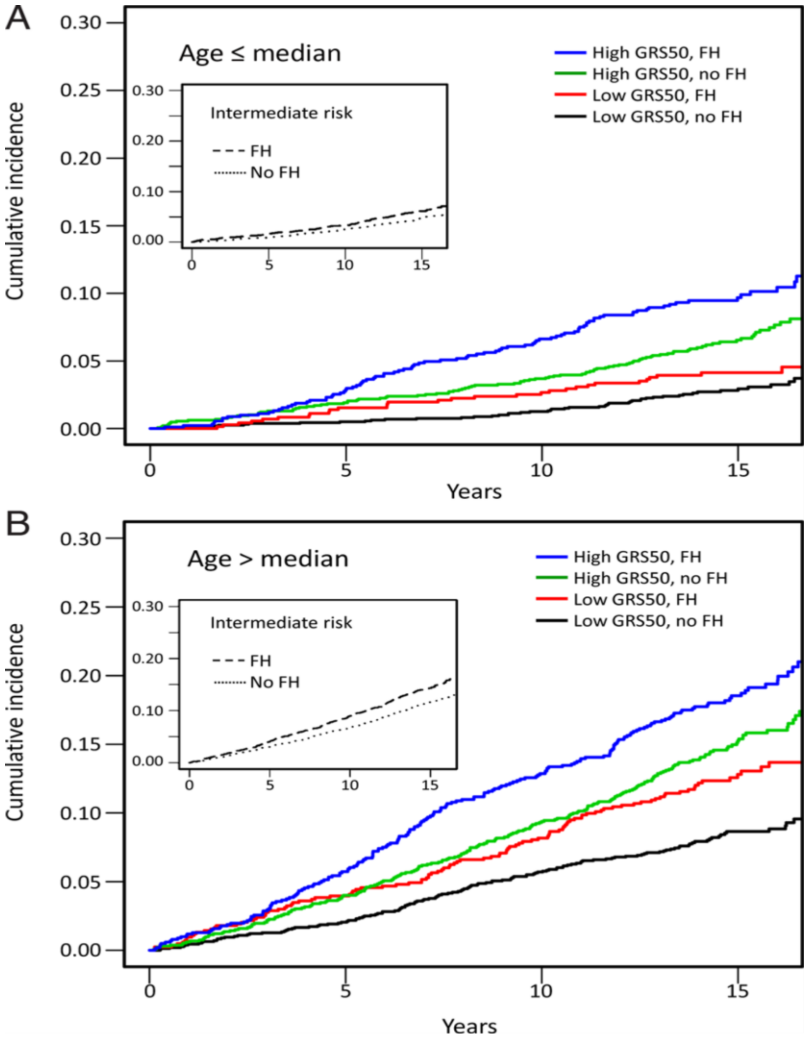
***Models***

***Predictions:***
Risk
Individualized Prognosis and Diagnosis
Drug Response
Environmental Response

Adapted from Ginsburg GS et al. *J Am Coll Cardiol* 2005;46:1615−1627.

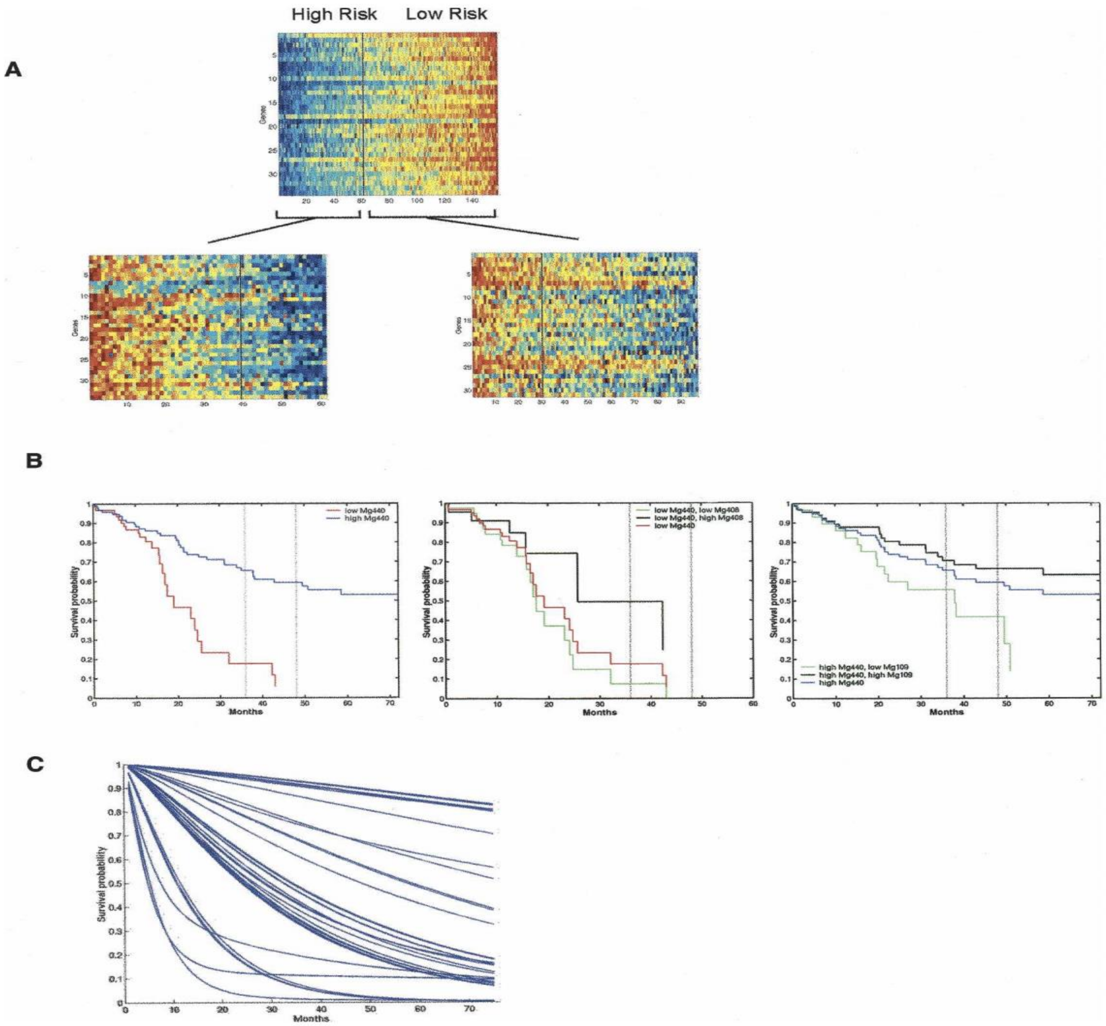
# Can We Do Better Than Clinical Models?

Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history



Tada et al EHJ 2016

# Can Genomic Analyses Refine Prognosis? (Breast Cancer)

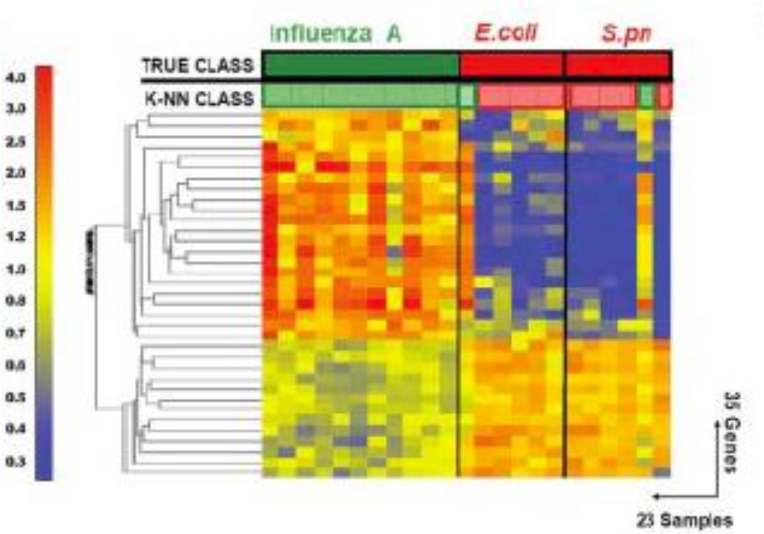


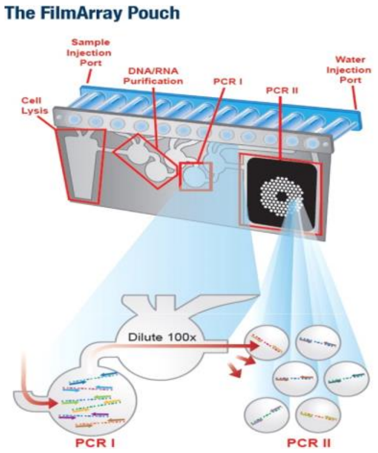
*West, Genome Res (2006)*

# Can Genomics Analyses Provide Better Diagnostics? (Viral vs Bacterial Respiratory Infection)

**Viral vs Bacterial Infection**

**< 60 min to result**





BIOFIRE
A BIOMÉRIEUX COMPANY

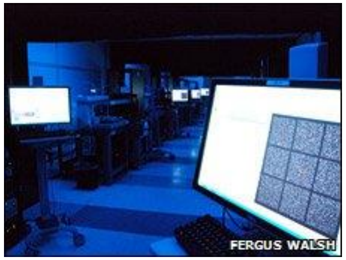
ARLG
Antibacterial Resistance Leadership Group

Zaas et al, Cell Host and Microbe, 2009
Woods et al PLoS ONE 2013
Ramilo et al Blood 2007
Tsalik et al Sci Trans Med 2016

# Genome Sequencing:
# *Affordable* Discovery and Clinical Application

HGP
2001
(13 years)
$2.7B

Jim Watson
2007
$1M

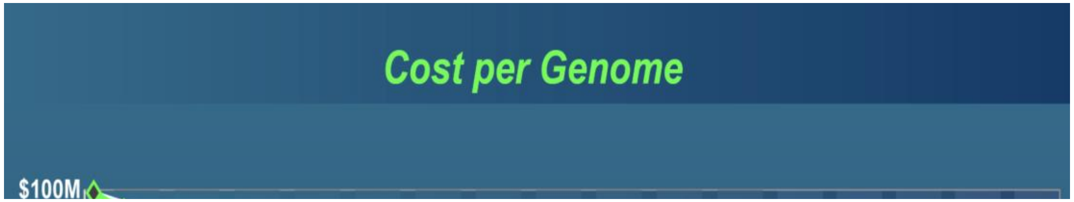

FERGUS WALSH

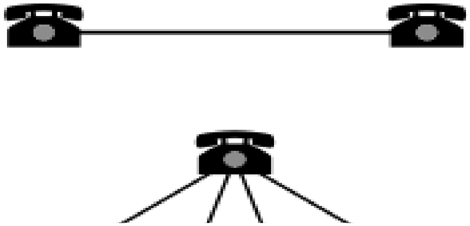
Complete Genomics
2009
$4,400

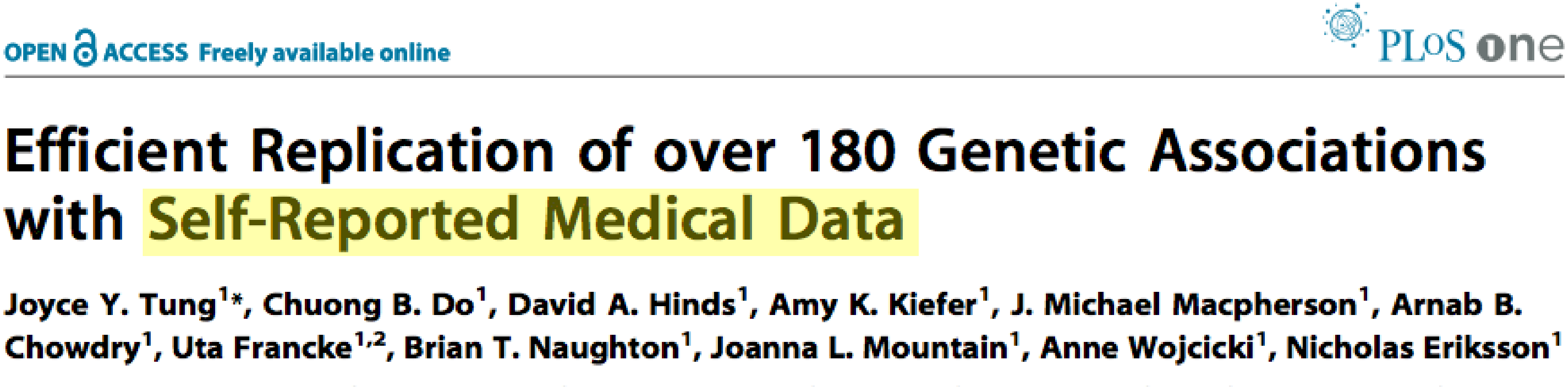
Ion Torrent
2012
$1,000 (1 day)

