Opportunities to Enhance Translation from Discovery to Health

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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”

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

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

Rong Chen¹,²,¹², Lisong Shi¹,²,¹², Jörg Hakenberg¹,², Brian Naughton³,¹¹, Pamela Sklar¹,²,⁴, Jianguo Zhang⁵, Hanlin Zhou⁵, Lifeng Tian⁶, Om Prakash⁷, Mathieu Lemire⁸, Patrick Sleiman⁶, Wei-yi Cheng¹,², Wanting Chen⁵, Hardik Shah¹,², Yulan Shen⁵, Menachem Fromer¹,²,⁴, Larsson Omberg⁹, Matthew A Deardorff⁶, Elaine Zackai⁶, Jason R Bobe¹,², Elissa Levin¹,², Thomas J Hudson⁸, Leif Groop⁷, Jun Wang¹⁰, Hakon Hakonarson⁶, Anne Wojcicki³, George A Diaz¹,², Lisa Edelmann¹,², Eric E Schadt¹,² & Stephen H Friend¹,²,⁹
Transitions over 50 Years

**Biology**
- Observational Science
- Genomic (Digital) Science
- Systems Science

**Medicine**

<table>
<thead>
<tr>
<th>Yesterday</th>
<th>Today</th>
<th>Tomorrow</th>
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<td>Symptom Based</td>
<td>Population Pattern Based</td>
<td>Individual Algorithm Based</td>
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<tr>
<td>Intuitive Medicine</td>
<td>Evidence-based Medicine</td>
<td>Precision Medicine</td>
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“People with this history and lab values also had... ... and responded to this treatment”
Diverse Data Enables Novel Predictive Models of Health and Disease

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

Environmental Data

Physiologic Data
- mHealth Data

Gene Expression Data

Signatures

Models

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

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

Zaas et al, Cell Host and Microbe, 2009
Woods et al PLoS ONE 2013
Ramilo et al Blood 2007
Genome Sequencing: Affordable Discovery and Clinical Application

HGP
2001
(13 years)
$2.7B

Jim Watson
2007
$1M

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

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

Joyce Y. Tung¹*, Chuong B. Do¹, David A. Hinds¹, Amy K. Kiefer¹, J. Michael Macpherson¹, Arnab B. Chowdry¹, Uta Francke¹,², Brian T. Naughton¹, Joanna L. Mountain¹, Anne Wojcicki¹, Nicholas Eriksson¹

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

Cost per Genome

OPEN ACCESS Freely available online

$10K

$1K

$100M


genome.gov/sequencingcosts
The Phone Has Changed Everything!

- > 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

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**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**
- Whole Genome Sequencing
- Transcriptome Sequencing
- Proteome Profiling
- Proteome Profiling
- Cytokine Profiling
- Metabolome Profiling
- Autoantibody Profiling
- Medical/Lab Tests
- Metabolome Profiling
- 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)
- Demographics
- Vital signs
- Lab orders
- Medication orders
- Up to 1017 Unique Clinical Lab Features

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**RESEARCH ARTICLE**

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

Xiao Li¹, Jessilyn Dunn¹,²,³, Denis Salinas¹,², Gao Zhou¹, Wenyu Zhou¹, Sophia Miryam Schüssler-Florenza Rose³,⁴, Dalia Perelman⁵, Elizabeth Colbert⁶, Ryan Runge⁷, Shannon Rego⁸, Ria Sonecha¹, Somalee Datta¹, Tracey McLaughlin⁹, Michael P. Snyder¹ *
Project Baseline: Human Health and Transition to Disease

- 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.
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.
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

Community Engagement & Data sharing
The ‘Translational Continuum’ for Biomarkers and Molecular Tests

We are here
“Vision Without Implementation is Hallucination” (Thomas Edison)

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
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