Various Vendors
2018
< $1000
> 50 Genomes/d

# Moore’s Law and Metcalf’s Law – Convergence and Opportunity





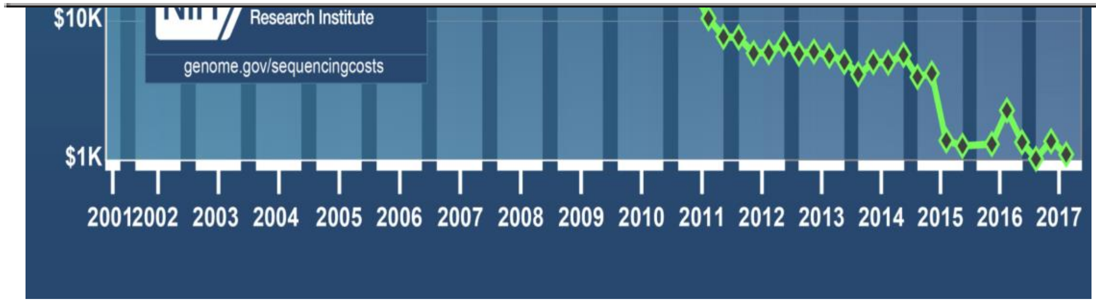

OPEN ACCESS Freely available online

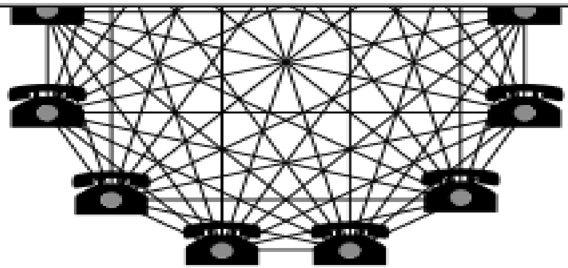
PLoS one

## Efficient Replication of over 180 Genetic Associations with Self-Reported Medical Data

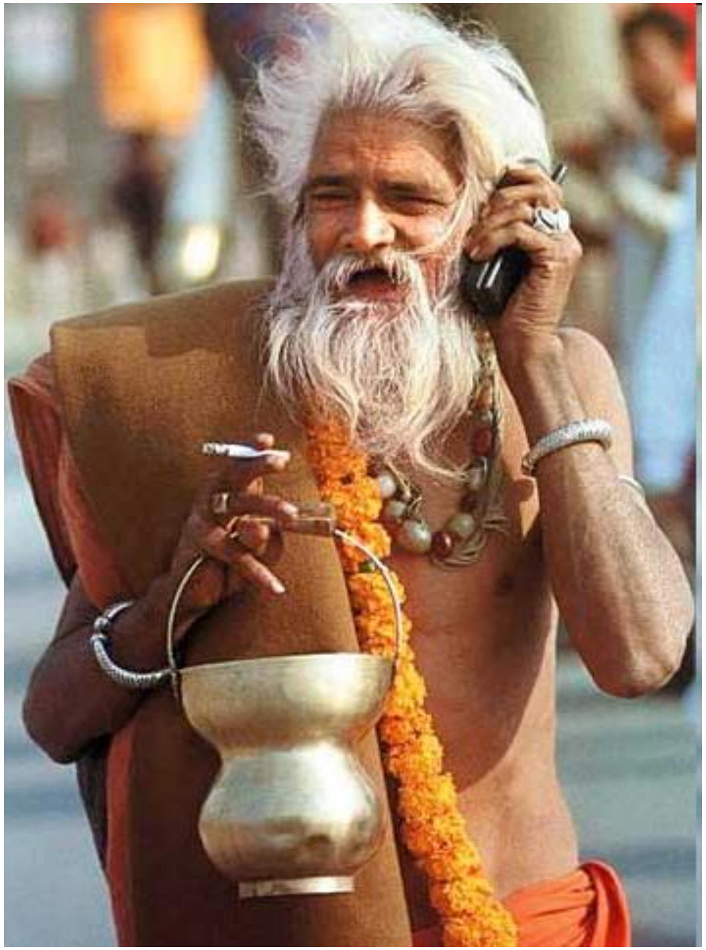
Joyce Y. Tung[1]*, Chuong B. Do[1], David A. Hinds[1], Amy K. Kiefer[1], J. Michael Macpherson[1], Arnab B. Chowdry[1], Uta Francke[1,2], Brian T. Naughton[1], Joanna L. Mountain[1], Anne Wojcicki[1], Nicholas Eriksson[1]

1 23andMe, Inc., Mountain View, California, United States of America, 2 Department of Genetics, Stanford University, Stanford, California, United States of America





# The Phone Has Changed Everything !

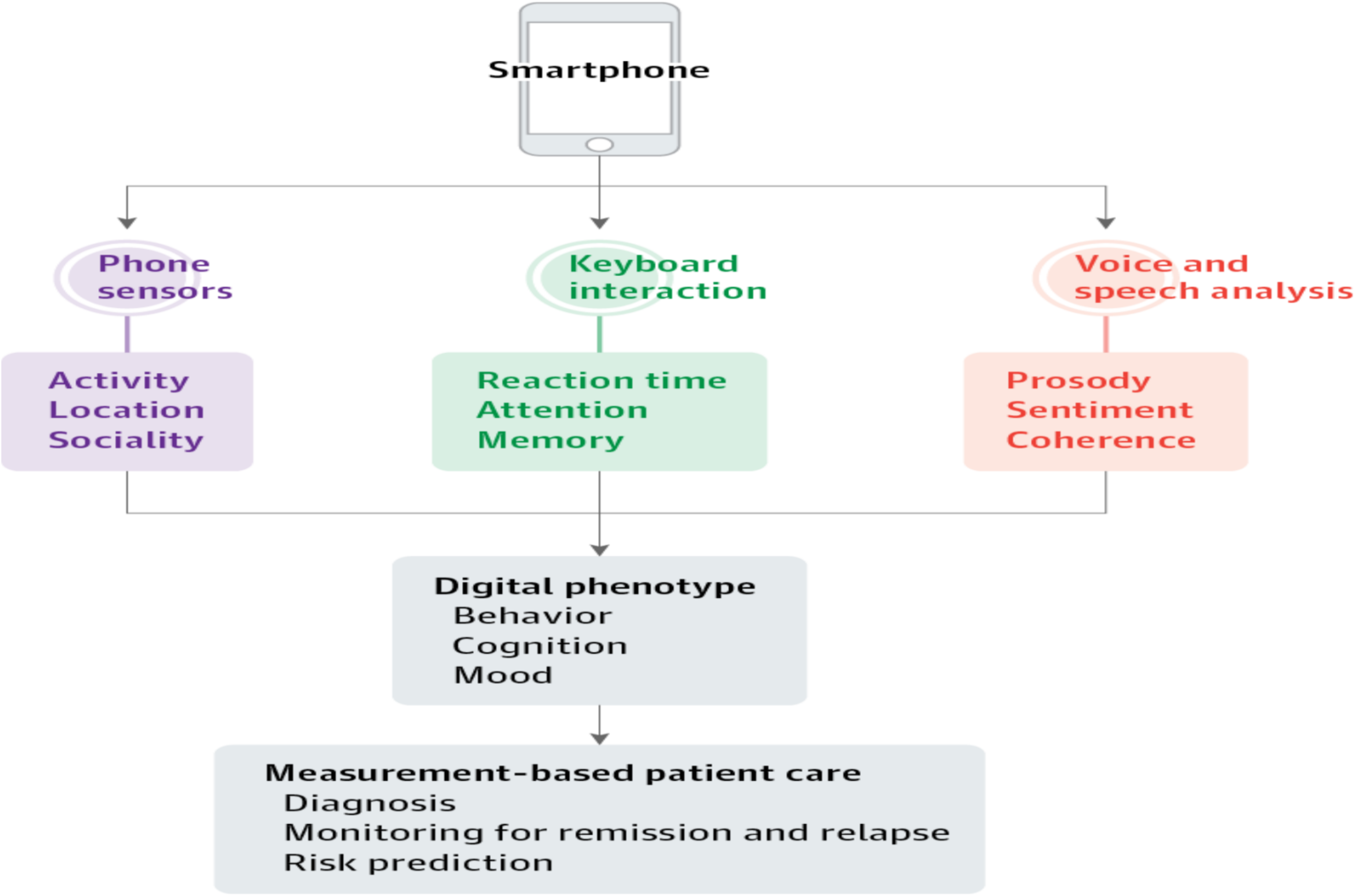


Source: W3C.org

- > 7 billion cell phone accounts
- > 80% of all people have one
- Health information
- Text messages
    - Cardiac health
    - HIV/AIDS
    - Diabetes
- **Data on Activity, Sleep, Nutrition**

Feder, 2010, *Health Affairs*

# Phone Enabled Digital Phenotyping: A New Science of Behavior



Smartphone

Phone sensors

- Activity
- Location
- Sociality

Keyboard interaction

- Reaction time
- Attention
- Memory

Voice and speech analysis

- Prosody
- Sentiment
- Coherence

**Digital phenotype**

- Behavior
- Cognition
- Mood

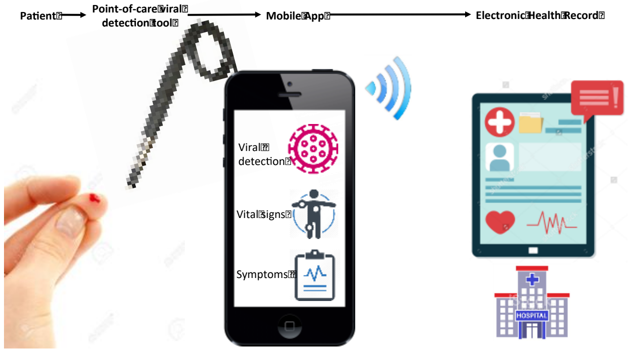
**Measurement-based patient care**

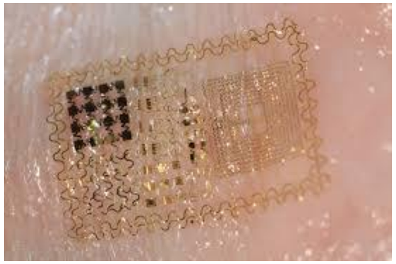
- Diagnosis
- Monitoring for remission and relapse
- Risk prediction

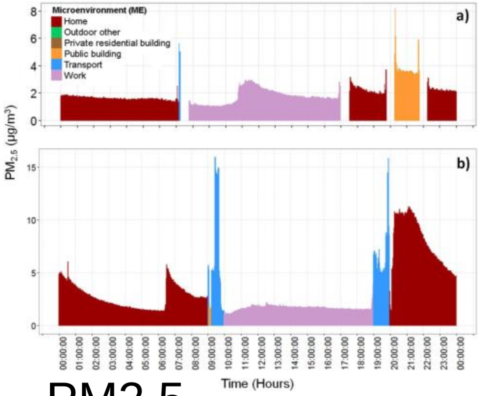
Insel JAMA. 2017;318(13):1215-1216

# Decentralization of Research (and Medicine)

- Point-of-care devices
- Environmental sensors
- Health Monitors
- Wearable tattoos



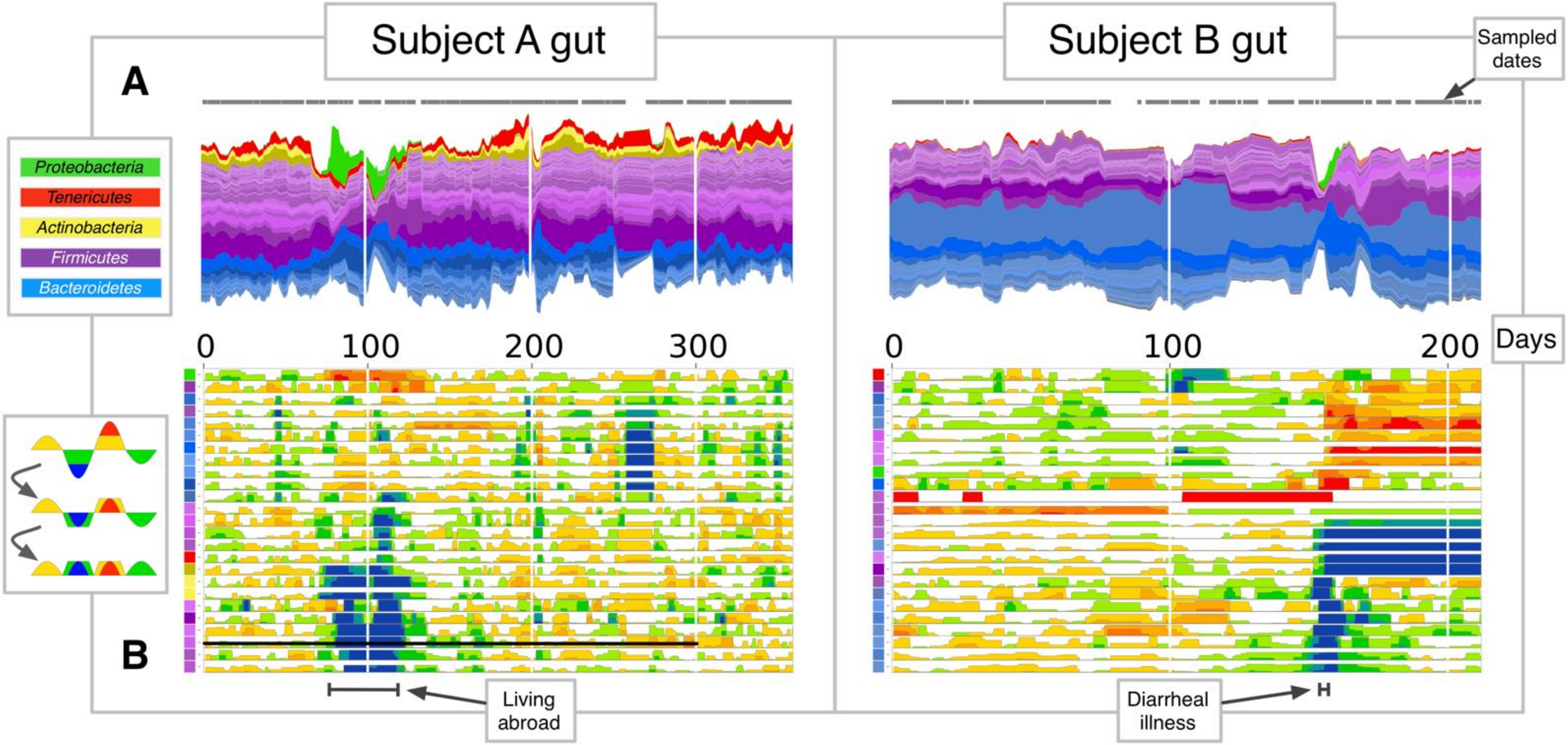




PM2.5

# Personal Microbiome Profiling

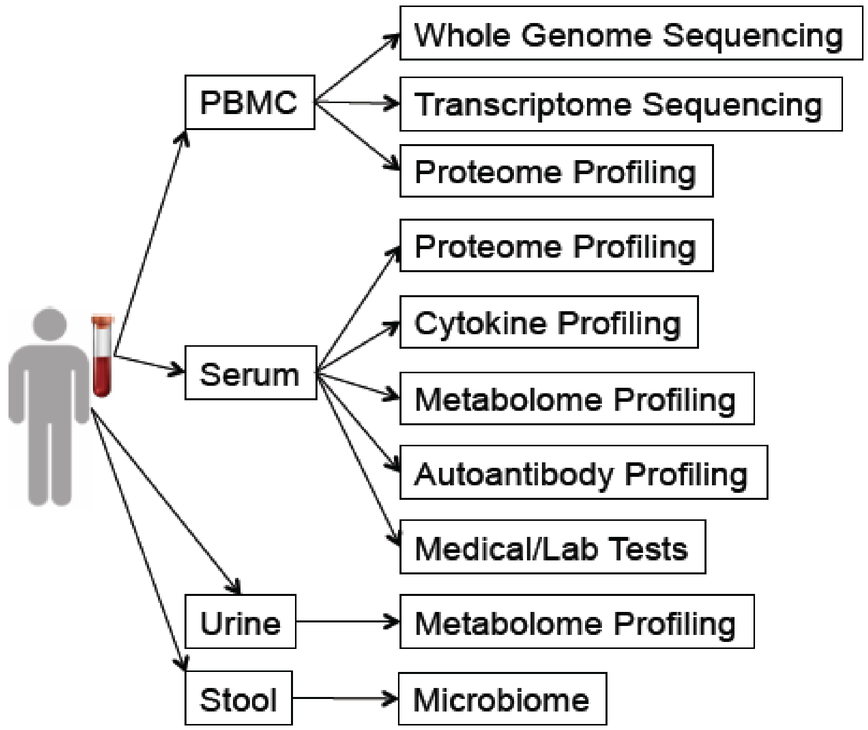
## Dynamic Changes in Gut Flora (N=2)



David et al, Genome Biology 2014

# Multiscale biomedical data integration

## Multi-omics



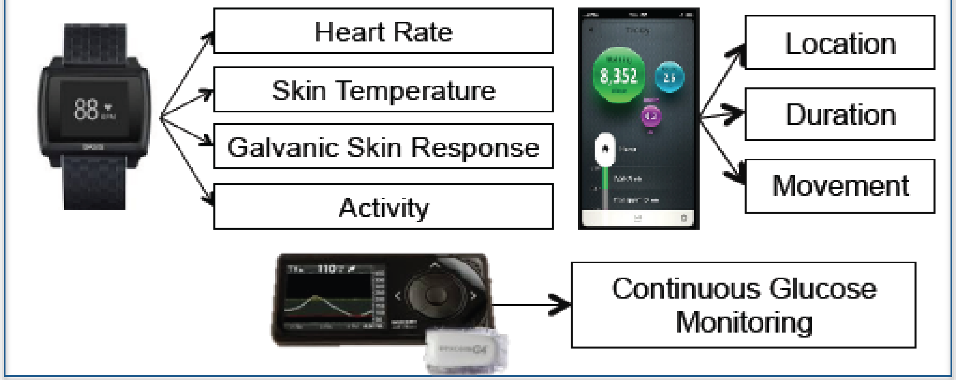
PBMC
Whole Genome Sequencing
Transcriptome Sequencing
Proteome Profiling

Serum
Proteome Profiling
Cytokine Profiling
Metabolome Profiling
Autoantibody Profiling
Medical/Lab Tests

Urine
Metabolome Profiling

Stool
Microbiome

## Wearable Devices



Heart Rate
Skin Temperature
Galvanic Skin Response
Activity

Location
Duration
Movement

Continuous Glucose Monitoring

## Electronic Health Records

Lipid Panel (7)
Comprehensive Metabolic Panel (17)
Complete Blood Count (19)
Urinalysis (15)
Electrolyte Panel (5)
----------------------------------------------------------
Up to 1017 Unique Clinical Lab Features

Demographics
Vital signs
Lab orders
Medication orders

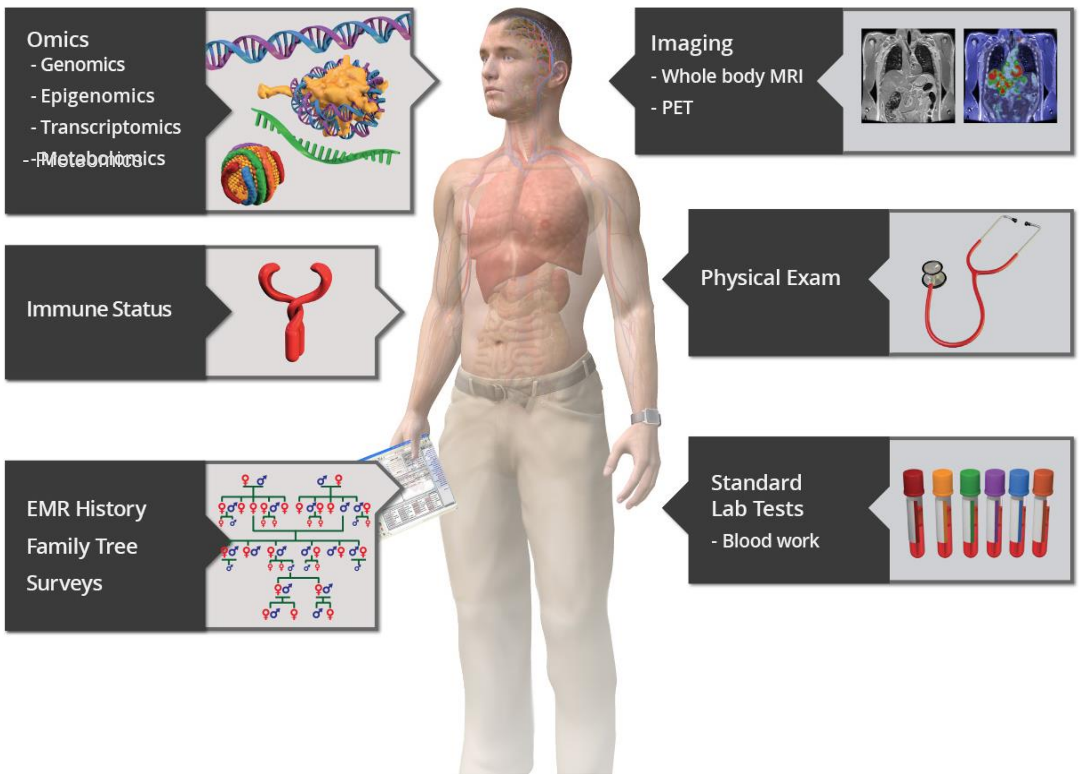
RESEARCH ARTICLE

Digital Health: Tracking Physiomes and Activity Using Wearable Biosensors Reveals Useful Health-Related Information

Xiao Li[1☯], Jessilyn Dunn[1,2☯], Denis Salins[1☯], Gao Zhou[1], Wenyu Zhou[1], Sophia Miryam Schüssler-Fiorenza Rose[3,4], Dalia Perelman[5], Elizabeth Colbert[3], Ryan Runge[1], Shannon Rego[3], Ria Sonecha[1], Somalee Datta[1], Tracey McLaughlin[5], Michael P. Snyder[1]*

PLoS ONE, 2017

# Project Baseline:
# Human Health and Transition to Disease



**Omics**
- Genomics
- Epigenomics
- Transcriptomics
- Metabolomics

**Immune Status**

**EMR History**
**Family Tree**
**Surveys**

**Imaging**
- Whole body MRI
- PET

**Physical Exam**

**Standard Lab Tests**
- Blood work

( Yearly Onsite Visits )

Screen → Baseline Visit → Year 1 Visit → Year 2 Visit → Year 3 Visit → Year 4 Visit

( Quarterly Onsite, Online, Phone )

- Develop a set of scalable and standardized tools for acquiring, organizing, and analyzing clinical, molecular, imaging, sensor, behavioral, self-reported, psychological, environmental, health records, and other health-related data
- Evaluate approved and investigational wearable and passive sensors
- Create a dataset encompassing a wide spectrum of phenotypic measures
- Identify biomarkers of disease-related transitions, including those related to cardiovascular disease and cancer

verily

Duke University
School of Medicine

Stanford
MEDICINE

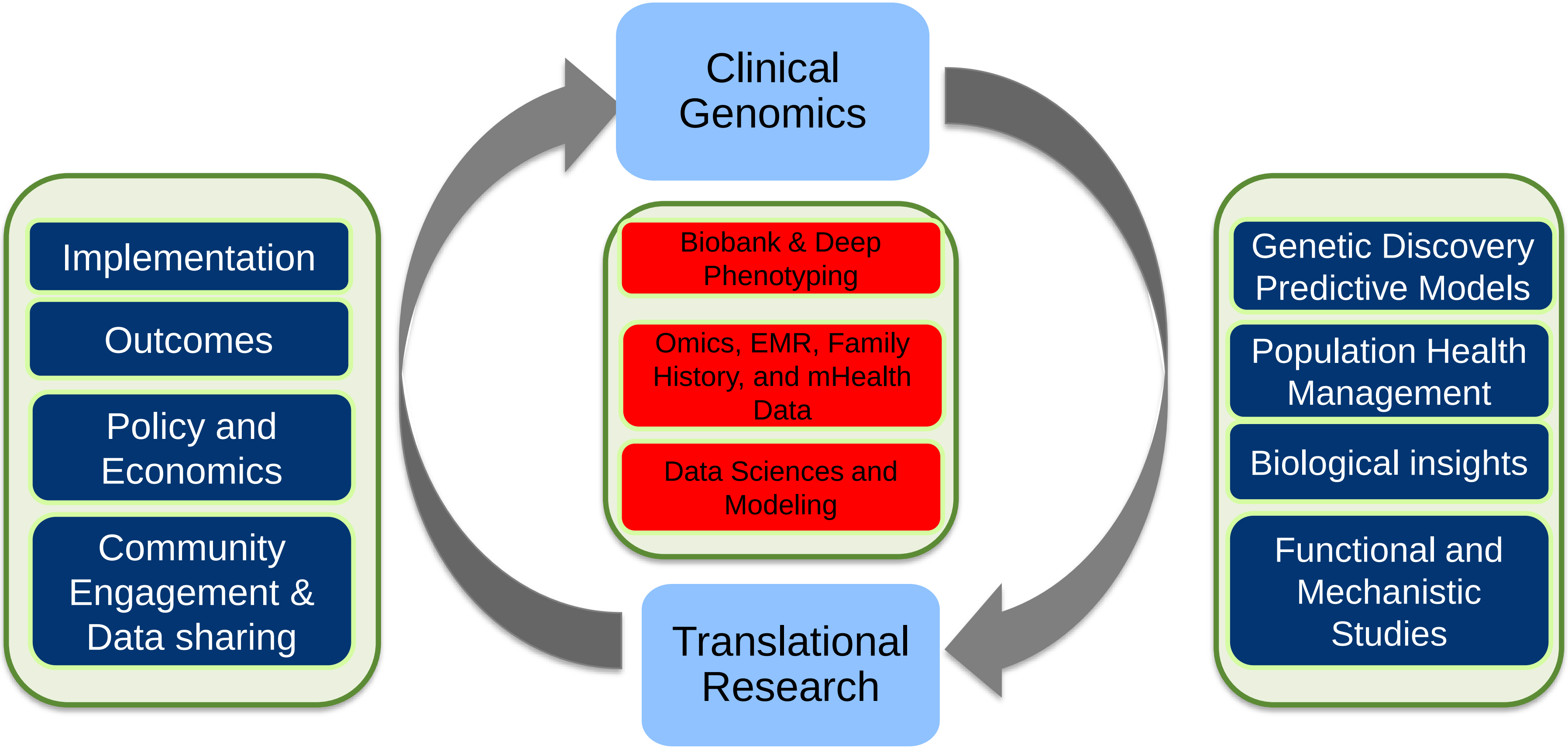
# Deriving Drug Discovery Value from Large Scale Genetic Bioresources: A US National Academies Workshop

- Large scale population cohorts with genetic and phenotypic data are rich sources of potential drug targets
- Phenotypes are critical - Self reported phenotypes are powerful
- For participants – Trust is paramount
  - Return of results is valued
- Data sharing and the power of collaborative frameworks will accelerate the field
- Computational solutions will be disruptive

**December 2016**

The National Academies of SCIENCES ENGINEERING MEDICINE

# Large Scale Bioresources: Cycles of Genomics and Precision Medicine Research and Clinical Applications



Clinical Genomics

Biobank & Deep Phenotyping

Omics, EMR, Family History, and mHealth Data

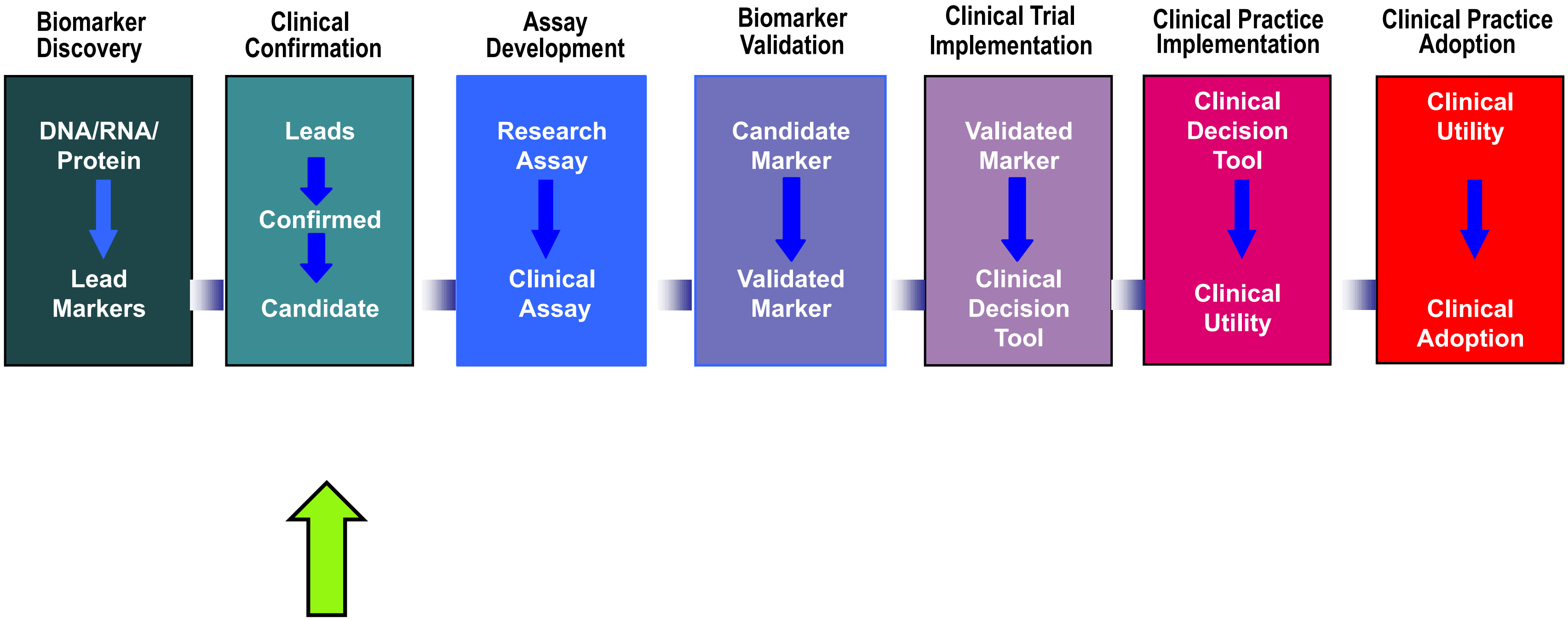
Data Sciences and Modeling

Translational Research

- Implementation
- Outcomes
- Policy and Economics
- Community Engagement & Data sharing

- Genetic Discovery Predictive Models
- Population Health Management
- Biological insights
- Functional and Mechanistic Studies

# The ‘Translational Continuum’ for Biomarkers And Molecular Tests



**Biomarker Discovery**

DNA/RNA/Protein
Lead Markers

**Clinical Confirmation**

Leads
Confirmed
Candidate

**Assay Development**

Research Assay
Clinical Assay

**Biomarker Validation**

Candidate Marker
Validated Marker

**Clinical Trial Implementation**

Validated Marker
Clinical Decision Tool

**Clinical Practice Implementation**

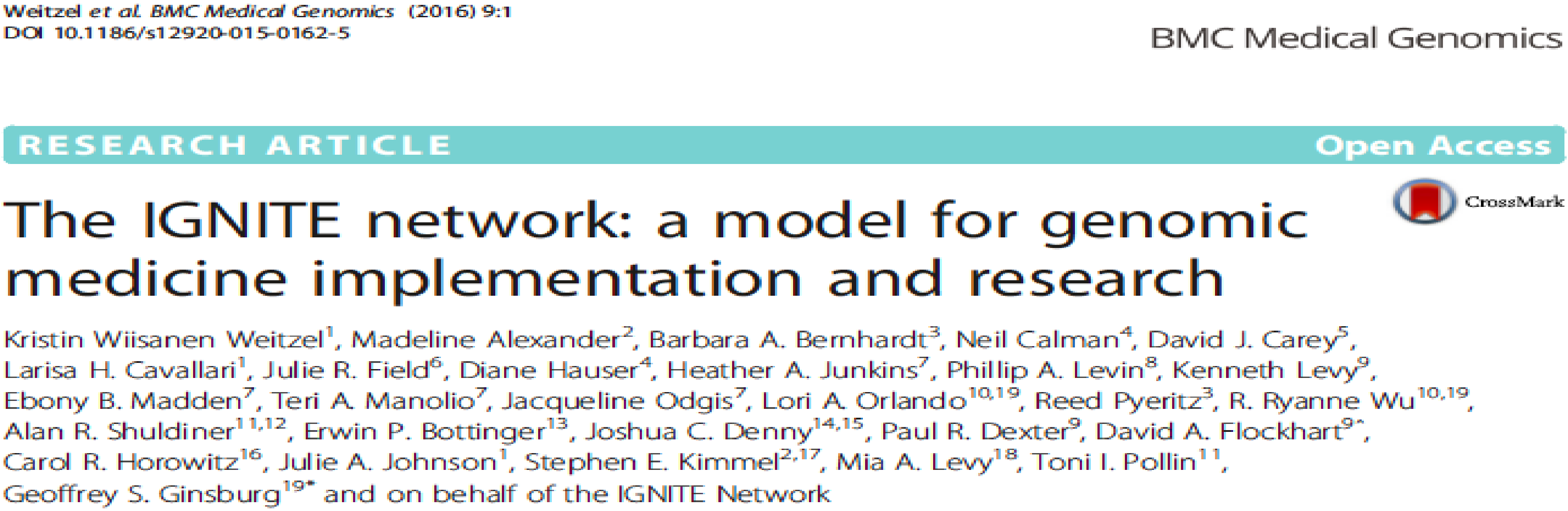
Clinical Decision Tool
Clinical Utility

**Clinical Practice Adoption**

Clinical Utility
Clinical Adoption

We are here

# “Vision Without Implementation is Hallucination” (Thomas Edison)



Weitzel *et al. BMC Medical Genomics* (2016) 9:1
DOI 10.1186/s12920-015-0162-5

BMC Medical Genomics

RESEARCH ARTICLE

Open Access

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

www.ignite-genomics.org

IGNITE
Implementing GeNomics In pracTicE

# Envisioning How Large Cohorts Might Enable Translational Research

- **Integration of personal, clinical, biological information**
  - Develop models for individual and population health
  - Prediction of health to disease transitions
  - Research in resistance, resilience, and rejuvenation
- **Provide researchers and healthcare systems with continuously updated estimates of individual risk and health behaviors of neighborhoods and populations**
  - Enable directed education, prevention and treatment programs
- **Use a more profound understanding of health and disease to inform development of new therapeutics and diagnostics**
  - Early disease detection
  - Bio-surveillance for public health impact
  - Drug Discovery
- **Provide and apply these data to our participants and our communities**